CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-498

Medical Review(s)

Medical Officer's Review of NDA [redacted] 21-498

Nitazoxanide (Oral Suspension)
Review of Efficacy and Safety for Diarrhea Caused by *C. parvum* and *G. lamblia*
in non-AIDS l Children

IDENTIFYING INFORMATION

Applicant identification

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Submission/review dates

Date of Submission: May 25, 2002
CDER Stamp Date: May 30, 2002
Date review begun: June 14, 2002
Date review complete: November 5, 2002

Orphan Drug Designation

Drug identification

Generic name: Nitazoxanide
Proposed Trade name: Cryptaz Tablets and Oral Suspension
Chemical Name: 2-acetolyloxy-N-(5-nitro 2-thiazolyl) benzamide
Molecular formula: $C_{12}H_9N_3O_5S$
Molecular weight: 307.3
Pharmacologic category: Synthetic antiprotozoal agent
Dosage Form

Suspension Strength: 100 mg/ 5 mL
Route of Administration: oral

Related IND: [redacted]

EXECUTIVE SUMMARY

The Applicant has submitted 2 NDA's for 2 different dosage forms of the same active ingredient:

NDA 21-498 Cryptaz (Nitazoxanide) Oral Suspension

The proposed indications and usage are

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- Treatment of diarrhea caused by *Giardia lamblia* and elimination of cysts from the intestinal tract in non-AIDS patients.

The proposed dosages are

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

The Applicant presented data from the following five controlled clinical studies (all from foreign sites) in seeking the above indications.

RM-NTZ-98-002	A double-blind placebo-controlled study in adults and children with diarrhea caused by *C. parvum* EGYPT (n=50 adults and n=49 children)
RM02-3007	A double-blind placebo-controlled study in HIV-seronegative children with diarrhea caused by *C. parvum* ZAMBIA (n=50 children)
RM02-3008	A double-blind placebo-controlled study in HIV-seropositive children with diarrhea caused by *C. parvum* ZAMBIA (n=50 children)
RM-NTZ-99-010	A single-blind metronidazole-controlled study in children with diarrhea caused by *G. lamblia* PERU (n=92 children)

Evidence of Efficacy

The efficacy data presented through these five studies will be viewed separately by the two NDAs since they represent two different formulations for two different age groups. There are no available guidelines or guidance for clinical trials to study *C. parvum* diarrhea. There is an Infectious Diseases Society of America (IDSA) guideline from 1992 (Cooperstock et al. Evaluation of New Anti-Infective Drugs for the Treatment of Diarrhea Caused by Giardia lamblia. *Clinical Infectious Diseases 1992; 15 (suppl 1): S244-8)* on studies for *G. lamblia*. The Applicant has largely used this guideline in the conduct of the above trials. The following Table summarizes the pertinent points from this guideline and compares these points to the five trials as they relate to the efficacy assessments and response.

Table 1: Efficacy Assessment and Response Summary

Study	Minimal Diag Criteria	Inclu/ Exclu Criteria	Pre	Day 0	Tx	Clinical Assess Day	Clinical Assess Resp	Parasit Assess Day	Parasit Assess Resp	KAPPA Clin/micro correlate?
IDSA Guideline For study of Giardia	**Diarrhea: Passage of ≥3 unformed stools/d Must have *G. lamblia* as sole pathogen**	**Adults must also have enteric symptoms Exclude if presence of additional intestinal pathogen**	**-48 hours to 0 hour Do clinical. Lab. and stool exam**	**Start Tx Do clinical. Lab. and stool exam**	**Maintain diary Median time from tx to passage of last unformed stool (MTTPLUS)**	**48 hours to 7 days after tx finishes**	**Well: first 24 hrs with only 2 soft stools or first 48 hrs w/no unformed stools Continued Illness Failure**	**At least 48 hours after the last dose of medication**	**At least two stool samples Eradicate Persistent**	
***Crypto* Egypt Adults Kids**	**Multiple Pathogens; #s w/ mixed pathogens NTZ n=14 PLB n= 8**	**Not all w/symp Ntz 44/50 Plb 39/49**	**Stool exam w/in 7d**	**No stool exam**	**3 days tx Adults 3 v 6d NS Kids 3.5 v 6d (p=.0001)**	**7 ± 2 d**	**Adults ITT or by Crypt (NS) Kids 88 v 38% (p=.0004)**	**7± 2 d 10 ± 2 d**	**Adults ITT or by Crypt (NS) Kids 75 v 24% (p=.0001)**	**Kids .333 (NTZ)**
Zambia HIV- Kids	**Crypto only**	**Malnour sick**	**Stool exam w/in 7d**	**Stool exam Excluded in ITT if neg**	**Poor Diary**	**7 ± 2 d**	**56 v 22 % (P=.037)**	**7 ± 2 d 10 ± 2 d**	**52 v 14% (P=.007)**	**.096 (NTZ)**
Zambia HIV+ Kids	**Crypto only**	**AIDS sick**	**Stool exam w/n 7d**	**Stool exam**	**Poor diary**	**7 ± 2 d**	**No effect over placebo**	**7 ± 2 d 10 ± 2 d**	**No effect over placebo**	
Peru ActiveC Kids	**Giardia only**	**Kids OK**	**Stool exam w/in 7d**	**Stool exam**	**3d NTZ v 5d MTN tx 4d v 4d MTTPLUS**	**7 ± 2 d**	**85 v 80% (-.10, .21)**	**7 ± 2 d 10 ± 2 d**	**71 v 75% (-.21, .13)**	**NTZ: .276 MTN .227**

