

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
21-818 and 21-498/S-003

MEDICAL REVIEW(S)

Medical Team Leader/Division Director's Review

Application Type:	administrative NDA and efficacy supplement
Submission number:	21-818 (administrative NDA, will revert to 21-497 after approval) 21-498/ S-003
Submission date:	17 December 2004
Established Name	Nitazoxanide
Trade Name	Alinia®
Therapeutic Class	antiparasitic
Applicant	Romark Laboratories, L.C.
Priority Designation	S
Formulation	21-818 tablets 21-498 suspension
Dosing Regimen	tablets: one 500mg tablet BID x 3 days PO w/ food suspension: 25ml (20mg/ml) BID x 3 days PO w/ food
Indication	treatment of diarrhea due to <i>Cryptosporidium parvum</i>
Intended Population	Immunocompetent adults and adolescents 12 years of age and older

RECOMMENDATION:

The Division recommends approval of Alinia® for the treatment of diarrhea due to *Cryptosporidium parvum* in non-HIV-infected adults and adolescents (>12 years of age) and has determined that the product is both safe and effective at the recommended dose regimen for this indication based on the review of one pivotal double blind placebo controlled study demonstrating that a 3 day regimen of Alinia® is superior to placebo and supportive evidence from smaller randomized placebo controlled study in a similar adult patient population (reviewed previously in NDA 21-497). Of note, Alinia® is already approved for the treatment diarrhea due to *Cryptosporidium parvum* in non-HIV-infected pediatric patients 1-11 years old. Pediatric studies in the 0-1 year age group have been deferred.

BACKGROUND: Scientific & Regulatory

Cryptosporidium parvum causes diarrhea in non-HIV infected patients that is usually self limited and no treatment is usually required. Epidemiologic studies indicate that seroconversion occurs in up to a third of healthy populations in the US by early adulthood. This contrasts with the studies in non US settings, where 50-90% of asymptomatic children have seroconverted by age 5. The disparity between the clinical and microbiologic findings in these populations may be a reflection of the varying endemicity of the pathogen, the difference in water quality in the developing world, or the more intimate zoonotic exposures in agrarian populations. In the US, however, diarrhea due to *Cryptosporidium* has occurred in point source epidemics in day care centers, institutions such as hospitals and nursing homes and in food and widespread, waterborne outbreaks. In these outbreak settings, approximately 50% of “healthy” populations are rendered symptomatic, usually individuals in the extremes of age, who are more severely ill. Although the diarrhea tends to be self-limited, data from previous studies submitted indicated that patients treated with Alinia® for 3 days have a higher resolution and shorter duration of diarrhea than placebo-treated patients. In this NDA/efficacy supplement, the applicant demonstrated superiority of a 3 day regimen of Alinia® over placebo in non-HIV infected adults in Egypt to support approval for an analogous patient population in the US. The applicant further presented evidence that clinical outcomes correlate with parasitological eradication and that treatment efficacy is durable up to 14 days following completion of treatment.

HIV-infected patients:

The product development for Alinia® tablets for the indication of *C. parvum* diarrhea began with clinical studies in HIV-infected patients initiated over 10 years ago and submitted as NDA 20-871. At an advisory committee meeting, during which the evidence of efficacy was presented, it was determined that outcomes were not sufficiently different from placebo to support approval of the product for HIV-infected patients. (See Appendix A for complete summary of *C. parvum* studies)

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Pediatric patients:

Romark refocused the drug development plan on non-HIV infected adults and children, and on May 29, 2002, submitted NDAs 21-497 (tablet) and 21-498 (oral suspension) for this indication with the Division, based on one study in adults (RM 98-002) conducted in Egypt that evaluated the efficacy of the tablet formulation and a new suspension formulation in pediatric patients that was also evaluated in study 98-002 and in study 3007 in Zambia (Table 1). A third pediatric study (3008) showed that the drug was not different from placebo in treating HIV-infected pediatric patients with diarrhea.

The data from the two studies in non-HIV-infected pediatric patients was adequate to support approval. For completeness, and to inform physicians that Alinia® had not been shown to work in patients with HIV, the results of study 3008 were also summarized in the labeling.

The pediatric indication for *C. parvum* was approved and the approved label bears a dosage and administration section that specifies the following dose of Alinia® suspension, to be taken with food:

1-3 yrs	5 mL of Alinia® Oral Suspension (100 mg nitazoxanide) q 12 hrs
4-11 yrs	10 mL of Alinia® Oral Suspension (200 mg nitazoxanide) q 12 hrs

A summary of the pediatric data that led to approval for the treatment of diarrhea caused by *C. parvum* is provided in Table 1, below.

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Table 1: Summary of efficacy of Alinia® suspension in non-HIV infected pediatric patients with *Cryptosporidium parvum* diarrhea

NDA	Study Site and Population Characteristics	Evidence in pediatric patients	p value	Kappa statistic
NDA 21-498 05-29-2002 suspension	HIV-negative Pediatric patients (Egypt RM 98-002) Ages 1-22	ITT CLINICAL* Alinia® 21/24 (88%) Placebo 9/24 (38%)	0.001	Alinia® 0.33 Placebo 0.04
		ITT PARASITOLOGICAL Alinia® 18/24 (75%) Placebo 6/25 (24%)	0.001	
		Median time to last unformed stool Alinia® 3.5 days Placebo 6 days	0.049	N/A
	Malnourished HIV-negative Pediatric patients (Zambia 02-3007) Ages 1-4 Mean CD4 cells 1532/mm ³ Weight for age z scores 3.5 Diarrhea duration: mean 20 days	CLINICAL Alinia® 14/25 (56%) Placebo 5/22 (23%)	0.037	Alinia® 0.12 Placebo 0.10
		MORTALITY Alinia® 0/25 (0%) Placebo 5/22 (23%)	Not stated	
		PARASITOLOGICAL Alinia® 13/25 (52%) Placebo 3/22 (14%)	0.007	
	Malnourished HIV infected Pediatric patients (Zambia 02-3008) Ages 1-11 Mean CD4 cells 620/mm ³ Weight for age z scores 5.5 More chronic diarrhea: mean 49 days	CLINICAL Alinia® 2/25 (8%) Placebo 6/24 (25%)	0.037	Alinia® 0.25 Placebo 0.31
		MORTALITY Alinia® 5/25 (20%) Placebo 4/24 (17%)	1.0	
		PARASITOLOGICAL Alinia® 4/25 (16%) Placebo 5/25 (20%)	1.0	

Outcomes differed according to age
 4-11 Alinia 85% of 13, kappa 0.76 Placebo 36% of 14 kappa -0.26
 <4 Alinia 91% of 11, kappa -0.16 Placebo 36% of 11 kappa 0.38

Adult Patients – Previous Study:

In Study 98-002, submitted May 29, 2002, the data in adult patients were suggestive of efficacy but not statistically robust: the clinical success was 15/21 (71%) on Alinia® and 9/21 (43%) on placebo, $p=.118$. The parasitological success rate was 12/21 (57%) on Alinia® and 6/21 (29%) on placebo, $p=.118$. The kappa value showed a poor correlation between the clinical and parasitologic outcomes. Given these results, the indication of treatment of diarrhea caused by *C.parvum* in non-HIV infected adults received an approvable action on November 22, 2002.

On January 28, 2004, in conjunction with the resubmission for the *G. lamblia* diarrhea indication in adults, the applicant again requested approval for the *C. parvum* diarrhea indication in adults and proposed that it be based on (a) efficacy data in *Giardia* in adults, by extrapolation (b) efficacy of the suspension formulation in pediatric patients with cryptosporidiosis [from the above 2 placebo-controlled studies] and (c) results of study 98-002 in adults. The Division agreed to consider this approach, but in the end determined that there was difficulty extrapolating efficacy from pediatrics to adults with this formulation, and efficacy of Alinia® in *Giardia* in adults was not known to be predictive of efficacy in *Cryptosporidium* therefore, on July 21, 2004, a second approvable letter was issued (NDA 21-497, Alinia® tablets, was administratively split at this time, and NDA 21-818 received the approvable action), requesting another controlled clinical study. Incidentally, study 3010 was stated to be in progress at that time.

ADULTS PATIENTS – CURRENT SUBMISSIONS:

In this NDA resubmission to 21-818 (tablet) and new efficacy supplement 21-498/S-003 (suspension), the applicant presents evidence from one multicenter double blind placebo controlled study of Alinia® tablets in the treatment of cryptosporidiosis in non-HIV infected adults and adolescents (>12 years). Ninety patients with diarrhea and *Cryptosporidium* positive stool were randomized to one of three treatment groups, (a) one 500 mg Alinia® tablet, (b) 25 ml of a 20mg/ml Alinia® suspension or (c) one placebo tablet, each given twice daily for 3 consecutive days (Study 3010). Patients were assessed for the primary outcome at 7-10 days post treatment initiation (day 4-7 after end of treatment). This clinical evaluation included physical examination and assessment of symptomatic response. At this time point, two stool samples were evaluated for parasitological outcome. A second post treatment visit was performed at day 14-17 for purposes of evaluation of parasitological response. In about half of the patients evaluated at this time point, a clinical evaluation was also performed. These findings are summarized by Dr. Meyer in her review and in the table below.

Criteria for evaluation were clinical or parasitological, with clinical response serving as the primary outcome of efficacy and parasitological outcome as a secondary endpoint of interest. Intra-patient correlation of clinical and parasitological response and stool examination at day 14-17 were compared using Fisher's exact tests, with 95% CI

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calculated round the differences in proportions of clinical and microbiological response rates.

Table2 Criteria and timing of clinical / parasitological assessments in RM 01-3010, treatment of *Cryptosporidium parvum* in adults.

Criteria (Duration)	Clinical response (Primary OUTCOME)			Parasitological response (Secondary OUTCOME)	
	WELL	Continuing illness	Failure	Eradication	Persistence
LAST 24 HRS					
Symptoms	None	Any	Removal from study for worsening of any symptom or sign after at least 24 hours of treatment	NO <i>C parvum</i> oocysts at the 7-10 day evaluations	<i>C parvum</i> oocysts in at least one stool exam at the 7-10 day evaluations
Watery stool	None	Any			
Soft stool	Not > 2	>2			
hematochezia ^a	None	Any			
LAST 48 HRS					
Symptoms AND	None				
Unformed stool	None				

a= hematochezia is not considered a finding in cryptococosis and was ignored as an inclusion and outcome evaluation criteria and was excluded from the label

Based on this pre-specified analysis, the efficacy was 96% (27/28) for nitazoxanide tablets in the treatment of diarrhea caused by *Cryptosporidium parvum* in non-HIV infected adults and adolescents (>12 years of age), compared to 41% (11/27) in the placebo patients. An open label assessment of Alinia[®] suspension in the same study concludes that the efficacy of the suspension formulation was 87% (27/31); while numerically lower than observed for the tablet formulation, the response was at least twice the response observed for the tablet placebo. Likewise eradication of *C. parvum* was superior to placebo and similar between the tablet and the suspension formulation. A threshold for noninferiority was not prespecified for the analyses of efficacy for the suspension formulation, nor were adjustments for multiple comparisons planned for these secondary analyses. The robust difference in efficacy between the tablet and placebo in adults with *C. parvum* diarrhea has previously been demonstrated in the supportive study reviewed in 2002, whereas the response rate for the suspension formulation, while similarly robust compared to placebo, is supported by evidence of efficacy in malnourished pediatric patients. The following table 3 depicts the findings for the current study in comparison to the findings in the supportive study previously reviewed by Dr. Johann-Liang in NDA 21-497.

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Table 3 Summary of efficacy of Alinia® tablets in treatment of *Cryptosporidium parvum* in non HIV infected adults.

NDA	Study Setting and Population Characteristics	Evidence of Efficacy in Adult non-HIV infected Patients	P value	Kappa statistic
NDA 21-497 (tablets in adults) reviewed previously	Adults (Benha, Egypt RM 98-002) screened 800 to get 200 patients mean age 35.5y M, 34.9 F Weight 70kg M 73.5kg F stool frequency 5-10 – 50/50 stool consistency liquid 11/50 semisolid 39/50 mean duration 9M, 10 F	ITT CLINICAL ^a Alinia® 15/21 (71%) Placebo 9/21 (43%)	0.118	Alinia® - 0.31 Placebo 0.06
		ITT PARASITOLOGICAL ^a Alinia® 12/21 (57%) Placebo 6/21 (29%)	0.118	
NDA 21-818 (tablets in adults) NDA 21-498/S-003 (suspension in adults) current submission	Adults (Alexandria & Benha, Egypt RM 01-3010) screened >3000 to get 90 mean age 30.87 race : all Caucasian mean weight 65 kg stool frequency 3-4 44/86 (51%) 5-10 39/86 (45%) >10 3/86 (3.5%) 59/86 had non diarrheal enteric symptoms mean duration 10.9 days better parasitological techniques	TABLET: ITT CLINICAL Alinia® 28/29 (97%) Placebo 14/30 (47%)	<0.001	Alinia® tablet 0.65 Alinia susp 0.84 Placebo 0.61 Alexandria 0.21 Benha 0.28 All 0.78
		TABLET: MITT CLINICAL Alinia® 27/28 (96%) Placebo 11/27 (41%)	<0.001	
		TABLET: ITT PARASITOLOGICAL Alinia® 26/29 (90%) Placebo 13/30 (43%)	0.003	
		TABLET: MITT PARASITOLOGICAL Alinia® 26/28 (93%) Placebo 10/27 (37%)	<0.001	
		suspension: ITT CLINICAL Alinia® 27/31 (87%) Placebo 14/30 (47%)	0.001	
		suspension: MITT CLINICAL Alinia® 27/31 (87%) ^b Placebo 11/27 (41%)	0.003	
		Suspension: ITT PARASITOLOGICAL Alinia® 28/31 (90%) Placebo 13/30 (43%)	<.001	
		Suspension: MITT PARASITOLOGICAL Alinia® 28/31 (90%) ^c Placebo 10/27 (37%)	<.001	

a= based on patients for whom *C. parvum* was the sole pathogen

b=95% CI of difference between suspension and TABLET =0.09 (- 0.095, 0.275)

c=95% CI of difference between suspension and TABLET = 0.025 (- 0.167, 0.207)

To understand how the populations studied in Egypt approximates the US population to whom the efficacy benefit is to be extrapolated, Dr. Meyer requested that the applicant characterize the study design and methodology, and patient demographics in the adult studies of nitazoxanide. In the current submission, over 3000 patients with diarrhea were screened to find the 90 patients enrolled in this study.

Previous studies submitted by the applicant indicate that some patients with positive stool findings can be asymptomatic (Study 98-002), or conversely, that symptoms can persist despite reduction in oocyst burden.

Following is the applicant's summary of the differences between the two studies in non-HIV infected adults. Missing from the applicant's table is the inclusion criteria for Study 98-002 that states that patients should have >4 stools per day. The corresponding inclusion criterion for Study 3010 is that patients should have at least 3 stools per day.