NTZ: nitazoxanide; PLB: placebo; MTN: metronidazole; Gl: Giardia lamblia

Redacted 1

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information

NDA 21-498: Nitazoxanide Suspension for Treatment in Children

For seeking the indication of treatment of diarrhea caused by *C. parvum* with a 3-day therapy of NTZ oral suspension in HIV sero-negative children (ages 1 to 11), the applicant has provided data from three studies (Egyptian study 98-002 and Zambian studies 3007 and 3008). It is important to point out that the population of children from the Zambian studies was mainly malnourished children. The Zambian study 3008 was a study in HIV sero-positive children where treatment effect of 3-day NTZ therapy over placebo was not demonstrated. When the remaining two studies (98-002 and 3007) were pooled for children (all HIV sero-negative) with *C. parvum* in the stool at the screening visit (children with mixed infections and children who did not take medication were excluded), 39 children in the NTZ arm and 46 children in the placebo arm constituted the comparison groups. For children, both clinical response (66.7% NTZ vs. 30.4% placebo; p=.0011) and parasitological response (59% NTZ vs. 21.7% placebo; p=.0007) rates were statistically significant. However, there was inconsistent correlation between clinical and micro endpoints across treatment subgroups with kappa coefficients for the overall comparison (+.182 for NTZ group and +.218 for the placebo group). Hence, although the numbers are small, efficacy has been demonstrated in terms of clinical endpoint (treatment of diarrhea caused by *C. parvum* in children who are HIV negative; NDA 21-498). Microbiological endpoint (eradication of the *C. parvum* oocyst) has not been adequately addressed due to the less than optimal microbiological assessments (parasitological assessment by the acid-fast stain method with one drop of stool sample and confirmed by immunofluorescent assay method in only 9 patients) and sub-optimal correlation with clinical response by the kappa statistic.

For seeking the indication for treatment of diarrhea caused by *G. lamblia* with a 3-day therapy of NTZ oral suspension in HIV sero-negative children (ages 1 to 11), the applicant provided data from a single-center study (Study in Peru 99-010). This was an active-controlled study with metronidazole as the comparator and *G. lamblia* as the sole baseline pathogen. The ITT population consisted of 110 patients with 55 in the NTZ group and 55 in the metronidazole group. It should be noted that children enrolled were actually 2 – 11 years in this study. The clinical response in children treated with NTZ (85.5% NTZ vs. 80% metronidazole; CI –8.64, 19.54) was shown to be non-inferior to that of metronidazole (an approved drug for treatment of giardiasis in Peru). However, for parasitological response (70.9% NTZ vs. 74.6% metronidazole; CI –20.3, 13), the rate for NTZ just missed the lower bound of the –20% CI. The correlation between clinical and microbiological endpoints (by kappa statistic) were slightly better and consistent across subgroups in this study in comparison to the other 4 studies with ITT kappa coefficients at (+.227 for NTZ group and +.276 for the metronidazole group). Hence, although the numbers are small, efficacy has been demonstrated in terms of clinical endpoint (treatment of diarrhea caused by *G. lamblia* in children who are HIV negative). NDA 21-498 is for age range 1-11 years although for this giardia study, children were enrolled down to 2 years only.

Nevertheless, since the pathophysiology of the giardia disease and pharmacokinetic parameters are similar in 1 and 2 year olds, and since data is available in 1 year olds from Cryptosporidiosis studies, the age range to be treated can remain as 1 – 11 years. The parasitological endpoint (eradication of the *G. lamblia* cysts) was not met statistically in this study.