Comparison of Clinical Trials RM-NTZ-98-002 and RM01-3010

	RM01-3010	RM-NTZ-98-002	Improvements (3010 over 98-002)
Study Design	<ul style="list-style-type: none"> • Double-blind, placebo-controlled • Third arm treated with suspension • Multi-center 	<ul style="list-style-type: none"> • Double-blind, placebo-controlled • Single center 	<ul style="list-style-type: none"> • Addition of suspension arm • Two study centers instead of single center.
Population	<ul style="list-style-type: none"> • Non-immunodeficient patients age \geq 12 years with diarrhea and <i>Cryptosporidium</i> as sole pathogen identified in stool at baseline. 	<ul style="list-style-type: none"> • Non-immunodeficient patients age \geq 12 years with diarrhea and <i>Cryptosporidium</i> in stool at screening. 	<ul style="list-style-type: none"> • Patients with other protozoal causes of diarrhea (<i>Giardia</i>, <i>Entamoeba</i>) at screening were excluded from the 3010 study. • Baseline stool sample was collected for 3010 study, and patients with no <i>Cryptosporidium</i> oocysts at baseline or with other causes of diarrhea at baseline were excluded from efficacy analyses.
Endpoints	<ul style="list-style-type: none"> • Clinical response (resolution of symptoms at day 7) • Parasitological response (no oocysts in either of 2 stool samples collected between days 7 and 10) 	<ul style="list-style-type: none"> • Clinical response (resolution of symptoms at day 7) • Parasitological response (no oocysts in either of 2 stool samples collected between days 7 and 10) 	<ul style="list-style-type: none"> • No differences
Study Procedures	<ul style="list-style-type: none"> • Screening within 7 days of enrollment • Baseline stool sample collected • Evaluate clinical response on day 7 • 2 post-treatment stool samples collected between days 7 and 10 • Follow-up evaluation on day 14 	<ul style="list-style-type: none"> • Screening within 7 days of enrollment • Evaluate clinical response on day 7 • 2 post-treatment stool samples collected between days 7 and 10 	<ul style="list-style-type: none"> • Collected baseline stool sample to confirm diagnosis and exclude other causes of diarrhea • Added day 14 follow-up examination.
Microbiology	<ul style="list-style-type: none"> • <i>Cryptosporidium</i> identified by MZN stain and confirmed by IFA. 	<ul style="list-style-type: none"> • <i>Cryptosporidium</i> identified by MZN stain. 	<ul style="list-style-type: none"> • Improved procedures for 3010 study: diagnosis confirmed by IFA.
Patient Demographics	<ul style="list-style-type: none"> • Gender: 40 M/46 F • Age: mean 51, range 12-67 • Weight: mean 65, range 25-109 • Duration of diarrhea: mean 11 days, range 4-100 	<ul style="list-style-type: none"> • Gender: 27M/23 F • Age: mean 35, range 15-62 • Weight: mean 72, range 35-104 • Duration of diarrhea: mean 15 days, range 5-90 	<ul style="list-style-type: none"> • No significant differences
Protocol Deviations	<ul style="list-style-type: none"> • 1 patient enrolled with no symptoms at baseline (excluded from efficacy analysis due to no oocysts in baseline stool sample) 	<ul style="list-style-type: none"> • 16 patients enrolled based on screening >7 days before enrollment (range 8-19 days) • 4 patients late for day 7 exam • 9 patients late for second follow-up stool collection 	<ul style="list-style-type: none"> • Recruitment procedures and patient attendance at study visits was significantly improved due to investigator experience, addition of study coordinator and better monitoring.

A close look at the baseline patient characteristics in the current study (Table 4) indicates that 35 patients were from Alexandria, and 51 from Benha, they were evenly divided between the 2 genders, had a mean age of 30.9 years and had a mean weight of 65 kg.

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Mean stool frequency was 3-4 per day for 51%, 5-10 per day for 45% and >10 per day for 3.5% of the studied population. The majority (67%, 59/86) had abdominal pain and cramping and a few had fever and other systemic symptoms. By comparison, the patients studied in 98-002 were all enrolled from the site in Benha, were on average about 10 kg heavier, and had 5-10 stools a day. Given the improved case finding afforded by the more rigorous parasitological methods employed in this current submission (Study 3010), the applicant succeeded in proving that the trend in efficacy noted in the earlier submission (Study 98-002) was confirmed with a statistically significant result in this submission/study.

The applicant performed kappa statistic analyses for each of the studies submitted to the nitazoxanide submissions. The FDA kappa statistic analyses are summarized below. Note that the placebo kappa was not constant from study to study in the various submissions, and is most robust for the population submitted in 3010. Similarly the treatment arm kappa varied: -0.33 (Alinia suspension, Study 98002) to 0.84 (Alinia suspension, Study 3010).

Table 4. Correlation of clinical and microbiologic findings in *Cryptosporidium* studies (FDA analysis)^a.

Study	Population	Treatment	N	Kappa statistic (+SD or 95% CI)	Overall kappa
98002	Adults (Egypt)	Tablet Placebo	21	0.06 (0.18)	
		Alinia [®] tablets	21	- 0.31 (0.16)	
	Pediatric (1-11)	Alinia suspension	24	- 0.33 (0.22)	
3007	Pediatric (<4)	Suspension Placebo	22	0.12 (0.20)	
		Alinia [®] suspension	25	0.10 (0.23)	
3008	HIV Pediatric (1-11)	Tablet Placebo	25	0.31	
		Alinia [®] suspension	25	0.25	
3007+98002	Non HIV Pediatric	Placebo ^b	46	0.22	
		Alinia [®] suspension	39	0.18	
3010	Non-HIV Adults	Tablet Placebo	29	0.61 (0.31, 0.92)	+0.78 (0.63, 0.94)
		Alinia [®] tablets	30	0.65 (0.02, 1.00)	
		Alinia [®] suspension	31	0.84 (0.53, 1.00)	

^a From Dr. Zalkikar and Dr. Davi's statistical reviews

^b Tablet (98002) and suspension (3007) placebo

Discussion:

The spectrum of infections in various populations may vary significantly from milder asymptomatic disease in "healthy" patients to debilitating and fatal infections, as occurred in the pediatric HIV-infected patients. As seen in the studies submitted in these applications, Alinia[®] may be effective for some of these patients, depending on the degree of relative immunosuppression by shortening the duration of diarrhea, and increasing the percentage of patients who achieve "wellness" by 7-10 days after start of treatment. Patients with mild self-limiting infection who would resolve their disease within a few days, or patients with intractable diarrhea and immunosuppression may represent two extremes of patients who do not need, or do not respond to therapy, respectively, to the same degree as those evaluated in these studies.

The natural history of the *Cryptosporidium* infection in non HIV infected patients in US is probably best described in the Milwaukee outbreak. The median duration of illness in

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these patients was 9 days (range 1-55 days), with a median maximum of 12 stools per day. The mean age of patients was 41 years (range 2 months to 93 years). Infection resulted in a mean 10 lb weight loss; 41% were hospitalized for a median of 5 days (range, 1-55). Recurrences occurred in 39% of patients. Nonetheless, this description of cryptosporidial diarrhea in an outbreak setting was based on the presentation of the sickest group of 285 patients with diarrheal disease evaluated by a physician and for whom stool examinations were requested. This sample represented a small minority of the 403,000 symptomatic individuals among those served by the water plant (MacKenzie WR *et al.* A massive outbreak in Milwaukee of cryptosporidium infection transmitted through the public water supply, N Engl J Med 1994 333(3):161-7). The infection in the broader population was not well described but assumed to range from asymptomatic infection, to illness characterized by a brief diarrheal episode, as seen in human volunteer studies.

To ascertain that the findings of efficacy in this NDA are relevant to an analogous US population, the Division requested that the applicant provide an analysis on how the placebo rate in the population studied in Egypt correlates to the natural history of *Cryptosporidium* in normal hosts in the United States. The applicant makes the following points and draws the following conclusions regarding the applicability of the efficacy findings for Alinia® from an *Cryptosporidium*-endemic area to that of an outbreak setting in areas of low prevalence:

1. "The anticipated spontaneous resolution rate in normal adults who are infected in an outbreak setting in the United States is near 100%.¹⁻⁴ ...it would be unusual for an immunocompetent adult, without other underlying complications, to die from cryptosporidiosis. Likewise, none of the patients enrolled in the pivotal study were in danger of death. While the patients were not followed-up beyond the end of the study, our expectation is that the patients' symptoms were eventually self-limiting.
2. The median duration of diarrhea ... in the United States has been reported to be approximately 9 days.^{1,4} The population enrolled in our pivotal study had a median duration of diarrhea at baseline of 9 days. Therefore, we would expect that approximately 50% of patients with symptomatic cryptosporidiosis in the United States (those with diarrhea >9 days) would be analogous to the Egyptian population in terms of duration of symptoms and burden of infection.
3. Patients enrolled in the placebo arm of the pivotal study had a median duration of diarrhea at baseline of 9 days (range: 6-12 days). 40.7% of the patients in the placebo group (11/27) responded by study day 7, indicating a total duration of illness between 9 and 16 days. One of 8 clinical failures at day 7 who were followed-up at study day 14 resolved symptoms before day 14, but the other 7 were still symptomatic at study day 14 (approximately 23 days after initiation of symptoms). In an outbreak setting in the United States, the duration of symptomatic cryptosporidiosis is commonly reported to be up to 4 to 8 weeks.^{1,2,4} Studies in healthy volunteers in the United States showed diarrheal illness of 6 hours to 9 days ... approximately 50% of the volunteers experiencing one to five recurrences of symptoms after initial resolution of diarrhea.^{5,7,8} the duration of

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illness reported for a limited number of healthy volunteers inoculated with *Cryptosporidium* oocysts is somewhat shorter than that reported for patients with naturally acquired infection.

4. 25.9% of the patients randomized to the placebo group in the pivotal trial were free of oocysts in each of three post-treatment stool samples. This suggests, consistent with published data from outbreak settings in the United States, that oocyst shedding is self-limiting but often extends for some time beyond the resolution of symptoms (total of 2 to 8 weeks).^{2,3} (references not included in this review)

The applicant concludes that the population studied in the pivotal study would be analogous to patients in the United States who seek medical attention, are diagnosed with cryptosporidiosis and remain ill at the time that the diagnosis is made, and demonstrated that Alinia® increases the rate of resolution of diarrhea, compared to placebo by day 7-10 after treatment.

There are remaining questions regarding some of the clinical and parasitological effects of Alinia® because the protocols and case report forms did not provide for the collection of these data. Therefore, the applicant was unable to provide additional analyses requested by the Division in prior communication with the applicant. These include:

- a) Data on the time to symptoms resolution (as done in pediatric study 98-002 where time to last unformed stool was 3.5 days on Alinia® vs >6 days with placebo).
- b) Food effect between the tablet and suspension formulations. The suspension formulation is not bioequivalent to the tablet, and when taken with food results in lower levels of active metabolites than the tablet formulation. However, because it is uncertain whether luminal or systemic levels are more important for treatment effect, and because of the range of outcomes observed in the pediatric trials of the suspension formulation, it may be difficult to address this question without further clinical data. However, it is reassuring to note that both tablet and suspension formulations, when administered with food, have demonstrated superior efficacy to placebo.
- c) Quantitation of oocysts over time (parasite clearance times) The correlation between clinical and parasitological outcome was variable and low in some studies. Whether this represents a real finding, or may be due to frequency of sampling and/or quantitation over time is unclear.

Conclusions:

This NDA/efficacy supplement provides data demonstrating that Alinia® tablets and Alinia® suspension is clinically and statistically superior to placebo in resolution of diarrhea (“wellness”) in a population of symptomatic patients, and demonstrates a correlation between symptom resolution and parasitologic clearance. These results are supported by data from a previously reviewed study 98-002 which showed a difference in outcome but was underpowered to show statistical significance. While the applicant concludes that the efficacy of Alinia® in adults may not translate into a mortality benefit,

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pediatric patient study 3007 did show a difference in mortality in malnourished children and provides strong support that Alinia® has activity in this disease.

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Labeling:

The labeling has been updated to reflect the approval of the indication for the treatment of diarrhea caused by *Cryptosporidium parvum*. The applicant's December 2004 proposed labeling was modified from the current approved labeling as follows:

1. Under Table 2: Mean plasma pharmacokinetic parameter values following administration of a single dose of Alinia for Oral Suspension with food in the **CLINICAL PHARMACOLOGY** section, the data for the age group '>18 years' were added.
2. Both the **INDICATIONS AND USAGE** section and the **DOSAGE & ADMINISTRATION** section were simplified by combining the subsections **Diarrhea caused by *Giardia lamblia*** and **Diarrhea caused by *Cryptosporidium parvum*** into one: **Diarrhea caused by *Giardia lamblia* or *Cryptosporidium parvum***.
3. The **ADVERSE REACTIONS** section was updated to include data from this study.
4. The subsection **Diarrhea caused by *Cryptosporidium parvum* in adults and adolescents 12 years of age or older** was added to the **CLINICAL STUDIES** section and includes a synopsis of the adult studies in non HIV infected adults to show that (1) the findings of efficacy in non HIV infected patients have been replicated and not due to chance alone and (2) efficacy varies (71% to 96%) based on the population and formulation tested, even in non-HIV infected patients.

Renata Albrecht , M.D.
Division Director

Eileen Navarro, M.D.
Medical Team Leader

Cc: NDA 21-818, 21-498 file
Miller K project manager
Nitazoxanide Review team

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APPENDIX A. Summary of efficacy of Alinia® tablets and suspension in the treatment of *C. parvum* diarrhea in NDA submissions

NDA	Indication	ACTION	Population	Outcome	Difference	
NDA 20-871 tablets	<i>C. parvum</i> HIV adults and peds	NOT APPROVABLE 12-26-97	HIV-infected patients with AIDS			
NDA 21-497 05-29-2002 tablets	<i>C. parvum</i> Non-HIV adults	APPROVABLE 11-22-02	1 DB, placebo controlled in healthy adults (n=50) and peds (RM 98002) Egypt limitations: CLINICAL: not all symptomatic	Efficacy in adults (RM 98002) CLINICAL Alinia® 15/21 (71%) Placebo 9/21 (43%) PARASITOLOGICAL Alinia® 12/21 (57%) Placebo 6/21 (29%)	P=0.118 P=0.118	
NDA 21-498 05-29-2002 suspension	<i>C. parvum</i> Non-HIV peds	APPROVAL for peds in non-HIV patients 11-22-02	Alinia 44/50 Placebo 39/49 PARASITOLOGIC AFB confirmed by IF in 9/50 No correlation with clinical	Efficacy in Peds (RM 98002) CLINICAL Alinia® 21/24 (88%) Placebo 9/24 (38%) PARASITOLOGICAL Alinia® 18/24 (75%) Placebo 6/25(24%)	P=0.001 P=0.001	
		Labeling includes results of HIV patient study showing lack of efficacy	Malnourished peds (Zambia) 02-3007)	CLINICAL Alinia® 14/25 (56%) Placebo 5/22 (23%) PARASITOLOGICAL Alinia® 13/25 (52%) Placebo 3/22 (14%)	P=0.037 P=0.007	
	<i>C. parvum</i> HIV peds	APPROVABLE 7-21-04	Data resubmitted from RM 98-002 and Request that <i>Giardia</i> study in adults and peds studies in <i>Cryptosporidium</i> support approval	HIV peds (Zambia) 02-3008)	CLINICAL Alinia® 2/25 (8%) Placebo 6/24 (25%) PARASITOLOGICAL Alinia® 4/25 (16%) Placebo 5/25 (20%)	P=0.037 P=1.0
					Efficacy in adults See above (RM 98-002) NOT SUBMITTED	
NDA 21-497/ 21-818 tablets 1-28-04	<i>C. parvum</i> Non-HIV adults	APPROVABLE 6-16-05	1 db placebo controlled study RM01-3010 THIS APPLICATION	CLINICAL Alinia® tablets 27/28 (96%) Placebo 11/27 (41%) PARASITOLOGICAL Alinia® tablets 26/28 (93%) Placebo 10/27 (37%) CLINICAL Alinia® suspension 27/31 (87%) Alinia® tablets 27/28 (96%) PARASITOLOGICAL Alinia® suspension 28/31 (90%) Alinia® tablets 26/28 (93%)	P<0.001 P<0.001 $\Delta = 0.09 (-0.095, 0.275)$ $\Delta = 0.025 (-0.167, 0.207)$	

ND. -818, nitazoxanide tablets
NDA 21-498/S-003 nitazoxanide for oral suspension
Treatment of *Cryptosporidium parvum* diarrhea in non-HIV infected adolescents and adults

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MEDICAL OFFICER

CLINICAL REVIEW

Application Type	NDA
Submission Number	21-818 and 21-498
Submission Code	AZ (21-818) and S-003 (21-498)
Letter Date	December 17, 2004
Stamp Date	December 20, 2004
PDUFA Goal Date	June 20, 2005
Reviewer Name	Joette M. Meyer, Pharm.D.
Review Completion Date	June 14, 2005
Established Name	Nitazoxanide
(Proposed) Trade Name	Alinia®
Therapeutic Class	Nitrothiazolyl salicylamide
Applicant	Romark Laboratories, L.C.
Priority Designation	S
Formulation	500 mg Tablets 100 mg/5 mL Oral Suspension
Dosing Regimen	500 mg BID x 3 days
Indication	Treatment of diarrhea caused by <i>Cryptosporidium parvum</i>
Intended Population	HIV-uninfected adults and adolescents 12 years of age and older

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1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

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* in HIV-uninfected children 1 through 11 years of age. The tablet formulation of nitazoxanide (NDA 21-497) was given an “Approvable” action on the same date for the treatment of diarrhea caused by *Cryptosporidium parvum* in HIV-uninfected adults and adolescents 12 years of age and older.

NDA 21-497 included results of Study RM-NTZ-98-002 a randomized, double-blind, placebo controlled study of adult and adolescents 12 years of age and older with diarrhea caused by *Cryptosporidium parvum* in Egypt. Pediatric patients 1 to 11 years of age were also included in this study and reviewed separately. Nitazoxanide tablets (500 mg twice daily with food for 3 days) were compared to placebo tablets. Patients were included in Study RM-NTZ-98-002 if they had cryptosporidial diarrhea, as defined by > 4 stools per day and presence of oocysts at baseline. Not all patients had enteric symptoms in addition to the diarrhea at baseline. The two primary endpoints of the study were clinical response (well, continuing illness or clinical treatment failure) on Day 7 (± 2) and parasitological response (eradication or persistence) based on examination of two stool samples collected between Days 7-10 (± 2). At Day 7 (± 2), nitazoxanide tablets in adults and adolescents with *Cryptosporidium parvum* as the sole pathogen showed a clinical response rate of 71.4% (15/21) compared to 42.9% (9/21) of patients who received placebo ($p=0.118$). Parasitological response was seen in 57.1% (12/21) adult and adolescent patients treated with nitazoxanide tablets compared to 28.6% (6/21) of placebo-treated patients ($p=0.118$).

In the current submission, Romark Laboratories, LC has provided results from Study RM01-3010. The protocol for this study was written by the applicant, with input from the Division, to satisfy the deficiencies noted in the Approvable letter of 2002.

Study RM01-3010 was also a randomized, double-blind, placebo controlled trial of adult and adolescents 12 years of age and older with diarrhea caused by *Cryptosporidium parvum* in Egypt. Patients were included in the study if they had cryptosporidial diarrhea, as defined by ≥ 3 stools per day with enteric symptoms and oocysts. Nitazoxanide tablets (500 mg twice daily with food for 3 days) were compared to placebo tablets. A third arm consisting of open-label treatment with nitazoxanide oral suspension (500 mg/25 mL) was also included. Clinical response, the primary endpoint, was evaluated 4 to 7 days following the end of treatment (Day 7-10). Parasitological response, a secondary endpoint, was also evaluated at the Day 7-10 visit with collection of two stool samples at least 24 hours apart. All patients returned between Days 14 and 17 and submitted one stool sample for examination for *Cryptosporidium* oocysts or trophozoites. Clinical data at the Day 14-17 visit were also collected from patients enrolled during the second half of the study.

Clinical responses recorded at the Day 7-10 visit for the nitazoxanide tablets, nitazoxanide suspension, and the placebo tablets are summarized in Table 1. The proportion of “well” clinical responses in the nitazoxanide tablet group (96%; 27/28) was significantly higher than in the placebo treatment group (41%; 11/27) ($p < 0.0001$). Therefore, the clinical response rate (primary endpoint of the study) with nitazoxanide tablets was superior to placebo. The proportion of “well” clinical responses in the nitazoxanide suspension group (87%; 27/31) was also non-inferior to placebo ($p = 0.0003$). The study was not designed to compare nitazoxanide tablets and suspension in a formal non-inferiority analysis.

The proportion of patients with a parasitological response (eradicated) in the nitazoxanide tablet group (93%; 26/28) was significantly higher than in the placebo treatment group (37%; 10/27) ($p < 0.001$). The number of patients with a parasitological response in the nitazoxanide suspension group (90%; 28/31) was also significantly higher than in the placebo group ($p < 0.0001$). The study was not designed to compare nitazoxanide tablets and suspension in a formal non-inferiority analysis.

The results of stool examinations at Day 14-17 were negative in all clinical responders (as assessed at Day 7-10) in the nitazoxanide tablet group (27/27), 96% (26/27) in the nitazoxanide suspension group, and 82% (9/11) in the placebo group.

Stool examinations were also performed at Day 14-17 for patients who were clinical failures (as assessed at Day 7-10). The one clinical failure in the nitazoxanide table group had a positive stool sample. All 3 clinical failures in the nitazoxanide suspension group had negative stools. In the placebo group, 53% (8-15) had negative stools and 47% (7-15) had a positive result.

During the study the protocol was amended to include a physical examination on Day 14-17. Data are available for 44 patients. A “well” clinical response was recorded for 100% (12/12) patients in the nitazoxanide tablet group, 88% (15/17) in the nitazoxanide suspension group, and 36% (4/11) in the placebo group.

In summary, in Study RM01-3010, 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) and response was maintained in most patients at the follow-up visit (Day 14-17). Study RM01-3010 was not designed to compare nitazoxanide tablets and suspension in a formal non-inferiority analysis. In Study RM-NTZ-98-002, clinical and parasitological response rates with nitazoxanide tablets at Day 7 (± 2), while not statistically significantly better than placebo, showed a favorable trend. The results obtained in Study RM-NTZ-98-002 were considered supportive of the efficacy of nitazoxanide tablets seen in Study RM01-3010. The efficacy of nitazoxanide suspension in adults and adolescents was not tested in Study RM-NTZ-98-002, but supportive data can be found in the studies which supported the approval of nitazoxanide suspension in the treatment of diarrhea caused by *Cryptosporidium parvum* in HIV-uninfected children 1 to 11 years of age (original NDA 21-497 approved in 2002).

Safety data are available from 1657 HIV-uninfected patients 12 years of age and older treated with various dosage regimens of nitazoxanide tablets for bacterial and parasitic infections. The

most common adverse events were gastrointestinal in nature and mild in severity. The most common events were: abdominal pain (6.6%), diarrhea (4.2%), headache (3.1%), and nausea (3.0%). Adverse events seen in 85 HIV-uninfected patients 12 years of age and older treated with nitazoxanide oral suspension were similar to those observed with nitazoxanide tablets.

In summary, nitazoxanide (Alinia®) tablets and oral suspension are safe and effective for the treatment of diarrhea caused by *Cryptosporidium parvum* in adults and adolescent patients 12 years of age and older. Safety and effectiveness of Alinia® tablets and oral suspension have not been established in HIV-infected patients or those with immunodeficiency.

1.2 Recommendation on Postmarketing Actions

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

1.2.1 Risk Management Activity

None.

1.2.2 Required Phase 4 Commitments

None.

1.2.3 Other Phase 4 Requests

None.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

Two clinical studies were conducted in adults and adolescents 12 years of age and older. The first study (RM-NTZ-98-002) was submitted and reviewed as part of the original NDA 21-498 submission. Study RM01-3010 was designed by the applicant with input from the Division in response to the deficiencies noted in the Approvable letter for NDA 21-497 and the results were submitted in the current NDA submission.

Clinical Reviewer's Comment: For the complete description and results of Study RM-NTZ-98-002, see the Medical Officer's Review by Dr. Rosemary Johann-Liang (Medical Officer) filed with the original NDA 21-498 (dated May 25, 2002).

Both studies were randomized, double-blind, placebo controlled and conducted in Egypt. Study RM-98-002 was conducted at a single center in Behna, Egypt and Study RM01-3010 was

conducted at the Benha site and also in Alexandria, Egypt. Nitazoxanide tablets (500 mg twice daily with food for 3 days) were compared to placebo tablets. Study RM01-3010 also included an open-label treatment arm of nitazoxanide oral suspension (500 mg/25 mL).

Patients were included in Study RM-NTZ-98-002 if they had cryptosporidial diarrhea, as defined by > 4 stools per day and presence of oocysts in the stool at screening. Not all patients had enteric symptoms in addition to the diarrhea at baseline. The two primary endpoints of the study were clinical response (well, continuing illness or clinical treatment failure) on Day 7 (\pm 2) and parasitological response (eradication or persistence) based on examination of two stool samples collected between Days 7-10 (\pm 2). Parasitological evaluation was limited to microscopic examination of a small amount of unconcentrated stool sample after staining with Ziehl-Neelsen's stain. Quantitation of oocysts was not done uniformly for all patients. Immunofluorescence was not routinely used.

Patients were included in Study RM01-3010 if they had cryptosporidial diarrhea, as defined by \geq 3 stools per day with enteric symptoms and oocysts in the stool at baseline. Clinical response, the primary endpoint, was evaluated 4 to 7 days following the end of treatment (Day 7-10). Parasitological response, a secondary endpoint, was also evaluated at the Day 7-10 visit with collection of two stool samples at least 24 hours apart. 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 ("Persistence") for oocysts of *Cryptosporidium* if any of these tests were positive.

The definition of clinical response was the same in both studies: 'well' was defined as 'no symptoms, no watery stools and no more than 2 soft stools with no hematochezia within the past 24 hours' or 'no symptoms and no unformed stools within the past 48 hours.'

Study RM-NTZ-98-002 did not include a late follow-up visit. In Study RM01-3010, all patients returned between Days 14 and 17 and submitted one stool sample for examination for *Cryptosporidium* oocysts or trophozoites. Clinical data at the Day 14-17 visit were also collected from patients enrolled during the second half of the study.

Evaluable patients in both studies included those with *Cryptosporidium* oocysts in their stool. In Study RM-NTZ-98-002 patients with bacterial causes of diarrhea were excluded from the analysis of clinical response. However, patients with other intestinal parasitic infections were not excluded from the study. Study RM01-3010 excluded patients with other identified causes of diarrhea at baseline, including other parasites (e.g., pathogenic bacteria, *Giardia lamblia*, and *E. histolytica*).

The demographics of patients enrolled in both studies were similar. In Study RM-NTZ-98-002 there were 27 males and 23 females enrolled; mean age of 35 years (range 15 to 62 years); mean weight of 72 kg (range 35 to 104 kg); mean duration of diarrhea prior to study enrollment of 15 days (range 5 to 90 days). In Study RM01-3010 there were 40 males and 46 females; mean age

of 31 years (range 12-67); mean weight of 65 kg (range 25 to 109 kg); mean duration of diarrhea prior to study enrollment of 11 days (range 4-100 days). Efficacy

1.3.1.1 Study RM-NTZ-98-002

According to the applicant's analysis, adult and adolescent patients at Day 7 (± 2) showed a clinical response rate of 72% (18/25) in the nitazoxanide tablet group compared to 44% (11/25) in the placebo group ($p=0.0423$). The parasitological response rate was 60% (15/25) in the nitazoxanide-treated patients and 24% (6/25) in the patients who received placebo ($p=0.0104$). There was a lack of correlation between clinical and parasitological response rates, as evidence by low kappa values.

Mixed pathogens were isolated at baseline in 8 of the adult patients (4 in each treatment arm). When these 8 patients were removed from the analysis by the FDA Reviewers, the clinical response rate was 71.4% (15/21) for nitazoxanide tablets and 42.9% (9/21) for placebo ($p=0.118$). Parasitological response was seen in 57.1% (12/21) patients treated with nitazoxanide tablets compared to 28.6% (6/21) of placebo-treated patients ($p=0.118$).

The results obtained in Study RM-NTZ-98-002 are considered supportive of the efficacy of nitazoxanide tablets seen in Study RM01-3010 (discussed below). The efficacy of nitazoxanide suspension in adults and adolescents was not tested in Study RM-NTZ-98-002.

1.3.1.2 Study RM01-3010

Clinical responses recorded at the Day 7-10 visit for the nitazoxanide tablets, nitazoxanide suspension, and the placebo tablets are summarized in Table 1. The proportion of "well" clinical responses in the nitazoxanide tablet group (96%; 27/28) was significantly higher than in the placebo treatment group (41%; 11/27) ($p < 0.0001$). Therefore, the clinical response rate (primary endpoint of the study) with nitazoxanide tablets was superior to placebo. The proportion of "well" clinical responses in the nitazoxanide suspension (87%; 27/31) was also non-inferior to placebo ($p = 0.0003$). The study was not designed to compare nitazoxanide tablets and suspension in a formal non-inferiority analysis.

The proportion of patients with a parasitological response (eradicated) in the nitazoxanide tablet group (93%; 26/28) was significantly higher than in the placebo treatment group (37%; 10/27) ($p < 0.001$). Patients with a parasitological response in the nitazoxanide suspension group (90%; 28/31) were also significantly higher than in the placebo group ($p < 0.0001$). The study was not designed to compare nitazoxanide tablets and suspension in a formal non-inferiority analysis.

The results of stool examinations at Day 14-17 were negative in all clinical responders (as assessed at Day 7-10) in the nitazoxanide tablet group (27/27), 96% (26/27) in the nitazoxanide suspension group, and 82% (9/11) in the placebo group.

Stool examinations were also performed at Day 14-17 for patients who were clinical failures (as assessed at Day 7-10). The one clinical failure in the nitazoxanide table group had a positive

stool sample. All 3 clinical failures in the nitazoxanide suspension group had negative stools. In the placebo group, 53% (8-15) had negative stools and 47% (7-15) had a positive result.