Evidence of Safety

Across 5 controlled trials submitted for —
21-498 (NTZ suspension for Children 1-11 years of age)

Major safety issues were not associated with the use of NTZ for 3 days in the 5 studies submitted to the two NDAs. In total, there were 47 adverse events across the 5 studies for the NTZ arms and 56 adverse events in the control arms with the most common adverse event being abdominal pain (13 events in NTZ arm, 12 events in the control arm). The overall adverse event rates across the 5 studies pooled were 21% overall for NTZ and 22% for control. There were no differences in the rate or character of adverse events between the NTZ-treated arms and control arms for 4 of the 5 studies. In study **3007** (Zambian study in HIV sero-negative malnourished children), adverse events in the NTZ-treated arm (including death) were significantly less (2 AE for NTZ, 13 AE for placebo: p<.0001) in comparison to the placebo arm. There were 18 deaths in all across the 5 studies (6 in the NTZ arm and 12 in the placebo arm). All 6 of the deaths in the NTZ arm were from study **3008** (Zambian study in HIV sero-positive children) and the deaths were deemed "not related" to treatment. The following is the integrated safety summary table of the five studies.

Table 2: Integrated Safety Summary of the Five Studies

Study	Exposure# to NTZ		Which arm (see next table)	Analysis of AE	SAE	Death	Labs
98-002	25 adults 24 children	26 total; 24 pts (11kids; 13adults) 25 AEs mild 1 AE moderate: dizziness (NTZ)	12 AE for NTZ 14 AE for placebo OR NTZ: 12AE/11pts PLA:14AE/13pts	No diff compared to placebo	none	none	None done
02-3007	25 children (total of 47 treatments due to re-tx)	15 total by 8 pts 3 mild (vomiting) 1 mod (tetany) 11 severe	2 AE for NTZ 13 AE for placebo OR NTZ; 2 AE/2 pts PLA: 13 AE/6 pts	P<.0001 For AE P=.018 For #pts	11 AEs from 4 pts PLA	4 all "not related" (Placebo)	No diff Bet Day 0 and 7
02-3008	25 children (total of 55 treatments due to re-tx)	18 Total by 14 pts 1 mild (anemia) 17 severe	8 AE for NTZ 10 AE for placebo OR NTZ: 8AE/ 7pts PLA: 10 AE 7pts	No diff Compared to placebo	17 AEs from 13 pts	13 death 7 placebo 6 NTZ "not related" (Placebo)	No diff Bet Day 0 and 7
—	47 adults	16 total by 13 pts 10 AEs mild	11 AEs for NTZ 5 AEs for placebo	No diff Compared	1 due to	1 due to	None done

Study	Exposure to NTZ		Which arm (see next table)	Analysis of AE	SAE	Death	Labs
		5 AEs mod (dizziness, nausea) 1 AE severe	OR NTZ; 11AE/ 7 pts PLA: 5 AE/ 5 pts	to placebo	status asthmaticus "not related"	status asthmaticus "not related"	
99-010	48 children 13 (2-3 yrs) 35 (4-11 y)	28 total by 25 pts all mild	14 AEs for NTZ 14 AEs for MTN OR NTZ:14 AE/13pts MTN: 14 AE/13pts	No diff compared to MTN	none	none	None done
In Total	NTZ 72 adults 122 children Control 70 adults 129 children	103 AEs total NTZ + Control 26 adults with AE 58 kids with AE	47 AE total NTZ 56 AE total Cont OR NTZ: 14 adultsAE 26 kidsAE Cont: 11 adultsAE 33 kids AE	4 studies no difference 1 study with difference in favor of NTZ	1 adult 28 AEs from 17 kids	18 death total 12 Control 6 NTZ	2 no diff 3 none done

AE: adverse event; SAE: serious adverse event

Since only NDA 21-498 is being recommended for approval at this time, it is important to examine the safety database in the specific population of children ages 1-11 years who are HIV negative to make certain that there are no additional or different safety issues specifically related to the young age or the suspension formulation.

Safety Database for All Children ages 1-11 years who are HIV negative and treated with NTZ suspension formulation in the overall NTZ program

Total exposure: All between 1-11 years (n=658; from 14 controlled and uncontrolled trials with HIV positive and negative children)
Males (n=337)
Females (n=321)

Non-AIDS patients: n=613
3 day exposure to NTZ (n=470)
>3 d – 1 wk exposure (n=22)

Adverse Reactions

In controlled and uncontrolled clinical studies of 613 pediatric non-AIDS patients who received nitazoxanide suspension, the most frequent adverse events reported regardless of causality assessment were: abdominal pain (7.8%), diarrhea (2.1%), vomiting (1.1%) and headache (1.1%). These were typically mild and transient in nature. In placebo-controlled clinical trials, the rates of occurrence of these events did not differ significantly from those of the placebo.

None of the 613 pediatric patients discontinued therapy because of adverse events.

Adverse events occurring in less than 1% of the patients participating in clinical trials are listed below:
Digestive System: nausea, anorexia, flatulence, appetite increase, enlarged salivary glands.
Body as a Whole: fever, infection, malaise.
Metabolic & Nutrition: increased creatinine, increased SGPT.
Skin: pruritus, sweat.
Special Senses: eye discoloration.
Respiratory System: rhinitis.
Nervous System: dizziness.
Urogenital System: discolored urine.
Significant AE: none
Death: none

No additional or different safety issues specifically related to the young age or the suspension formulation was identified. The following is a brief summary of the current safety database for the overall program. Again, for patients without AIDS, no significant adverse experiences were identified when nitazoxanide was given orally for 3 days.

Safety Database for the Overall Nitazoxanide Clinical Program
For the overall NTZ clinical program (32 studies in total), the applicant listed the total number of NTZ exposure at 2,789 patients with 2,453 receiving at least 3 days of treatment. Among the 2,349 patients who did not have AIDS, no serious adverse events have been reported, and no drug-related adverse effects on hematology, clinical chemistry or urinalysis laboratory parameters were detected. The frequency and nature of adverse events reported by patients receiving nitazoxanide in double-blind placebo-controlled studies did not differ significantly from those of patients receiving the placebo.

Table 3: Adverse Experience in the Overall NTZ Clinical Program

	Non-AIDS patients on NTZ	AIDS patients on NTZ
Most Common AE	Abdominal pain 6.7% Diarrhea 3.7% Headache 2.5% Nausea 2.4% (Mild, no different in rate from placebo)	Vomiting 19.1% Abdominal pain 10.9% Death 8.9% Discoloration sclera 8.9% Pneumonia 5.5% Discoloration of urine 5.2% (mainly serious in nature)
Serious AE	None reported	Many including death
Kids 1-11 years Deaths, Drop-outs Due to AE and Other Serious or Potentially Serious AE 658 children exposed to NTZ in total	None on NTZ 11 on Placebo	10 on NTZ 2 on placebo

Risk / Benefit Analysis

Before the final recommendations for regulatory action on — NDA 21-498 can be made, it is important to consider the evidence/lack of evidence regarding efficacy and safety of the new drug from the risk / benefit balance perspective. In regards to safety, there does not appear to be any major or irreversible risk associated with 3-day course of oral nitazoxanide therapy in non-AIDS patients. What then might be the possible benefits? What population of patients would most benefit from this potential therapy? The Applicant has stated the following regarding how this drug therapy will fulfill the current unmet medical needs.

"*Cryptosporidium parvum* and *Giardia lamblia* are each causes of persistent diarrhea in humans. *C. parvum* has been reported to cause malnutrition, impaired growth and death in children in developing countries. *C. parvum* is also associated with wasting and death in adults with immune disorders such as AIDS in the United States. *G. lamblia* has been reported to cause impaired growth in children in developing countries. The prevalence of *C. parvum* and *G. lamblia* in the United States is currently low. However, with increasing travel and immigration, the prevalence of diarrhea caused by these organisms may increase. At present, there is no drug approved for treating diarrhea caused by *C. parvum* in the United States. There is only one drug, furazolidone, approved for treating diarrhea caused by *G. lamblia* (this drug is no longer manufactured however). Metronidazole is not approved for treating giardiasis in the United States, but is commonly used for this indication. Metronidazole is not available as a pediatric formulation, and while not recognized as prevalent, metronidazole resistance has been reported for *G. lamblia*."

Thus, for non-AIDS patients, it is the population of children ("*C. parvum* has been reported to cause malnutrition, impaired growth and death in children in developing countries; *G. lamblia* has been reported to cause impaired growth in children in developing countries; metronidazole is not available as a pediatric formulation") who would most benefit from a potential new treatment of the two parasitic infections. There were no additional safety issues specifically raised concerning the use of nitazoxanide in the pediatric non-AIDS population.

Another factor to be considered in the risk/benefit balance is that *C. parvum* is now classified as an emerging pathogen by the Center for Disease Prevention and Control (CDC) and listed under Category 2, water safety threats, in the critical biological agent categories for public health preparedness. Since there are no currently approved treatment for *C. parvum* infections, the approval and availability of safe and effective treatment will be of benefit to public health preparedness.

Recommendations for Regulatory Action

- [redacted]

- It is recommended that the regulatory action for NDA 21-498 (NTZ oral suspension) be an APPROVAL action for the treatment of clinical disease only. Efficacy and safety of NTZ treatment for diarrhea due to *C. parvum* and *G. lamblia* were adequately demonstrated for children 1 years to less than 12 years of age. However, neither vigorous microbiological data nor substantial evidence of the correlation between clinical and microbiological endpoints was shown at this time to warrant the granting of the indication "eradication of oocysts or cysts". Phase IV commitments should include food-effect pK studies with the suspension dosage form, absorption studies with the major metabolites of nitazoxanide, and a study of the use of nitazoxanide for oral suspension (prescribers, diagnoses, dose and duration of treatment) in clinical practice in the United states.