During the study the protocol was amended to include a physical examination on Day 14-17. Data are available for 44 patients. A “well” clinical response was recorded for 100% (12/12) patients in the nitazoxanide tablet group, 88% (15/17) in the nitazoxanide suspension group, and 36% (4/11) in the placebo group.

In summary, 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 addition, clinical and parasitological response in most patients was maintained at the follow-up visit (Day 14-17). The study was not designed to compare nitazoxanide tablets and suspension in a formal non-inferiority analysis.

1.3.2 Safety

In 1657 HIV-uninfected patients 12 years of age and older treated with various dosage regimens of nitazoxanide tablets for bacterial and parasitic infections, the most common adverse events were gastrointestinal in nature and mild in severity. The most common events were abdominal pain (6.6%), diarrhea (4.2%), headache (3.1%), and nausea (3.0%). Adverse events seen in 85 HIV-uninfected patients 12 years of age and older treated with nitazoxanide oral suspension were similar to those observed with nitazoxanide tablets.

1.3.3 Dosing Regimen and Administration

The proposed dosing regimen in adolescent and adult patients aged 12 years and older with diarrhea caused by *Cryptosporidium parvum* is one tablet (500 mg nitazoxanide) or 25 mL of oral 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 oral suspension when administered with food in adolescent and adult patients, although the two formulations are not bioequivalent.

1.3.4 Drug-Drug Interactions

No new information was included in this submission. See the current package insert for information on drug-drug interactions.

1.3.5 Special Populations

Nitazoxanide oral suspension was approved for the treatment of *Cryptosporidium parvum* in HIV-uninfected children from 1 to 11 years of age on November 22, 2002 (NDA 21-497). In the current submission, nitazoxanide tablets were studied in adults and adolescents aged 12 years and older.

Clinical Reviewer's Comment: Based on data obtained from patients 1 to 11 years of age treated with nitazoxanide oral 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 RM01-3010 there were only 3 patients aged 65 and over; therefore, it is not possible to determine whether or not they respond differently from younger patients. 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.

Clinical Reviewer's Comment: People at the extremes of age (i.e., elderly and young children) are more likely than average adults to become symptomatic following exposure to oocysts of Cryptosporidium, due to compromised immunity. Studies RM-NTZ-98-002 and RM01-3010 both demonstrated the efficacy of nitazoxanide in patients (some of whom were children) living in a developing country with relatively poor nutritional status, which may have led to immunodeficiency. Therefore, although the efficacy of nitazoxanide has not been established in geriatric patients in the US, these patients may derive the greatest benefit from treatment with nitazoxanide.

1.3.5.1 Efficacy in Special Populations

Differences, if any, seen in the clinical or parasitological eradication rates in Study RM01-3010 between the following patient groups are not considered clinically meaningful: adolescents (12 to < 18 years) and adults (\geq 18 years); males and females. No adjustments to the adult dosing of nitazoxanide tablets or oral suspension in adolescents are warranted based on age or sex. All patients in Study RM01-3010 were of Caucasian race, so analysis of the effect of race on efficacy was not performed.

1.3.5.2 Safety in Special Populations

Differences, if any, in adverse events seen in adolescents (12 to < 18 years) and adults (\geq 18 years); males and females; Caucasians, Hispanics, and Blacks were not considered clinically meaningful. Safety data from 1657 HIV-uninfected patients 12 years of age and older treated with nitazoxanide tablets and 85 patients treated with nitazoxanide oral suspension were used for this evaluation. Reporting of adverse events by age, sex, or race is not warranted in the labeling of nitazoxanide tablets and oral suspension.

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

Established Name	Nitazoxanide
(Proposed) Trade Name	Alinia®
Therapeutic Class	Nitrothiazolyl salicylamide
Applicant	Romark Laboratories, L.C.
Priority Designation	Resubmission (6 months)
Formulation	Tablet and Oral Suspension
Dosing Regimen	500 mg BID x 3 days
Proposed Indication	Treatment of diarrhea caused by <i>Cryptosporidium parvum</i> in adults and adolescent patients greater than 12 years of age. Safety and effectiveness of Alinia® tablets have not been established in patients with immunodeficiency.
Intended Population	HIV-uninfected adults and adolescents 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 Currently Available Treatment for Indications

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

No other medications are currently approved in adults and adolescents 12 year of age and older, or in patients with immunodeficiency, to treat diarrhea caused by *Cryptosporidium parvum*.

2.3 Availability of Proposed Active Ingredient in the United States

Nitazoxanide (Alinia®) oral suspension has been marketed by Romark Laboratories in the United States since March 2003 for the treatment of diarrhea caused by *Cryptosporidium parvum* and *Giardia lamblia* in HIV-uninfected pediatric patients 1 through 11 years of age. The dosing regimen is 100 mg b.i.d. for 3 days in patients 1 through 3 years of age and 200 mg b.i.d. for 3 days in patients 4 through 11 years of age. Romark has also been marketing nitazoxanide (Alinia®) tablets and oral suspension for the treatment of diarrhea caused by *Giardia lamblia* in adults and adolescents 12 years of age and older since September 2004.

Romark estimates that approximately 5 bottles of the Alinia® oral suspension (60 mL) and 1 Alinia® Tablets have been used by patients in the United States since they were first marketed. No adverse events have been reported.

2.4 Important Issues With Pharmacologically Related Products

2.5 Presubmission Regulatory Activity

Nitazoxanide oral suspension (NDA 21-498) was approved by the FDA on November 22, 2002 for the treatment of diarrhea caused by *Cryptosporidium parvum* in HIV-uninfected 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 re-submission of nitazoxanide tablets for the treatment of Giardia lamblia in adults and adolescents (NDA 21-497) on January 30, 2004. All three commitments were considered fulfilled by the Division. See Clinical Pharmacology and Biopharmaceutics review by Dakshina Chilukuri, Ph.D, filed with the submission.

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

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

On January 28, 2004, Romark submitted a complete response to the November 22, 2002 Approvable letter for the *Cryptosporidium* indication (administrative NDA 21-818). The resubmission included a proposal from Romark to support the approval of nitazoxanide in patients 12 years and older for the treatment of *Cryptosporidium parvum* based on the data described below.

- Safety and efficacy results from *Giardia* studies in adults and adolescents 12 of age and older
- Safety and efficacy results from *Giardia* studies in children 1 to 11 years of age
- A small study in adults with *Cryptosporidium parvum*

Data from an ongoing study (RM01-3010) were not submitted. Study RM01-3010 was designed to satisfy the deficiencies in the November 22, 2002 Approvable letter. The protocol was submitted by the applicant 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 the protocol.

The Division issued an Approvable letter for NDA 21-818 on July 21, 2004 in which the Division rejected the applicant’s proposal based on the available data and determined that the results of Study RM01-3010 were necessary for approval of an indication of *Cryptosporidium parvum* in adults and adolescents. The Division’s rationale is summarized below (abstracted from the Division Director’s memo dated July 21, 2004).

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 was no convincing justification or regulatory precedent for approving an adult indication for one pathogen based on evidence of an adult indication for another pathogen (i.e., *Giardia lamblia* extrapolated to *Cryptosporidium parvum*). 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, was not considered adequate because the dosing is different and the pharmacokinetic properties of the oral suspension and the tablets are different. The results of one study (RM02-3008) in HIV-seropositive patients actually failed to show superiority of nitazoxanide compared to placebo.

Finally, it is unknown whether there are relevant host differences between pediatric and adult patients for this infection. Another study in pediatric and adult HIV-seronegative patients (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.

In the current submission, the applicant has conducted a placebo-controlled study of nitazoxanide tablets and oral suspension in adult and adolescent patients with diarrhea caused by *Cryptosporidium parvum* (Study RM01-3010).

2.6 Other Relevant Background Information

Nitazoxanide is being sold as a treatment of a broad spectrum of intestinal parasitic infections in 7 countries of Latin America. The countries and dates of approval for marketing are presented below:

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 oral 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 1 to 3 years. 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.

Approximately — 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 CMC (and Product Microbiology, if Applicable)

No new chemistry, manufacturing and controls information was included in this submission.

3.2 Animal Pharmacology/Toxicology

No new pharmacology/toxicology information was included in this submission.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

- Report of Study RM01-3010 (paper copy)
- Literature articles provided by the applicant
- Medical Officer's Review of original NDA 21-498 (nitazoxanide oral suspension for the treatment of *Cryptosporidium parvum* in children 1 to 11 years of age) by Rosemary Johann-Liang, M.D. (DFS date January 1, 2003)
- Clinical Review of re-submission of NDA 21-498 (nitazoxanide tablets for *Giardia lamblia* in adults and adolescents) by Joette Meyer, Pharm.D. (DFS date July 21, 2004).
- Electronic datasets for Study RM01-3010: \\Cdsub1\n21818\N_000\2004-12-17\CRT\DATASETS\RM013010
- Integrated Summary of Safety: paper copy, volume 2.2
- Safety datasets (electronic) for 1657 HIV-uninfected patients treated with nitazoxanide for a variety of infections: \\Cdsub1\n21818\N_000\2004-12-17\CRT\DATASETS\ISS

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 *Cryptosporidium parvum*.

TABLE 1
Summary of Clinical Studies of Nitazoxanide Tablets to Treat Diarrhea Caused by
Cryptosporidium parvum

Study	Number of Patients Enrolled	Study Design	Number of Patients Evaluable (MITT)**	Clinical Response (Primary Endpoint)	Parasitological Response (Secondary Endpoint)
RM-NTZ-98-002	50 adults and adolescents ≥ 12 years of age*	Randomized, double-blind: NTZ tablets (500 mg) vs. placebo tablets; Regimen: 500 mg twice daily with food x 3 days	NTZ tablets 21; Placebo tablets 21	71.4% NTZ tablets; 42.9% placebo; p=0.118	57.1% NTZ tablets; 28.6% placebo; p=0.118
RM01-3010	90 adults and adolescents ≥ 12 years of age	Randomized, double-blind: NTZ tablets (500 mg) vs. placebo tablets; open-label NTZ oral suspension (25 mL; 100 mg/5mL) Regimen: 500 mg twice daily with food x 3 days	NTZ tablets 28; NTZ suspension 31; placebo 27	96% NTZ tablets; 87% NTZ suspension; 41% placebo; 95% CI of difference between NTZ tablets and placebo (-9.5%, 27.5%)	93% NTZ tablets; 90% NTZ suspension; 37% placebo 95% CI of difference between NTZ tablets and placebo (-16.7%, 20.7)

* Study RM-NTZ-98-002 also enrolled pediatric patients 1 to 11 years of age; pediatric results are not discussed in this review.

** *Cryptosporidium parvum* as the sole pathogen

Clinical Reviewer's Comment: On June 13, 2005 the Division requested that the applicant compare and contrast the study design, procedures, definition of endpoints of Studies RM-NTZ-98-002 and RM01-3010. The table below was submitted by the applicant on the same day as the Division's request.

Comparison of Clinical Trials RM-NTZ-98-002 and RM01-3010

	RM01-3010	RM-NTZ-98-002	Improvements (3010 over 98-002)
Study Design	<ul style="list-style-type: none"> • Double-blind, placebo-controlled • Third arm treated with suspension • Multi-center 	<ul style="list-style-type: none"> • Double-blind, placebo-controlled • Single center 	<ul style="list-style-type: none"> • Addition of suspension arm • Two study centers instead of single center.
Population	<ul style="list-style-type: none"> • Non-immunodeficient patients age \geq 12 years with diarrhea and <i>Cryptosporidium</i> as sole pathogen identified in stool at baseline. 	<ul style="list-style-type: none"> • Non-immunodeficient patients age \geq 12 years with diarrhea and <i>Cryptosporidium</i> in stool at screening. 	<ul style="list-style-type: none"> • Patients with other protozoal causes of diarrhea (<i>Giardia</i>, <i>Entamoeba</i>) at screening were excluded from the 3010 study. • Baseline stool sample was collected for 3010 study, and patients with no <i>Cryptosporidium</i> oocysts at baseline or with other causes of diarrhea at baseline were excluded from efficacy analyses.
Endpoints	<ul style="list-style-type: none"> • Clinical response (resolution of symptoms at day 7) • Parasitological response (no oocysts in either of 2 stool samples collected between days 7 and 10) 	<ul style="list-style-type: none"> • Clinical response (resolution of symptoms at day 7) • Parasitological response (no oocysts in either of 2 stool samples collected between days 7 and 10) 	<ul style="list-style-type: none"> • No differences
Study Procedures	<ul style="list-style-type: none"> • Screening within 7 days of enrollment • Baseline stool sample collected • Evaluate clinical response on day 7 • 2 post-treatment stool samples collected between days 7 and 10 • Follow-up evaluation on day 14 	<ul style="list-style-type: none"> • Screening within 7 days of enrollment • Evaluate clinical response on day 7 • 2 post-treatment stool samples collected between days 7 and 10 	<ul style="list-style-type: none"> • Collected baseline stool sample to confirm diagnosis and exclude other causes of diarrhea • Added day 14 follow-up examination.
Microbiology	<ul style="list-style-type: none"> • <i>Cryptosporidium</i> identified by MZN stain and confirmed by IFA. 	<ul style="list-style-type: none"> • <i>Cryptosporidium</i> identified by MZN stain. 	<ul style="list-style-type: none"> • Improved procedures for 3010 study: diagnosis confirmed by IFA.
Patient Demographics	<ul style="list-style-type: none"> • Gender: 40 M/46 F • Age: mean 31, range 12-67 • Weight: mean 65, range 25-109 • Duration of diarrhea: mean 11 days, range 4-100 	<ul style="list-style-type: none"> • Gender: 27M/23 F • Age: mean 35, range 15-62 • Weight: mean 72, range 35-104 • Duration of diarrhea: mean 15 days, range 5-90 	<ul style="list-style-type: none"> • No significant differences
Protocol Deviations	<ul style="list-style-type: none"> • 1 patient enrolled with no symptoms at baseline (excluded from efficacy analysis due to no oocysts in baseline stool sample) 	<ul style="list-style-type: none"> • 16 patients enrolled based on screening >7 days before enrollment (range 8-19 days) • 4 patients late for day 7 exam • 9 patients late for second follow-up stool collection 	<ul style="list-style-type: none"> • Recruitment procedures and patient attendance at study visits was significantly improved due to investigator experience, addition of study coordinator and better monitoring.

MZN = modified Ziehl Neelsen; IFA = immunofluorescence assay

4.3 Review Strategy

Study RM01-3010 was considered the pivotal study demonstrating efficacy of nitazoxanide tablets and oral suspension for the treatment of diarrhea caused by *Cryptosporidium parvum* in HIV-uninfected adults and adolescents 12 years of age and older. Study RM-NTZ-98-002 was considered supportive of the efficacy of nitazoxanide tablets. However, the efficacy of nitazoxanide suspension was not tested in adults and adolescents in Study RM-NTZ-98-002. Supportive data of the efficacy of nitazoxanide suspension in adults and adolescents can be found in the studies which supported the approval of nitazoxanide suspension in the treatment of diarrhea caused by *Cryptosporidium parvum* in HIV-uninfected children 1 to 11 years of age (original NDA 21-497 approved in 2002).