Recommendations for Labeling

- [redacted]

- NDA 21-498: Labeling for this approval recommended application should be directed to the pediatric prescriber treating pediatric patients ages 1-11 years of age who are HIV negative, and should include the following.
  - *Clinical Pharmacology* section (please see Biopharmaceutics review for specific recommendations): The pK specifics (including the absorption Table) should be data from pediatric patients 1 – 11 years of age and not from adults. Pediatric patients less than 1 years of age should be included under special populations as a population without clinical information.

- *Microbiology* section (please see Microbiology review for specific recommendations): Substantial evidence of *in vitro* activity coupled with causing similar clinical symptomatology (as the parasites with clinical evidence of effectiveness) is needed at a minimum to be listed under the activity *in vitro* section.
- *Indications and Usage* section: Suggested wording for this section would be the following. "Nitazoxanide for Oral Suspension is indicated for the treatment of diarrhea caused by *Cryptosporidium parvum* and *Giardia lamblia* in pediatric patients 1- 11 years of age. Safety and effectiveness of Nitazoxanide Oral Suspension has not been established in patients who are HIV positive or patients with immunodeficiency. Safety and effectiveness of Nitazoxanide Oral Suspension in pediatric patients less than one year of age, pediatric patients > 11 yeas of age, and adults have not been studied".
- *Human Dose Equivalents* (please see Pharmacology/Toxicology review for the specific recommendations): The human dose equivalents given under fertility and under pregnancy/reproduction sections should be based on the 11 year old weight (the high end of the 1-11 years age range being approved under this label) rather than an adult weight.
- Under the *Precautions*, the following additions are suggested to clarify for the prescriber which populations the drug is not to be used.

  Pediatric Patients < 1 year of age and > 11 years of age

  Safety and effectiveness of Nitazoxanide for Oral Suspension in pediatric patients less than one year of age and > 11 years of age have not been studied.

  Adult and Geriatric Patients

  Safety and Effectiveness of Nitazoxanide for Oral Suspension in adult and geriatric patients has not been studied.

  Patients with Immunodeficiency (all ages)

  Safety and effectiveness of Nitazoxanide in HIV positive patients or patients with immunodeficiency has not been established.
- The Adverse Events section should list AE data from the safety database of 1 – 11 year old pediatric patients who were HIV negative (n=613).
- Clinical Studies Section should be included with information from pediatric patient (1-11 years of age) data for clinical response (studies 98-002 and 3007 for *C. parvum* and study 99-010 for *G. lamblia*)

Recommendation for Trade Name

-DDMAC and DMETS are not recommending the use of the trade name "Cryptaz" at this time because 1) it is specific only for the indication for treatment of cryptosporidium (and *G. lamblia* infection treatment is also being approved) 2) safety issues in confusing this name with other drugs already on market (especially Ceftaz).

-The applicant submitted an alternative name: "Alinia" which was acceptable upon consultation with DDMAC and DMETS and thus is recommended as the trade name.

TABLE OF CONTENTS

Please note that a smaller Arial font is used throughout this document to represent text copied verbatim from cited reference(s) or when the content closely approximates cited reference(s).

APPLICANT'S PROPOSED LABELING

Proposed INDICATIONS AND USAGE

[redacted]

NDA 21-498 *Cryptaz* for Oral Suspension is indicated for the treatment of diarrhea caused by *Cryptosporidium parvum* and *Giardia lamblia* and elimination of oocysts or cysts from the intestinal tract. Clinical experience with nitazoxanide for the treatment of diarrhea caused by *C. parvum* in persons with AIDS has not been fully and systematically studied. Cryptaz tablets are, therefore, not indicated in these patients.

Proposed DOSAGE AND ADMINISTRATION

[redacted]

NDA 21-498 For each of the therapeutic indications, the recommended dose is indicated below:

Age 4-11 years: 10 mL (200 mg nitazoxanide) every 12 hours for 3 days.
Age 12-47 months: 5 mL (100 mg nitazoxanide) every 12 hours for 3 days.

Proposed CLINICAL STUDIES Section

The Applicant has proposed no CLINICAL STUDIES Section in the two labels.

LABELING FOR RELATED DRUGS

- Currently, no drug is approved for treating diarrhea caused by *C. parvum* in the US.
- Furazolidone is the only approved drug for treating diarrhea caused by *G. lamblia* in the US, but is no longer manufactured.
- Metronidazole is not approved for treating giardiasis in US but is the recommended treatment of choice for giardiasis and is commonly used. However, suspension formulation of this drug for use in children is not available in the US.

Because the Applicant used Metronidazole as the active control for their study in Peru for the treatment of diarrhea due to *G. lamblia* in children, the Flagyl Package Insert used in Peru was requested. The Applicant submitted the English version of the Package Insert and it is as follows.

Flagyl (Metronidazole) Package Insert from Peru

Indications:

They are based on the antiparasitic and antibacterial activity of metronidazole, as well as its pharmacokinetic characteristics related to infections that are caused by metronidazole-sensitive pathogens:

- Intestinal and extraintestinal amebiasis (i.e., amoebic liver abscess) caused by Entamoeba histolytica
- Skin and skin structure infections caused by Bacteroides species including the B. fragilis group, Clostridium species, Eubacterium species, Peptococcus and Peptostreptococcus species
- Trichomoniasis caused by Trichomonas vaginalis
- Giardiasis

CLINICAL REVIEW METHODS

Materials Reviewed

Vols 1.1 (sections 1.0 –4.0, 14.0-20.0); 1.32-1.61 (Clinical Section with Safety Update Report); NDA 21-498 Volume 1.1 (sections 1.0 – 4.0; 14.0-20.0); 1.7 (section 9.0); 1.8 (section 10.0); 1.10 (section12.0 Case Report Tabulations via electronic document room – SAS transport to JMP tables: tabulations for studies RM-NTZ-98-002, RM02-3007, RM02-3008, and RM-NTZ-99-010); 1.11 (section 13; Case Report Forms: 20% random and directed).

Applicant's additional submissions to [redacted] NDA 21-498 dated July 7, 2002, July 24, 2002, August 30, 2002, September 23, 2002, and September 27, 2002

Previous Medical Officer's Notes from Pre-NDA meeting with Romark Laboratories.

NDA 20-871 Medical Officer Review of Nitazoxanide for the treatment of diarrhea associated with cryptosporidiosis in AIDS patients.

NDA [redacted]

Were Trials Conducted in Accordance with Accepted Ethical Standards

It appeared as if all trials were conducted ethically and after IRB approval. Informed consent was obtained in all enrolled subjects. This was verified by the FDA's Division of Scientific Investigations' field inspectors.

Evaluation of Financial Disclosure

There was no conflict of interest with regards to the indications under review.

BACKGROUND

Regulatory Background

This new molecular entity drug, nitazoxanide, was first submitted to the Agency by Unimed Pharmaceuticals, Inc. (Unimed had licensed the product from Romark Laboratories, Inc.) for treatment of diarrhea associated with cryptosporidiosis in AIDS patients as NDA 20-871 in December 26, 1997. The data from that NDA submission was presented at the FDA Antiviral Drug Products Advisory Committee Meeting held on May 6, 1998. A non-approval letter was issued to Unimed Pharmaceuticals, Inc. on June 30, 1998 because

For seeking future approval, adequate and well-controlled studies preferably performed in double-blind manner as well as an adequate safety database was recommended.

After the non-approval of the initial application, Romark Laboratories Inc. took back the development program of this product. A number of protocols and correspondences were submitted to the nitazoxanide IND —— in the ensuing years. In April 2001, Romark asked the Office of Orphan Products Development to amend the indication stated in the orphan drug-designation (#95-0918) of nitazoxanide from "treatment of immunocompromised patients with cryptosporidiosis" to "treatment of cryptosporidiosis". This amendment was

granted in June 2001. In February 2002, orphan designation of nitazoxanide for the treatment of intestinal giardiasis (designation request #01-1504) was also granted to Romark.

(Questions are what Romark had posed and the answers are from the previous MO, Dr. Eileen Navarro for the Division NTZ team)

1. **Does the FDA have any questions or concerns regarding the clinical trials substantiating effectiveness of the drug products?**

YES, specifically:

a)Cryptosporidiosis:

can foreign data from malnourished children be translated to the US population? did severity of malnutrition vary with a successful outcome

b)Giardiasis

prevalence reported to be 2.5 M, is this consistent w/ orphan drug designation? If not, can approval be based on a single (investigator) center non-US study?

c),

2. **Does the FDA have any questions or concerns regarding the sufficiency of the data submitted in substantiation of safety?**

YES. The methodology for assessing laboratory safety in , 002 and RMNTZ 99-010 should be described. Details on the deaths in the placebo arm (including post-mortem examinations) in study RM NTZ 02-3007, should be in the NDA.

3. **Is the proposed wording of the indication acceptable, and if so, should the orphan drug designation reflect this exact wording?**

YES. The label should probably be limited and include the phrase that the drug "has not been studied in patients with HIV/AIDS or other form of immunocompromise"

4. **How should the prescribing information of the proposed NDA address the use of the products in treating persons with AIDS related cryptosporidiosis?**

See above

5. **Are there any special requirements or arrangements that need to be made for auditing clinical sites or manufacturing facilities?**

No. Only administrative issues that pertain to overseas audits. Since the pivotal studies for two of the three indications were single sites, it is likely that a site for each of the indications needs to be audited.