Clinical Reviewer's Comment: NDAs 21-497 (nitazoxanide oral suspension) and 21-498 (nitazoxanide tablets), both of which include Study RM-NTZ-98-002, were submitted 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. One of the two study sites which enrolled adult patients into Study RM01-3010 also enrolled patients into the pediatric studies performed under NDA 21-498 (nitazoxanide oral suspension for *Cryptosporidium* 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):

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, both of —)
- 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=10) enrolled in Study RM01-3010 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 01-3010 was performed in compliance with Good Clinical Practices.

4.6 Financial Disclosures

The applicant obtained certification from each investigator (Drs. El-Gohary and Kabil) who enrolled patients in Study RM01-3010. No investigator had any disclosable information to reveal.

Clinical Reviewer's Comment: The financial disclosure statement was sent by the applicant, upon request of the Reviewer, on June 9, 2005.

5 CLINICAL PHARMACOLOGY

No new pharmacokinetic data was included in the current submission. The current approved package insert contains information on the pharmacokinetics of nitazoxanide tablets in subjects \geq 12 years of age and nitazoxanide oral suspension in subjects 1 to 18 years of age.

In the re-submission of NDA 21-497 (nitazoxanide tablets for the treatment of *Giardia lamblia* in adults and adolescents), the applicant conducted a food effect study which evaluated the pharmacokinetics of nitazoxanide oral suspension in adult subjects (\geq 18 years). This information will be added to the package insert.

Clinical Reviewer's Comment: See Clinical Pharmacology and Biopharmaceutics review by Dakshina Chilukuri, Ph.D, filed with the re-submission of NDA 21-497 (dated January 30, 2004).

5.1 Pharmacokinetics

Not applicable.

5.2 Pharmacodynamics

Not applicable.

5.3 Exposure-Response Relationships

Not applicable.

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

Treatment of diarrhea caused by *Cryptosporidium parvum* in HIV-uninfected adults and adolescents 12 years of age and older.

6.1.1 Methods

Study RM01-3010 was considered the pivotal study for the efficacy of nitazoxanide tablets and suspension for the treatment of *Cryptosporidium parvum* in adult and adolescent patients 12 years of age and older. Study RM-NTZ-98-002 was considered supportive of the efficacy of nitazoxanide tablets in adults and adolescents.

6.1.2 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 oral 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.

6.1.3 Study Design

6.1.3.1 Study RM-NTZ-98-002

Study RM-NTZ-98-002 was a randomized, double-blind, placebo controlled study that determined the safety and efficacy of 3 days of treatment with nitazoxanide tablets (500 mg) in adults and adolescents (12 years of age and older) nitazoxanide oral suspension in children 1 to 11 years) with cryptosporidial diarrhea (> 4 stools per day and presence of oocysts) in Benha, Egypt. The dosage regimen was nitazoxanide (500 mg tablets in adults and adolescents) twice daily with food for 3 days. The study was stratified to enroll 50 adults and adolescents and 50 children. A total of 100 patients were enrolled. Data from 99 subjects was analyzed in total, and 50 adults and adolescents constituted the intent-to-treat population for analysis.

The study was designed to evaluate efficacy for two primary endpoints: clinical response (well, continuing illness or clinical treatment failure) on Day 7 and parasitological response (eradication or persistence) based on examination of two stool samples collected between Days 7-10.

Parasitological evaluation in this study was limited to microscopic examination of a small amount of unconcentrated stool sample after staining with Ziehl-Neelsen's stain. Quantitation of oocysts was not done uniformly for all patients. Immunofluorescence staining of unconcentrated stool sample was performed in only 2 of the 21 patients.

Clinical Reviewer's Comment: Study RM-NTZ-98-002 was submitted in the original NDA 21-498 dated May 25, 2002. For a complete description of the study design, see the Medical Officer's Review by Dr. Rosemary Johann-Liang (Medical Officer).

6.1.3.2 Study RM01-3010

A double-blind, controlled study conducted in Egypt in adults and adolescents with diarrhea caused by *Cryptosporidium parvum* (≥ 3 stools per day and presence of oocysts), a three-day course of treatment with Alinia Tablets administered 500 mg BID was compared with a placebo tablet for 3 days. A third group of patients received open-label Alinia for Oral Suspension administered 500mg/25mL of suspension BID with food for 3 days.

Clinical response, the primary endpoint, was evaluated 4 to 7 days following the end of treatment (Day 7-10). A clinical response of 'well' was defined as 'no symptoms, no watery stools and no more than 2 soft stools with no hematochezia within the past 24 hours' or 'no symptoms and no unformed stools within the past 48 hours.'

Parasitological response was also evaluated at the Day 7-10 visit with collection of two stool samples at least 24 hours apart. 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 ("Persistence") for oocysts of *Cryptosporidium* if any of these tests were positive.

All patients returned between Days 14 and 17 and submitted one stool sample for examination for *Cryptosporidium* oocysts or trophozoites. Clinical data at the Day 14-17 visit were also collected from patients enrolled during the second half of the study.

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*).

6.1.4 Efficacy Findings

6.1.4.1 Study RM-NTZ-98-002

Results from the 50 adult and adolescent patients 12 years of age and older are summarized below.

Nitazoxanide tablets showed a clinical response rate of 72% (18/25) compared to 44% (11/25) of patients who received placebo ($p=0.0423$). The parasitological response rate was 60% (15/25) in the nitazoxanide-treated patients and 24% (6/25) in the patients who received placebo ($p=0.0104$). There was a lack of correlation between clinical and parasitological response rates, as evidence by low kappa values.

Mixed pathogens were isolated at baseline in 8 of the adult patients (4 in each treatment arm). When these 8 patients were removed from the analysis, the clinical response rate was 71.4% (15/21) for nitazoxanide tablets and 42.9% (9/21) for placebo (p=0.118). Parasitological response was seen in 57.1% (12/21) patients treated with nitazoxanide tablets compared to 28.6% (6/21) of placebo-treated patients (p=0.118).

Clinical Reviewer's Comment: The reason for the differences in the overall response rates and lack of statistical significance for clinical and parasitological response in this study compared to Study RM01-3010, which is discussed below, is unclear.

For a complete description of the study design, results and analyses of Study RM-NTZ-98-002 see the Medical Officer's Review by Dr. Rosemary Johann-Liang (Medical Officer) filed with the original NDA 21-498 (dated May 25, 2002).

6.1.4.2 Study RM01-3010

The clinical responses recorded at the Day 7-10 visit for the nitazoxanide tablets, nitazoxanide suspension, and the placebo tablets are summarized in Table 1. 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). The study was not designed to compare nitazoxanide tablets and nitazoxanide suspension in a formal non-inferiority analysis.

TABLE 1
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

The parasitological response rates at Day 7-10 for the group receiving nitazoxanide tablets, nitazoxanide suspension, and placebo tablets are summarized in Table 2. 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). The study was not designed to compare nitazoxanide tablets and nitazoxanide suspension in a formal non-inferiority analysis.

TABLE 2
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

The inpatient correlation of clinical and parasitological response rates at Day 7-10 for the nitazoxanide tablet, nitazoxanide suspension, and placebo groups are presented in Table 3.

TABLE 3
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

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 4.

TABLE 4
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 5.

TABLE 5
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 6.

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 6
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

6.1.5 Clinical Microbiology

The NDA is approvable from the Microbiology perspective.

Clinical Reviewer's Comment: The information below was obtained from the Microbiology Review conducted by Kala Suvarna, Ph.D. For additional information, see the complete review filed with this NDA.

The methods used to detect *C. parvum* oocysts in the stool samples are described below:

Iodine stained unconcentrated stool sample: A small portion of stool sample was mixed with a drop of iodine solution and entire smear examined for the presence or absence of parasites under high power (40x) magnification. The *C. parvum* oocysts in the stool samples were not quantified.

Iodine stained concentrated stool sample: Fecal sediment (0.5 to 1 ml) was obtained by straining fecal sample mixed with 10 ml saline through a wet gauze and centrifugation at 1500-2000 rpm. The fecal sediment was mixed with 10 ml of 10% formalin and 3 ml of ether and the mixture centrifuged at 1500 rpm for 2 minutes. The sediment at the bottom of the tube was mixed with a drop of iodine and examined under high power (40x) magnification for the detection of parasites. The *C. parvum* oocysts in the stool samples were not quantified.

Unconcentrated stool sample stained with ZNN stain: A smear was prepared using a pin-head sized drop of well mixed fecal sample and a drop of saline. The smear was stained by the ZNN staining procedure and the entire smear was examined under oil-immersion lens (100x magnification).

Immunofluorescence assay: The FDA approved _____ direct immunofluorescence assay (DFA) kit manufactured by _____ was used to detect *C. parvum* oocysts in unconcentrated stool samples. Using Ziehl Neelsen stained stool samples as the gold standard, the sensitivity and specificity of the DFA assay was 92% and 85%, respectively (_____ DFA kit package insert). The kit manufacturer has stated that variation in the rate of positivity could occur due to low oocyst count, age, location, and health status of the patient population under study. Restaining of stool specimens was shown to improve sensitivity of the test kit.

A total of 90 patients were enrolled from 2 study sites (Benha and Alexandria) in Egypt. Sensitivity of the different methods used to identify baseline *C. parvum* oocysts was compared. Baseline stool samples (both unconcentrated and concentrated) stained with iodine from all 90 patients were negative (Table 1). The sensitivity of ZNN was greater (94%; 85/90) compared to DFA (51%; 46/90) for identification of *C. parvum* using unconcentrated stool samples. The sensitivity of the DFA observed in this study (51%) was lower than that reported in the package insert (92%) by the manufacturer of the DFA kit. Please note that quality control data using the DFA kit in the laboratory where the clinical trial samples were tested were not included for review. The reason for the lower sensitivity of DFA is unclear.

Table 1. Analysis of the sensitivity of the different methods used to detect *C. parvum* oocysts in a baseline stool sample from all patients enrolled in study RM01-3010

UC/ZNN	UC/DFA		UC/I		C/I	
	+	-	+	-	+	-
+	45	40	0	85	0	85
-	1	4	0	5	0	5

UC/ZNN = unconcentrated stool sample stained with Ziehl-Neelsen stain;

UC/DFA = unconcentrated stool sample stained using an immunofluorescence assay kit;

UC/I = iodine stained unconcentrated stool sample;

C/I = iodine stained concentrated stool sample;

+ = presence of oocysts; - = absence of oocysts;

On days 4 to 7 after discontinuation of therapy (test of cure/visit 2), absence of oocysts in 2 stool samples by ZNN staining and resolution of diarrhea was observed in 24 (92%) of the 26 patients treated with NTZ tablets. Of the 2 patients who showed persistence of oocysts, one showed resolution of diarrhea and was also positive for oocysts by DFA (Tables 2 and 3). Of the 29 patients treated with NTZ oral suspension, one patient did not return for evaluation and was considered to be a clinical and parasitological failure as per protocol design. Resolution of diarrhea and absence of oocysts in the stool samples were observed in 86% (25/29) of the patients (Table 2). The 3 remaining patients continued to have diarrhea. Absence of oocysts was observed in 1 of the 3 patients by ZNN staining. One patient was positive for oocysts by both ZNN and DFA (Table 3). Placebo was less effective than NTZ. Resolution of diarrhea and eradication of oocysts was observed in 35% (8/23) patients (Table 2). Two patients with resolution of diarrhea continued to shed oocysts. The patients were positive for oocysts by ZNN and DFA staining. Of the remaining 13 patients who continued to have diarrhea, 2 showed eradication of oocysts.

Table 2. Parasitological and clinical response of patients with cryptosporidiosis from Egypt at visit 2 (end of therapy)

Treatment group	Parasitological and clinical responses			Patients with eradication of oocysts N (%)	Patients with clinical well response N (%)	Patients clinically well and showing eradication of oocysts N (%)
	Oocysts Eradicated by ZNN and DFA (CR)	Oocysts Persisted (CR)				
		ZNN alone	ZNN + DFA			
500 mg NTZ tablet BID 3 days (n = 26)	24 (24 well, 0 CI)	1 (1 CI)	1 (1 well)	24 (92)	25 (96)	24 (92)
500 mg NTZ oral suspension BID 3 days (n = 29)	26 (25 well, 1 CI)	2* (2 CI)	1 (1 CI)	26 (90)	25 (86)	25 (86)
Placebo BID 3 days (n = 23)	10 (8 well, 2 CI)	5 (5 CI)	8 (2 well, 6 CI)	10 (43)	10 (43)	8 (35)

NTZ = Nitazoxanide; CR = clinical response; N = number of subjects; CI = continuing illness;

* one patient did not return for end of therapy evaluation and was considered to be a failure (continuing illness with persistence of oocysts) by sponsor

Table 3. Correlation of the ZNN and DFA staining method in the post-treatment stool samples obtained at visit 2 (4 to 7 days after discontinuation of therapy) or visit 3 (11 to 14 days after discontinuation of therapy)

Tablets (n = 26):

Visit 2

ZNN	DFA	
	+	-
+	1*	1*
-	0	24

Visit 3

ZNN	DFA	
	+	-
+	1	0
-	0	25

* patient had positive result in one of the 2 stool samples

Suspension (n = 29, one patient did not return for follow-up and was considered as failure by sponsor):

Visit 2

ZNN	DFA	
	+	-
+	1*	1
-	0	26

Visit 3

ZNN	DFA	
	+	-
+	0	1
-	0	27

* Patient had 2 stool samples positive by ZNN and 1 stool sample positive by DFA

Placebo (n = 23):

Visit 2

ZNN	DFA	
	+	-
+	8 [#]	5 [^]
-	0	10

Visit 3*

ZNN	DFA	
	+	-
+	4	3
-	0	15

for 7 patients, positive result in 1 of 2 stool samples

^ for 3 patients, positive result in 1 of 2 stool samples

* data not available for 1 patient

At 11 to 14 days after discontinuation of therapy, 60 clinically well patients (NTZ tablets, n = 25; NTZ suspension, n = 25; and placebo, n = 10) returned for follow-up of parasitological and/or clinical evaluation (Table 4). All 25 patients treated with NTZ tablets continued to be free of oocysts based on evaluation of 1 stool sample by ZNN staining. However, only 11 patients had follow-up clinical evaluations and all 11 continued to be free of diarrhea. Of the 25 patients treated with NTZ suspension, follow-up clinical and parasitological evaluations were performed in 13 patients, while parasitological evaluation alone was performed in the remaining 12 patients (Table 4). All 13 patients were clinically well at 11 to 14 days after discontinuation of therapy; however, 1 showed shedding of oocysts by ZNN staining. Of the 12 patients who had parasitological evaluation only, all were free of oocysts at 11-14 days after discontinuation of therapy. Of the 10 patients in the placebo group, follow-up clinical and parasitological evaluations were performed in 3 patients (Table 4). All 3 patients continued to be well; however,

1 patient showed shedding of oocysts in the stool sample. The remaining 7 patients had only parasitological evaluation at follow-up. Shedding of oocysts was detected by ZNN staining in 1 patient who had previously showed absence of oocysts at EOT.

Overall, the parasitological response correlated with the clinical response at 4 to 7 and 11 to 14 days after discontinuation of therapy.