6. **Given that the indications proposed for this NDA are all intestinal tract infections, and given the very short proposed duration of treatment, the sponsor does not believe it is necessary to conduct another pharmacokinetic study in children (other than the ACTG oral suspension pK in children in AIDS related cryptosporidiosis that is to start by the end of 2001). Would FDA concur with this conclusion?**

No. NTZ's drug-drug interaction with the antiretrovirals have not been studied. The durations of treatment in the ACTG studies differ from the 3 days utilized in the NDA. Further, the drug is intended to be taken with food and no data has been submitted to address the interaction with food.

Subsequently, [redacted] 21-498 were submitted with the stamp date of 5/30/02 seeking the indications of treatment of diarrhea caused by *C. parvum* and *G. lamblia* [redacted]

> ***MO COMMENT:*** *Note that the Applicant is not seeking the [redacted] indication with these NDAs. Note also that the answer for question #6 still holds: all 5 pivotal trials for the two submitted NDAs administered the study drug with food, and no data has been submitted to address the interaction with food.*

During the filing meeting held internally for these two applications on 6/21/02, it was decided that these applications would be given Priority Review status (6 months review clock) according to MAPP 6020.3 because nitazoxanide therapy may offer evidence of increased effectiveness in the treatment of disease since

1. Currently no drug is approved for treating diarrhea caused by *C. parvum* in the US
2. Furazolidone is the only approved drug for treating diarrhea caused by *G. lamblia* in the US, but now is no longer being manufactured.
3. Metronidazole is not approved for treating giardiasis in US but is commonly used; not available in suspension formulation for children
4. Applicant was claiming that with this NDA, the efficacy of NTZ (by suspension) is demonstrating a significant improvement in resolution of diarrhea and [redacted] (two placebo-controlled studies for *C. parvum* and 1 placebo + 1 active-controlled studies for *G. lamblia*)
5. Applicant was claiming that after 6 years of use in Latin America with more than 6 million patients treated, no serious adverse events have been reported from post-marketing experience with NTZ.

Scientific Background

Cryptosporidium parvum

Cryptosporidium parvum **is an intracellular protozoan parasite with a worldwide distribution. Although over 20 different "species" of Cryptosporidium have been "named" in the literature, biologic, ribosomal RNA and genetic studies suggest that three larger "gastric" species *C. muris*, *C. serpentis*, and *C. baileyi*, (in rodents, reptiles, and chickens, respectively) are distinct from the smaller, intestinal *C. parvum*, (both the human genotype 1 and the bovine and human genotype 2) and its close "relatives" such as *C. felis* and *C. meleagridis* (seen in turkeys).**

Cryptosporidiosis was first described in 1907 in mice, but it was not until 1976 that it was first reported in humans (in an immunocompetent child and in an immunosuppressed adult with diarrhea). The organism infects the gastrointestinal epithelium to produce a diarrhea that is self-limited in immunocompetent persons (accounts for up to 6% of all diarrheal disease) but potentially life-threatening in immunocompromised persons, especially those with the AIDS, accounting for up to 24% of persons with both AIDS and diarrhea worldwide.

C. parvum is now classified as an emerging pathogen by the Centers for Disease Control and Prevention (CDC) and listed under Category B and Water Safety Threats of the Critical Biological Agent Categories for Public Health Preparedness. A large water-borne outbreak (contaminated waterworks) in Milwaukee in 1993 affected over 400, 000 persons. Critical to the epidemiology and spread of Cryptosporidium are five remarkable, distinguishing characteristics: 1) its impressively hardy oocysts that are highly resistant to chlorine and to acid; 2) its relatively small size; 3) its apparent low infectious dose; 4) its fully sporulated and infectious nature immediately upon shedding, and 5) its zoonotic potential. Despite the magnitude and severity of cryptosporidial infection, its biology is poorly understood and there is currently no fully effective therapy.

The life cycle is completed in a single host. The oocyst is shed in the stool of an infected host, and ingested by the new host via direct transmission (person to person, or animal to person), or from fecally contaminated environmental transmission (i.e., water). The oocyst undergoes excystation after being exposed to digestive enzymes and/or bile salts, but sometimes spontaneously. Four motile sporozoites are released, which are capable of attaching to the epithelial cell wall. The next phases of development occurs in a vacuole that is composed of two host cell-derived and two parasite-derived membranes, thus the parasite is developing intracellularly, but extracytoplasmically. The sporozoite matures asexually into a meront, which will then release merozoites into the lumen. Some of the merozoites will reinvade the host cell, providing an opportunity for an autoinfection cycle to be established, while others will continue their sexual maturation that will lead to zygote formation. It is the zygote that will mature into the oocyst, which will then pass on into the environment. However, it is noted that the oocyst may excyst in the host's intestinal tract, again creating the opportunity for an autoinfectious cycle that can lead to a severe form of the disease, particularly in immunocompromised patients.