Table 4. Evaluation of sustained parasitological and clinical response at follow-up (11-14 days after discontinuation of therapy) in the 60 patients with cryptosporidiosis who were clinically well at end of therapy

Treatment group	Day 4-7	Day 11-14	
	Clinical well	Clinical well	Absence of oocysts by ZNN*
	absence of oocysts	absence of oocysts by ZNN	
<i>NTZ Tablet</i>	24/25	11/11	14/14
<i>NTZ Suspension</i>	25/25	12/13	12/12
<i>Placebo</i>	8/10	2/3 [#]	6/7

NTZ = Nitazoxanide;

ZNN = Ziehl-Neelsen stain

* No clinical evaluation performed. The data was obtained prior to protocol amendment.

[#] One of the 3 patients showed presence of oocysts using both ZNN and DFA staining

6.1.6 Efficacy Conclusions

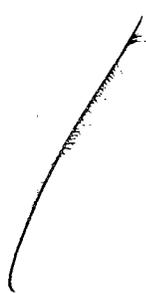
In Study RM01-3010, nitazoxanide tablets and nitazoxanide oral suspension were shown to be superior to placebo in terms of clinical and parasitological response at the test-of-cure visit (Day 7-10) and response was maintained in most patients at the follow-up visit (Day 14-17). Study RM01-3010 was not designed to compare nitazoxanide tablets and suspension in a formal non-inferiority analysis. In Study RM-NTZ-98-002, clinical and parasitological response rates with nitazoxanide tablets at Day 7 (± 2), while not statistically significantly better than placebo, showed a favorable trend. The results obtained in Study RM-NTZ-98-002 were considered supportive of the efficacy of nitazoxanide tablets seen in Study RM01-3010. The efficacy of nitazoxanide suspension in adults and adolescents was not tested in Study RM-NTZ-98-002, but supportive data can be found in the studies which supported the approval of nitazoxanide suspension in the treatment of diarrhea caused by *Cryptosporidium parvum* in HIV-uninfected children 1 to 11 years of age (original NDA 21-497 approved in 2002).

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

The nitazoxanide tablet development program contains safety information from 1657 HIV-uninfected adults and adolescent patients aged 12 years and older who received nitazoxanide tablets in controlled and uncontrolled studies, as shown in Table 7.

TABLE 7
Summary of Controlled and Uncontrolled Studies of Nitazoxanide Tablets in Patients Aged 12 Years and Older (HIV-uninfected)

Study Number	Indication Studied	Number of Patients	Dosage Regimen
RM01-3010	Diarrhea caused by <i>Cryptosporidium parvum</i>	29	500 mg bid x 3 days
RM01-3011	Diarrhea caused by <i>Giardia lamblia</i>	54	500 mg bid x 3 days
RM-NTZ-98-001	Diarrhea caused by <i>Giardia lamblia</i> or <i>Entamoeba histolytica</i>	47	500 mg bid x 3 days
RM-NTZ-98-002	Diarrhea caused by <i>Cryptosporidium parvum</i>	25	500 mg bid x 3 days
CL-NTZ-95-001	Mixed intestinal parasitic infection	121	500 mg bid x 3 days
PRC-94-NTZ03	Mixed intestinal parasitic infection	415	500 mg bid x 3 days
RM-96-401	Mixed intestinal parasitic infection	129	Various doses (500 to 2000 mg qd) and durations (1 to 7 days)
RM-NTZ-99-008		40	500 mg bid x 7 days
RM-94-NTZ-04		393	500 mg bid x 6 or 7 days
RM-NTZ-96-001		195	500 mg or 100 mg x 7 or 14 days
RM-NTZ-95-01		17	500 mg bid x 10 days
RM-NTZ-99-001		68	2000 or 3000 mg x 1 day; and 500 or 1000 mg bid x 3 days
RM-NTZ-99-002		124	2000 or 3000 mg x 1 day; and 500 or 1000 mg bid x 3 or 7 days

Source: Table 1 in the applicant's submission dated January 21, 2005

There were 85 HIV-negative patients aged 12 years and older who received nitazoxanide oral suspension as a comparator in controlled clinical trials (i.e., Studies RM01-3011 and RM01-3010). No deaths, drop-outs due to adverse events, or other serious or potentially serious adverse events occurred in these patients.

7.1.1 Deaths

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

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

7.1.2 Other Serious Adverse Events

One serious adverse event (appendicitis requiring hospitalization) occurred in 12 year old female patient enrolled in Study RM01-3011 three days after the end of 3 days of treatment with nitazoxanide tablets. The appendicitis, reported as abdominal pain, was considered to be unrelated to treatment. No serious adverse events were reported in patients who received nitazoxanide oral suspension.

7.1.3 Dropouts and Other Significant Adverse Events

Eight patients discontinued nitazoxanide tablets due to adverse events as shown in Table 8. No patients discontinued nitazoxanide oral suspension due to adverse events.

TABLE 8
Discontinuations Due to Adverse Events

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

Source: Table 5 in the applicant's submission dated January 21, 2005

7.1.4 Common Adverse Events

Adverse events reported in patients ≥ 12 years of age treated with nitazoxanide tablets (N=1657), nitazoxanide suspension (N=85), or placebo (N=137) are shown in Tables 9, 10, and 11, respectively, respectively. The rates of occurrence of the adverse events for nitazoxanide tablets and nitazoxanide suspension do not appear to be different from those of placebo.

Clinical Reviewer's Comment: Tables 9-11 were created by the applicant and submitted to the NDA on January 21, 2005.

TABLE 9
Adverse Events: Patients (Aged 12 Years and Older) Who Received Nitazoxanide Tablets in Controlled and Uncontrolled Studies (N=1657)

Body system Adverse event	Patients Reporting AEs	
	Number	%
BODY		
PAIN ABDO	110	6.6
HEADACHE	51	3.1
ASTHENIA	12	0.7
FEVER	6	0.4
PAIN	5	0.3
ALLERG REACT	3	0.2
PAIN PELVIC	2	0.1
PAIN BACK	1	0.1
FLU SYND	1	0.1
CHILLS	1	0.1
CHILLS FEVER	1	0.1
DIG		
DIARRHEA	70	4.2
NAUSEA	50	3.0
VOMIT	7	0.4
DYSPEPSIA	4	0.2
NAUSEA/VOMIT	3	0.2
NAUSEA VOMIT DIAR	2	0.1
ANOREXIA	2	0.1
FLATUL	1	0.1
CONSTIP	1	0.1
THIRST	1	0.1
DRY MOUTH	1	0.1
NER		
DIZZINESS	16	1.0
SOMNOLENCE	11	0.7
HYPESTHESIA	1	0.1
INSOMNIA	1	0.1
TREMOR	1	0.1
UG		
URIN ABNORM	14	0.8
DYSURIA	3	0.2
METRORRHAGIA	1	0.1
PAIN KIDNEY	1	0.1
AMENORRHEA	1	0.1
EDEMA LABIA	1	0.1

Source: Table 2 in the applicant's submission dated January 21, 2005

TABLE 9 (continued)
Adverse Events: Patients (Aged 12 Years and Older) Who Received Nitazoxanide Tablets
in Controlled and Uncontrolled Studies (N=1657)

Body system Adverse event	Patients Reporting AEs	
	Number	%
MAN SGPT INC	14	0.8
SKIN RASH PRURITUS RASH VESIC BULL	3 2 1	0.2 0.1 0.1
SS EYE DIS PAIN EAR	3 1	0.2 0.1
RES EPISTAXIS LUNG DIS PHARYNGITIS	1 1 1	0.1 0.1 0.1
CV SYNCOPE TACHYCARDIA	1 1	0.1 0.1
MS MYALGIA BONE FRACT SPONTAN	1 1	0.1 0.1
MS/NER CRAMPS LEG	1	0.1
CV/NER HYPERTENS	1	0.1

Source: Table 2 in the applicant's submission dated January 21, 2005

TABLE 10
Adverse Events: Patients (Aged 12 Years and Older) Who Received Nitazoxanide Oral suspension in Controlled and Uncontrolled Studies (N=85)

Body system Adverse event	Patients Reporting AEs	
	Number	%
BODY		
PAIN ABDO	15	17.6
ASTHENIA	7	8.2
HEADACHE	6	7.1
ABDO ENLARGE	1	1.2
DIG		
NAUSEA	5	5.9
VOMIT	1	1.2
DYSPEPSIA	1	1.2
NER		
SOMNOLENCE	5	5.9
DIZZINESS	2	2.4
REFLEXES INC	1	1.2
UG		
URIN ABNORM	5	5.9
RES		
RHINITIS	1	1.2

Source: Table 4 in the applicant's submission dated January 21, 2005

TABLE 11
Adverse Events: Patients (Aged 12 and older) in Placebo Control Groups (N=137)

Body system Adverse event	Patients Reporting AEs	
	Number	%
BODY		
PAIN ABDO	9	6.6
HEADACHE	4	2.9
ASTHENIA	3	2.2
EDEMA FACE	1	0.7
DEATH	1	0.7
DIG		
DIARRHEA	4	2.9
NAUSEA	1	0.7
DYSPEPSIA	1	0.7
NER		
SOMNOLENCE	4	2.9
DIZZINESS	2	1.5
EMOTION LABIL	1	0.7
UG		
URIN ABNORM	2	1.5
DYSURIA	1	0.7

Source: Table 3 in the applicant's submission dated January 21, 2005

7.1.5 Other Search Strategies

An evaluation of the safety of nitazoxanide tablets (N=1657) and oral suspension (N=85) compared to placebo (N=137) in patients ≥ 12 years of age was compared by age (12 to < 18 years and ≥ 18 years), sex, and race (Caucasians, Hispanics and Blacks, for nitazoxanide tablets only) in controlled and uncontrolled trials is reported below. The safety data are collected from efficacy trials of various bacterial and parasitic infections. The dosage of nitazoxanide tablets, as well as the duration of treatment, varied across trials (see Table 7 in the Section 7.1: “Methods and Findings”). Nitazoxanide oral suspension in patients 12 years of age and older was used at a dose of 500 mg twice daily for 3 days in Studies RM01-3010 and RM01-3011 (N=85).

Clinical Reviewer’s Comment: Tables 12 through 31 were created by the applicant and submitted to the NDA on January 21, 2005.

Adolescents (12 to < 18 years) and Adults (≥ 18 years): Tables 12-14 list the incidence of adverse events in for nitazoxanide tablets, suspension, and placebo, respectively, in adolescent patients (12 to < 18 years). For comparison, adverse events from patients ≥ 18 years treated with nitazoxanide tablets, suspension, and placebo are shown in Tables 15-17, respectively. Adverse events are similar between nitazoxanide tablets, suspension, and placebo in both adolescents and adults.

TABLE 12
Adverse Events: Patients Treated with Nitazoxanide Tablets
Aged 12 through 17 Years (N=204)

Body system Adverse event	Patients Reporting AEs	
	Number	%
BODY		
PAIN ABDO	29	14.2
HEADACHE	13	6.4
FEVER	3	1.5
ASTHENIA	3	1.5
PAIN	1	0.5
CHILLS	1	0.5
DIG		
DIARRHEA	9	4.4
NAUSEA	7	3.4
NAUSEA VOMIT DIAR	1	0.5
NER		
DIZZINESS	5	2.5
SOMNOLENCE	2	1.0
UG		
URIN ABNORM	2	1.0
DYSURIA	1	0.5
EDEMA LABIA	1	0.5
SS		
EYE DIS	2	1.0

Source: Table 2b in the applicant’s submission dated January 21, 2005

TABLE 13
Adverse Events: Patients Treated with Nitazoxanide Oral Suspension
Aged 12 through 17 Years (N=43)

Body system Adverse event	Patients Reporting AEs	
	Number	%
BODY		
PAIN ABDO	9	20.9
HEADACHE	4	9.3
ASTHENIA	4	9.3
NER		
DIZZINESS	2	4.7
SOMNOLENCE	2	4.7
REFLEXES INC	1	2.3
DIG		
NAUSEA	2	4.7
VOMIT	1	2.3
UG		
URIN ABNORM	2	4.7
RES		
RHINITIS	1	2.3

Source: Table 4b in the applicant's submission dated January 21, 2005

TABLE 14
Adverse Events: Patients in Placebo Control Groups
Aged 12 through 17 Years (N=44)

Body system Adverse event	Patients Reporting AEs	
	Number	%
BODY		
PAIN ABDO	6	13.6
HEADACHE	3	6.8
ASTHENIA	1	2.3
NER		
SOMNOLENCE	2	4.5
EMOTION LABIL	1	2.3
DIG		
NAUSEA	1	2.3
UG		
URIN ABNORM	1	2.3

Source: Table 3b in the applicant's submission dated January 21, 2005

TABLE 15
Adverse Events: Patients Treated with Nitazoxanide Tablets
Aged 18 Years and Older (N=1453)

Body system Adverse event	Patients Reporting AEs	
	Number	%
BODY		
PAIN ABDO	81	5.6
HEADACHE	38	2.6
ASTHENIA	9	0.6
PAIN	4	0.3
FEVER	3	0.2
ALLERG REACT	3	0.2
PAIN PELVIC	2	0.1
PAIN BACK	1	0.1
FLU SYND	1	0.1
CHILLS FEVER	1	0.1
DIG		
DIARRHEA	61	4.2
NAUSEA	43	3.0
VOMIT	7	0.5
DYSPEPSIA	4	0.3
NAUSEA/VOMIT	3	0.2
ANOREXIA	2	0.1
NAUSEA VOMIT DIAR	1	0.1
FLATUL	1	0.1
CONSTIP	1	0.1
THIRST	1	0.1
DRY MOUTH	1	0.1
NER		
DIZZINESS	11	0.8
SOMNOLENCE	9	0.6
HYPESTHESIA	1	0.1
INSOMNIA	1	0.1
TREMOR	1	0.1
UG		
URIN ABNORM	12	0.8
DYSURIA	2	0.1
METRORRHAGIA	1	0.1
PAIN KIDNEY	1	0.1
AMENORRHEA	1	0.1

Source: Table 2a in the applicant's submission dated January 21, 2005

TABLE 15 (continued)
Adverse Events: Patients Treated with Nitazoxanide Tablets
Aged 18 Years and Older (N=1453)

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

Source: Table 2a in the applicant's submission dated January 21, 2005

TABLE 16
Adverse Events: Patients Treated with Nitazoxanide Oral Suspension
Aged 18 Years and Older (N=42)

Body system Adverse event	Patients Reporting AEs	
	Number	%
BODY		
PAIN ABDO	6	14.3
ASTHENIA	3	7.1
HEADACHE	2	4.8
ABDO ENLARGE	1	2.4
UG		
URIN ABNORM	3	7.1
DIG		
NAUSEA	3	7.1
DYSPEPSIA	1	2.4
NER		
SOMNOLENCE	3	7.1

Source: Table 4a in the applicant's submission dated January 21, 2005

TABLE 17
Adverse Events: Patients in Placebo Control Groups
Aged 18 Years and Older (N=93)

Body system Adverse event	Patients Reporting AEs	
	Number	%
BODY		
PAIN ABDO	3	3.2
ASTHENIA	2	2.2
HEADACHE	1	1.1
EDEMA FACE	1	1.1
DEATH	1	1.1
DIG		
DIARRHEA	4	4.3
DYSPEPSIA	1	1.1
NER		
DIZZINESS	2	2.2
SOMNOLENCE	2	2.2
UG		
URIN ABNORM	1	1.1
DYSURIA	1	1.1

Source: Table 3a in the applicant's submission dated January 21, 2005

Males and Females: Adverse events in HIV-uninfected patients who received nitazoxanide tablets, suspension, or placebo in controlled and uncontrolled studies are shown for males in Tables 18-20 and for females in Tables 21-23, respectively.

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

TABLE 18
Adverse Events: HIV- Uninfected Patients Who Received
Nitazoxanide Tablets in Controlled and Uncontrolled Studies
Males Only (N=864)

Body system Adverse event	Patients Reporting AEs	
	Number	%
BODY		
PAIN ABDO	34	3.9
HEADACHE	10	1.2
ASTHENIA	5	0.6
FEVER	3	0.3
PAIN BACK	1	0.1
PAIN	1	0.1
CHILLS	1	0.1
DIG		
DIARRHEA	11	1.3
NAUSEA	11	1.3
DYSPEPSIA	3	0.3
VOMIT	1	0.1
NAUSEA VOMIT DIAR	1	0.1
UG		
URIN ABNORM	7	0.8
DYSURIA	1	0.1
EDEMA LABIA	1	0.1
MAN		
SGPT INC	6	0.7
NER		
DIZZINESS	2	0.2
SOMNOLENCE	2	0.2
SS		
EYE DIS	1	0.1
PAIN EAR	1	0.1
RES		
EPISTAXIS	1	0.1
LUNG DIS	1	0.1

Source: Table 2c in the applicant's submission dated January 21, 2005

TABLE 19
Adverse Events: HIV- Uninfected Patients Who Received
Nitazoxanide Oral Suspension in Controlled and Uncontrolled Studies
Males Only (N=46)

Body system Adverse event	Patients Reporting AEs	
	Number	%
BODY		
PAIN ABDO	9	19.6
HEADACHE	5	10.9
ASTHENIA	2	4.3
ABDO ENLARGE	1	2.2
NER		
SOMNOLENCE	3	6.5
DIZZINESS	2	4.3
REFLEXES INC	1	2.2
UG		
URIN ABNORM	3	6.5
DIG		
NAUSEA	2	4.3
VOMIT	1	2.2
DYSPEPSIA	1	2.2

Source: Table 4c in the applicant's submission dated January 21, 2005

TABLE 20
Adverse Events: HIV- Uninfected Patients (Ages 12 Years and Older)
in Placebo Control Groups Males Only (N=86)

Body system Adverse event	Patients Reporting AEs	
	Number	%
BODY		
PAIN ABDO	9	10.5
HEADACHE	4	4.7
ASTHENIA	3	3.5
DEATH	1	1.2
NER		
SOMNOLENCE	3	3.5
DIZZINESS	2	2.3
EMOTION LABIL	1	1.2
DIG		
DIARRHEA	2	2.3
DYSPEPSIA	1	1.2
NAUSEA	1	1.2
UG		
URIN ABNORM	2	1.2
DYSURIA	1	1.2

Source: Table 3c in the applicant's submission dated January 21, 2005

TABLE 21
Adverse Events: HIV-Uninfected Patients Who Received Nitazoxanide Tablets in
Controlled and Uncontrolled Studies
Females Only (N=793)

Body system Adverse event	Patients Reporting AEs	
	Number	%
BODY		
PAIN ABDO	76	9.6
HEADACHE	41	5.2
ASTHENIA	7	0.9
PAIN	4	0.5
FEVER	3	0.4
ALLERG REACT	3	0.4
PAIN PELVIC	2	0.3
FLU SYND	1	0.1
CHILLS FEVER	1	0.1
DIG		
DIARRHEA	59	7.4
NAUSEA	39	4.9
VOMIT	6	0.8
NAUSEA/VOMIT	3	0.4
ANOREXIA	2	0.3
DYSPEPSIA	1	0.1
NAUSEA VOMIT DIAR	1	0.1
FLATUL	1	0.1
CONSTIP	1	0.1
THIRST	1	0.1
DRY MOUTH	1	0.1
NER		
DIZZINESS	14	1.8
SOMNOLENCE	9	1.1
HYPESTHESIA	1	0.1
INSOMNIA	1	0.1
TREMOR	1	0.1
UG		
URIN ABNORM	7	0.9
DYSURIA	2	0.3
METRORRHAGIA	1	0.1
PAIN KIDNEY	1	0.1
AMENORRHEA	1	0.1

Source: Table 2d in the applicant's submission dated January 21, 2005

TABLE 21 (continued)
Adverse Events: HIV-Uninfected Patients Who Received Nitazoxanide Tablets in
Controlled and Uncontrolled Studies
Females Only (N=793)

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

Source: Table 2d in the applicant's submission dated January 21, 2005

TABLE 22
Adverse Events: HIV-Uninfected Patients Who Received Nitazoxanide Oral Suspension in
Controlled and Uncontrolled Studies
Females Only (N=793)

Body system Adverse event	Patients Reporting AEs	
	Number	%
BODY		
PAIN ABDO	6	15.4
ASTHENIA	5	12.8
HEADACHE	1	2.6
DIG		
NAUSEA	3	7.7
UG		
URIN ABNORM	2	5.1
NER		
SOMNOLENCE	2	5.1
RES		
RHINITIS	1	2.6

Source: Table 4d in the applicant's submission dated January 21, 2005

TABLE 23
Adverse Events: HIV- Uninfected Patients (Ages 12 Years and Older)
in Placebo Control Groups
Females Only (N=51)

Body system Adverse event	Patients Reporting AEs	
	Number	%
DIG DIARRHEA	2	3.9
BODY EDEMA FACE	1	2.0
NER SOMNOLENCE	1	2.0

Source: Table 3d in the applicant's submission dated January 21, 2005

Race: Adverse events in HIV-uninfected patients who received nitazoxanide tablets, suspension or placebo in controlled and uncontrolled studies are shown in Tables 24-26 for Caucasian patients and Tables 27-29 for Hispanic patients , and Table 30 for Black patients (nitazoxanide tablets only), respectively.

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TABLE 24
Adverse Events: HIV-Uninfected Patients Who Received Nitazoxanide Tablets in
Controlled and Uncontrolled Studies
Caucasian Only (N=1115)

Body system Adverse event	Patients Reporting AEs	
	Number	%
BODY		
PAIN ABDO	35	3.1
ASTHENIA	10	0.9
HEADACHE	7	0.6
PAIN BACK	1	0.1
FEVER	1	0.1
DIG		
NAUSEA	18	1.6
DIARRHEA	11	1.0
DYSPEPSIA	3	0.3
VOMIT	1	0.1
ANOREXIA	1	0.1
CONSTIP	1	0.1
DRY MOUTH	1	0.1
MAN		
SGPT INC	14	1.3
NER		
DIZZINESS	8	0.7
SOMNOLENCE	4	0.4
UG		
URIN ABNORM	7	0.6
DYSURIA	3	0.3
MS		
BONE FRACT SPONTAN	1	0.1

Source: Table 2e in the applicant's submission dated January 21, 2005

TABLE 25
Adverse Events: HIV-Uninfected Patients Who Received Nitazoxanide Oral Suspension in Controlled and Uncontrolled Studies Caucasian Only (N=49)

Body system Adverse event	Patients Reporting AEs	
	Number	%
BODY		
ASTHENIA	7	14.3
HEADACHE	1	2.0
PAIN ABDO	1	2.0
ABDO ENLARGE	1	2.0
NER		
SOMNOLENCE	4	8.2
DIG		
DYSPEPSIA	1	2.0
NAUSEA	1	2.0
UG		
URIN ABNORM	1	2.0

Source: Table 2e in the applicant's submission dated January 21, 2005

TABLE 26
Adverse Events: HIV- Uninfected Patients (Ages 12 Years and Older) in Placebo Control Groups Caucasian Only (N=109)

Body system Adverse event	Patients Reporting AEs	
	Number	%
BODY		
ASTHENIA	3	2.8
PAIN ABDO	2	1.8
EDEMA FACE	1	0.9
HEADACHE	1	0.9
DEATH	1	0.9
NER		
SOMNOLENCE	4	3.7
DIZZINESS	2	1.8
DIG		
DIARRHEA	1	0.9
NAUSEA	1	0.9
DYSPEPSIA	1	0.9
UG		
URIN ABNORM	2	1.8
DYSURIA	1	0.9

Source: Table 3e in the applicant's submission dated January 21, 2005

TABLE 27
Adverse Events: HIV-Uninfected Patients Who Received Nitazoxanide Tablets in
Controlled and Uncontrolled Studies
Hispanic Only (N=512)

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

Source: Table 2f in the applicant's submission dated January 21, 2005

TABLE 27 (continued)
Adverse Events: HIV-Uninfected Patients Who Received Nitazoxanide Tablets in
Controlled and Uncontrolled Studies
Hispanic Only (N=512)

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

Source: Table 2f in the applicant's submission dated January 21, 2005

TABLE 28
Adverse Events: HIV-Uninfected Patients Who Received Nitazoxanide Oral Suspension in
Controlled and Uncontrolled Studies
Hispanic Only (N=36)

Body system Adverse event	Patients Reporting AEs	
	Number	%
BODY		
PAIN ABDO	14	38.9
HEADACHE	5	13.9
DIG		
NAUSEA	4	11.1
VOMIT	1	2.8
NER		
DIZZINESS	2	5.6
SOMNOLENCE	1	2.8
REFLEXES INC	1	2.8
UG		
URIN ABNORM	4	11.1
RES		
RHINITIS	1	2.8

Source: Table 4f in the applicant's submission dated January 21, 2005

TABLE 29
Adverse Events: HIV- Uninfected Patients (Ages 12 Years and Older) in Placebo Control
Groups Hispanic Only (N=28)

Body system Adverse event	Patients Reporting AEs	
	Number	%
BODY		
PAIN ABDO	7	25.0
HEADACHE	3	10.7
DIG		
DIARRHEA	3	10.7
NER		
EMOTION LABIL	1	3.6

Source: Table 3f in the applicant's submission dated January 21, 2005

TABLE 30
Adverse Events: HIV-Uninfected Patients Who Received Nitazoxanide Tablets in
Controlled and Uncontrolled Studies
Black Only (N=30)

Body system Adverse event	Patients Reporting AEs	
	Number	%
BODY		
PAIN ABDO	3	10.0
DIG		
NAUSEA	2	6.7
UG		
URIN ABNORM	1	3.3
SKIN		
RASH	1	3.3
CV		
SYNCOPE	1	3.3

Source: Table 2g in the applicant's submission dated January 21, 2005

7.1.6 Laboratory Findings

Laboratory values were not routinely collected in all studies. The values reported for patients with laboratory adverse events are summarized in Table 31. Most of the changes represent only slight deviations from the normal laboratory range.

TABLE 31
Adverse Events Related to Laboratory Abnormalities for Patients (Aged 12 Years and Older) Who Received Nitazoxanide Tablets in Controlled and Uncontrolled Trials

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

Units: SGPT: IU/L

Source: Table 7 in the applicant's submission dated January 21, 2005

7.1.7 Vital Signs

No clinically significant findings.

7.1.8 Electrocardiograms (ECGs)

Not applicable. ECGs were not recorded during clinical trials

7.1.9 Immunogenicity

Not applicable. No information on immunogenicity was included in the NDA submission.

7.1.10 Human Carcinogenicity

Not applicable information on immunogenicity was included in the NDA submission.

7.1.11 Special Safety Studies

No special safety studies were performed.

7.1.12 Withdrawal Phenomena and/or Abuse Potential

Not applicable. Nitazoxanide does not have the potential for dependence or abuse.

7.1.13 Human Reproduction and Pregnancy Data

Nitazoxanide is pregnancy category B. No new information was included in the NDA submission. No adequate and well-controlled studies in pregnant women have been performed.

7.1.14 Assessment of Effect on Growth

Not applicable. This product does not have the potential for growth suppression.

7.1.15 Overdose Experience

Not applicable. This product does not have the potential for overdose.

7.1.16 Postmarketing Experience

The applicant estimates that approximately — bottles of nitazoxanide oral suspension (60 mL) and — nitazoxanide tablets have been used by patients in the United States since they were first marketed. No adverse events have been reported.

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

For the evaluation of the safety in patients 12 years of age and older, there were 1657 patients exposed to nitazoxanide tablets, 85 exposed to nitazoxanide oral suspension and 137 exposed to placebo in various controlled and uncontrolled trials of bacterial and parasitic infections (see Table 7 in the Section 7.1: “*Methods and Findings*”). The dosage of nitazoxanide tablets, as well as the duration of treatment, varied across the trials. Nitazoxanide oral suspension was only used in Studies RM01-3010 and RM01-3011. The dose was 500 mg twice daily for 3 days

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

Not applicable. Secondary clinical data sources were not used to evaluate safety.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

In 1657 HIV-uninfected patients 12 years of age and older treated with various dosage regimens of nitazoxanide tablets for bacterial and parasitic infections, the most common adverse events were gastrointestinal and mild in severity. The most common adverse events were abdominal pain (6.6%), diarrhea (4.2%), headache (3.1%), and nausea (3.0%). Adverse events seen in 85 HIV-uninfected patients 12 years of age and older treated with nitazoxanide oral suspension were similar to those observed with nitazoxanide tablets.

7.4 General Methodology

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

As discussed above in Section 7.1.2, safety in patients 12 years of age and older safety of nitazoxanide tablets and oral suspension was evaluated across various controlled and uncontrolled trials of bacterial and parasitic infections.

7.4.2 Explorations for Predictive Factors

Not applicable. No additional exploratory analyses were performed.

7.4.3 Causality Determination

Causality was assessed by the study investigators. No additional assessments of causality were performed.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

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

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

Clinical Review

Joette M. Meyer, Pharm.D.

NDA 21-818 and 21-498/S-003

Nitazoxanide tablets and oral suspension (Alinia®)

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

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

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

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

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

In re-submission of NDA 21-497 (dated January 24, 2004); the applicant submitted a bioavailability study evaluating the rate and extent of absorption of a 500 mg dose of nitazoxanide suspension given in the fed (standard FDA high-fat meal) versus fasted state. The results showed that the AUC of tizoxanide and tizoxanide glucuronide were increased by 39% and 49%, respectively, in the presence of food. The resulting in 90% confidence interval of the AUC test/reference ratio was shifted up and fell outside the acceptable limits of 80% to 125%. The peak plasma concentrations of both tizoxanide and tizoxanide glucuronide were relatively unchanged and the 90% confidence intervals of the C_{max} test/reference ratio were within the acceptable limits of 0.8-1.25. In summary, administration of nitazoxanide suspension with food results in higher exposure, in terms of AUC but not C_{max} .

Clinical Reviewer's Comment: The pharmacokinetic results quoted here came from the Clinical Pharmacology/Biopharmaceutics Review by Dakshina Chilukuri, Ph.D. filed with the re-submission of NDA 21-498 (dated January 30, 2004).

In Study RM01-3010 the applicant compared the efficacy of nitazoxanide tablets to the nitazoxanide suspension in adult and adolescent patients aged 12 years and older and was able to show that there was no significant effect of dosage form on clinical or parasitological efficacy, as determined by a lower bound of the 95% confidence interval of the treatment difference lying above -15%.

In Study RM01-3010 the applicant was unable to characterize the contribution of food-effect on clinical efficacy due to incomplete reporting of meals in the patients' study diaries. However, since the clinical efficacy of the tablets was comparable to the suspension when administered with food in adults, it can be concluded that an increase in the systemic exposure to tizoxanide does not adversely affect the efficacy of the tablets, although the relative contribution of systemic versus local antimicrobial activity is still unclear.

8.2 Drug-Drug Interactions

No new information was included in the current submission. See the package insert for information on drug-drug interactions with nitazoxanide.

8.3 Special Populations

Clinical and parasitological response rates observed in Study RM01-3010 by sex (males compared to females) and race (Caucasians compared to Hispanics), and can be found in the Review of Study RM01-3010 (Section 10.1 of this document). Differences, if any, seen in the response rates between males and females are not considered clinically meaningful. No adjustments to the adult dosing of nitazoxanide tablets or oral suspension in adolescents are warranted based on sex or race.

In Study RM01-3010 there were only 3 patients aged 65 and over, therefore it is not possible to determine whether or not they respond differently from younger patients. 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.

Clinical Reviewer's Comment: People at the extremes of age (i.e., elderly and young children) are more likely than average adults to become symptomatic following exposure to oocysts of Cryptosporidium, due to compromised immunity. Studies RM-NTZ-98-002 and RM01-3010 both demonstrated the efficacy of nitazoxanide in patients (some of whom were children) living in a developing country with relatively poor nutritional status, which may have led to

immunodeficiency. Therefore, although the efficacy of nitazoxanide has not been established in geriatric patients in the US, these patients may derive the greatest benefit from treatment with nitazoxanide.

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

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

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

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

8.4 Pediatrics

The efficacy and adverse event profile of nitazoxanide tablets and oral suspension in adolescent patients (aged 12 years to < 18 years) are similar to adults. Therefore, no adjustments to the adult dosing of nitazoxanide tablets or oral suspension in adolescents are warranted based on efficacy. Reporting of adverse events for adolescents separate from adults in the product labeling is also not warranted.

Children less than 12 years of age should be dosed with the oral suspension formulation of nitazoxanide. Nitazoxanide oral suspension is currently approved for the treatment of diarrhea caused by *Giardia lamblia* and *Cryptosporidium parvum* in children 1 to 11 years of age. The approved package insert contained safety and efficacy results for children 1 to 11 years of age separately from adults and adolescents.

8.5 Advisory Committee Meeting

No advisory committee meeting was held.

8.6 Literature Review

Not performed.

8.7 Postmarketing Risk Management Plan

No postmarketing risk management plan is planned.

8.8 Other Relevant Materials

On May 17, 2005, the Division asked the applicant to clarify how the placebo rate in the population studied in Egypt correlates to the natural history of *Cryptosporidium* in normal hosts in the United States. Specifically, the applicant was asked to address the following:

1. What is the anticipated spontaneous resolution rate in normal adults who are infected in an outbreak setting in the United States?
2. What proportion of adults who develop symptomatic diarrhea in the US would likely be analogous to the Egyptian population in terms of duration of clinical symptoms and burden of oocysts infection?
3. What is the correlation between the time to resolution in symptoms from US normal volunteers and that found in the pivotal study?
4. What is the correlation between the time of eradication of oocysts in normal hosts in the United States to the timing of the microbiological endpoint in the pivotal study for nitazoxanide?

On May 25, 2005 the applicant submitted the following response, which was felt to adequately address the Division's questions:

This pattern of disease for the population studied in the pivotal clinical trial is consistent with the natural history of cryptosporidiosis in non-immunodeficient adults in the United States.

- The natural course of cryptosporidiosis described for non-immunodeficient persons in the United States varies widely and may include asymptomatic infection, enteric symptoms without diarrhea, mild-to-moderate acute diarrheal illness lasting only a few days, severe acute diarrheal illness requiring hospitalization and persistent diarrheal illness lasting from 7 days to two months. Factors that may affect the severity and duration of illness include the number of oocysts ingested, the virulence of the strain and immune status of the host.¹⁻⁸
- Reports of outbreaks in the United States typically report a mean duration of illness in non-immunodeficient adults between 6 and 18 days with further recurrences of illness following initial resolution.^{1,4} Thus, the mean duration of illness for patients in the United States should actually be 6 to 18 days plus the duration of recurrences.
- The median duration of diarrhea for placebo patients in the pivotal study was >16 days (median duration of diarrhea at baseline = 9 days + 7 days to follow-up, at which time only 40.7% of placebo patients had resolved symptoms). Therefore, we can conclude that the duration of diarrhea for patients enrolled in the pivotal trial was at least as long as that typically reported for patients developing cryptosporidiosis in an outbreak setting in the United States.
- Patients included in the pivotal study were selected from a population that visited an outpatient clinic seeking medical attention for diarrheal illness. Due to the time required for screening and enrollment in the pivotal trial, we inevitably selected out patients with longer courses of disease, thus eliminating patients with only a few days of diarrheal illness. It is, therefore, quite reasonable to expect that the

duration of illness of patients enrolled in the pivotal trial might be slightly longer than that typically observed in the United States in an outbreak setting.

Thus, the population studied in the pivotal study would be analogous to patients in the United States who seek medical attention, are diagnosed with cryptosporidiosis and remain ill at the time that the diagnosis is made.

To address each of the specific points:

1. The anticipated spontaneous resolution rate in normal adults who are infected in an outbreak setting in the United States is near 100%.¹⁻⁴ While hospitalization is not unusual for patients in the United States,¹ it would be unusual for an immunocompetent adult, without other underlying complications, to die from cryptosporidiosis, and we are not aware of any reports of this in the published literature. Likewise, none of the patients enrolled in the pivotal study were in danger of death. While the patients were not followed-up beyond the end of the study, our expectation is that the patients' symptoms were eventually self-limiting.
2. The median duration of diarrhea reported for persons with symptomatic cryptosporidiosis in the United States has been reported to be approximately 9 days.^{1,4} The population enrolled in our pivotal study had a median duration of diarrhea at baseline of 9 days. Therefore, we would expect that approximately 50% of patients with symptomatic cryptosporidiosis in the United States (those with diarrhea >9 days) would be analogous to the Egyptian population in terms of duration of symptoms and burden of infection.
3. Patients enrolled in the placebo arm of the pivotal study had a median duration of diarrhea at baseline of 9 days (range: 6-12 days). 40.7% of the patients in the placebo group (11/27) responded by study day 7, indicating a total duration of illness between 9 and 16 days. One of 8 clinical failures at day 7 who were followed-up at study day 14 resolved symptoms before day 14, but the other 7 were still symptomatic at study day 14 (approximately 23 days after initiation of symptoms). In an outbreak setting in the United States, the duration of symptomatic cryptosporidiosis is commonly reported to be up to 4 to 8 weeks.^{1,2,4}

Studies in healthy volunteers in the United States who were given oral doses of *Cryptosporidium* oocysts generally showed diarrheal illness of 6 hours to 9 days duration with approximately 50% of the volunteers experiencing one to five recurrences of symptoms after initial resolution of diarrhea.^{5,7,8} The total duration of diarrheal illness including the time for recurrences was not reported. Nevertheless, it is apparent that the duration of illness reported for a limited number of healthy volunteers inoculated with *Cryptosporidium* oocysts is somewhat shorter than that reported for patients with naturally acquired infection.

4. 25.9% of the patients randomized to the placebo group in the pivotal trial were free of oocysts in each of three post-treatment stool samples. This suggests, consistent with published data from outbreak settings in the United States, that oocyst shedding is self-limiting but often extends for some time beyond the resolution of symptoms (total of 2 to 8 weeks).^{2,3}

Summary of relevant data from the published literature:

Outbreak Setting in the United States:

Mean duration of diarrhea in Milwaukee outbreak among patients with laboratory-confirmed infection was 12 days (range: 1 to 55 days).¹ 39% reported a recurrence of diarrhea after at least 2 days of normal stools.¹

Among workers in a Florida daycare setting, the duration of diarrhea ranged from 3 to 31 days (mean: 18.8 days). The duration of oocyst shedding among the adults ranged from 2 to 8 weeks.²

Among 160 persons attending a fair in central Maine who were infected by ingesting fresh-pressed apple cider, the median duration of diarrhea was 6 days (range: 1 to 16 days). Among patients who submitted serial stool samples for analysis, oocyst excretion continued for a median of 28 days (range, 10 to 65 days; interquartile range, 23 to 42 days).³

In an outbreak attributed to a recreational swimming pool in Minnesota, the duration of symptoms ranged from 3 to 28 days with a median of 9 days.⁴

Studies in Healthy Volunteers:

Of 29 healthy adult volunteers given a single dose of oocysts (Iowa strain), only 18 had oocysts identified in their stools. Only 7 of these 18 became clinically ill with diarrhea and other symptoms of *Cryptosporidium* infection.⁵

Duration of illness for 7 healthy adult volunteers ranged from 58 to 87 hours (mean: 74 hours).⁵

Duration of oocyst excretion ranged from 1 to 38 days. Mean duration of oocyst excretion was 10 to 13 days for patients inoculated with >300 oocysts.⁵

There was an apparent relationship between higher doses of *Cryptosporidium* oocysts and the duration of oocyst excretion.⁵

Volunteers with diarrheal illness excreted more oocysts over the course of the infection than did volunteers without diarrhea.⁶

19 of these volunteers were re-challenged with *Cryptosporidium* oocysts one year later to evaluate protective immunity following one exposure. 11 of the 19 subjects experienced diarrheal illness demonstrating that an initial exposure was not sufficient to protect against clinical illness one year later.⁷

Mean duration of diarrheal illness: 67 hours after first exposure, 60 hours after second exposure.⁷

Relapses were common after the first challenge: 64% had one relapse, 18% had 2 or 3 relapses. After the second challenge, 45% had one relapse, 18% had 3 or 5 relapses.⁷

29 volunteers were exposed to the Iowa strain, 17 to the UCP strain and 14 to the TAMU strain. Attack rates were 52%, 59% and 86% respectively. Duration of diarrhea was similar among groups ranging from 6 to 223 hours. Relapse rates were 18%, 46% and 58% respectively. Mean duration of oocyst shedding was 8.4, 3.3 and 3.4 days respectively. The study suggested that the virulence can vary among strains.⁸

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Clinical Review

Joette M. Meyer, Pharm.D.

NDAs 21-818 and 21-498/S-003

Nitazoxanide tablets and oral suspension (Alinia®)

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9 OVERALL ASSESSMENT

9.1 Conclusions

Nitazoxanide (Alinia®) tablets and oral suspension are safe and effective for the treatment of diarrhea caused by *Cryptosporidium parvum* in HIV-uninfected adults and adolescent patients 12 years of age and older. Nitazoxanide tablets and oral suspension are recommended for approval for this indication. Safety and effectiveness of nitazoxanide tablets have not been established in patients with immunodeficiency.

9.2 Recommendation on Regulatory Action

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

9.3 Recommendation on Postmarketing Actions

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

9.3.1 Risk Management Activity

None.

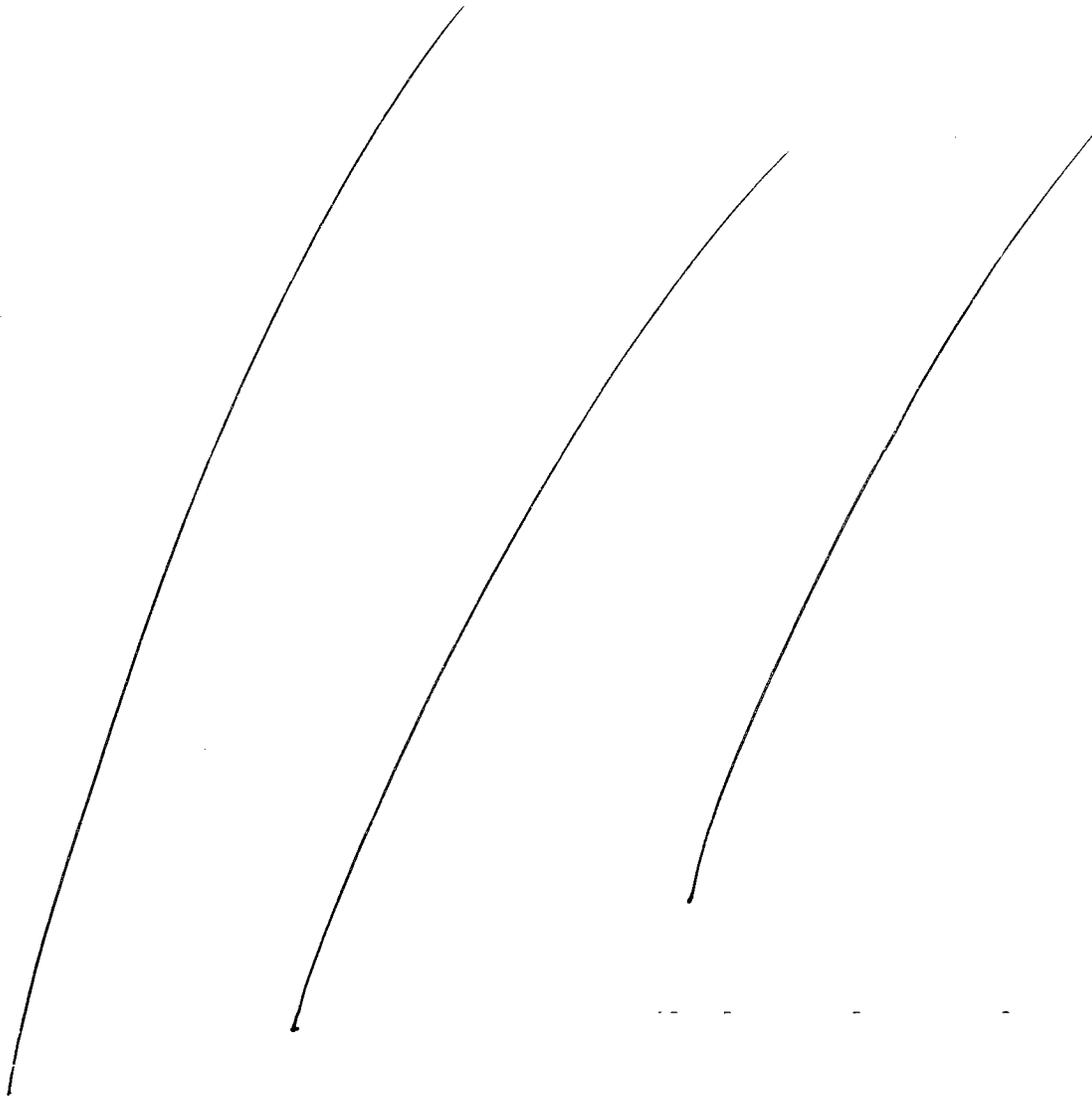
9.3.2 Required Phase 4 Commitments

None.

9.3.3 Other Phase 4 Requests

None.

9.4 Labeling Review



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