C. parvum attaches intimately to the microvillous membrane and causes loss of microvilli and effacement, which results in malabsorption. The organism activates second-signal pathways, such as the NF-kB and c-src systems. Activation of NF-kB induces the production of cytokines and chemokines, such as interluekin-8, to trigger an inflammatory reaction and stimulates anti-apoptotic survival signals in directly infected cells. Activation of c-src is associated with host-cell cytoskeletal reorganization and perhaps dysfunction of tight junctions. *C. parvum* induces secretion of 5-hydroxytryptamine and prostaglandin E_2 into the lumen. "Enterotoxin" activity, which produces chloride secretion in vitro, has been detected in fecal extracts from infected calves. *C. parvum* induces apoptosis in epithelial cells, resulting in damage to the epithelial barrier. *C. parvum* produces varying degrees of villous atrophy by an unknown mechanism, resulting in malabsorption. Both humoral and cell-mediated immunity are involved in the resolution of cryptosporidiosis and resistance to infection. However, the mechanisms by which *C. parvum*-infected gastrointestinal epithelial cells elicit host immune response are not understood; one possible mechanism in human cells involves the production of cytokines and chemokines by infected mucosa, with M cells in the intestine having a role.

The interplay of organism versus the host ability to respond is seen clinically. For immunocompetent hosts, the three major clinical manifestations are asymptomatic carriage, acute diarrhea (profuse watery diarrhea containing mucus but rarely blood or leukocytes), and persistent diarrhea that may continue for several weeks. After an incubation period of 7 to 10 days, more than 90 percent of infected patients present with acute watery diarrhea that lasts approximately 2 weeks, accompanied by nausea, vomiting, and cramp-like abdominal pain; 36% also have fever. In the outbreak in Milwaukee, the mean duration of illness was 12 days, and the median maximal number of stools per day was 12. The clinical manifestations included watery diarrhea (93% of patients), abdominal cramps (84%), fever (57%), vomiting (48%), and weight loss (75%).

For population of children in developing countries, acute and chronic diarrhea due to *C. parvum* is associated with malnutrition and high morbidity and mortality rates. The diarrhea also has lasting

adverse effects on weight and height. For other non-immunocompetent populations such as patients with AIDS, the severity and duration of diarrhea and the extraenteric manifestations of the infection differ from immunocompetent patients. The four clinical patterns of disease in patients with AIDS are aymptomatic infection (4%), transient infection in which diarrhea lasts for less than two months (29%), chronic diarrhea lasting two months or more with persistence of parasites in stool or in biopsy specimens (60%), and fulminant infection in which patients pass at least 2 liters of watery stool daily (8%).

The simplest method of detecting oocysts is modified acid-fast staining of the organism on microscopical examination of stool. The sensitivity and specificity of the test are improved by newer tools, such as immunofluorescent assays and antigen-capture enzyme-linked immunosorbent assays, which are now commonly used in diagnostic laboratories. Polymerase-chain-reaction-based techniques are available as research tests.

> ***MO COMMENT:*** *The complexity of the life cycle phases, as well as the sites of maturation, have complicated the development of therapeutic agents. At the time of the NDA 20-871 (Cryptaz for C. parvum diarrhea in AIDS patients) non-approval, it was recommended that since it it was not known whether systemic absorption is necessary for efficacy, and which one of the developmental forms would be more susceptible to therapeutic intervention, the following areas needed additional investigation: a) The interaction between nitazoxanide and the different life cycle stages of C. parvum. b) The metabolism of nitazoxanide, with particular attention to the possible metabolism of nitazoxanide by microbial nitroreductases.*

For the current applications (NDA 21- —— 498), the Applicant has stated that the mechanism of action of nitazoxanide has been studied in protozoa (*Giardia lamblia, Trichomonas vaginalis, Entamoeba histolytica*), anaerobic bacteria (*Clostridium difficile and Clostridium perfringens*) and in the microaerophilic bacterium, *Helicobacter pylori*. The Applicant has proposed that these studies have demonstrated that nitazoxanide directly inhibits pyruvate:ferredoxin oxidoreductase (PFOR), an essential enzyme of central intermediary metabolism in these organisms. The activity of nitazoxanide is not dependent on the presence of ferredoxin, and nitazoxanide does not induce mutation in the DNA of susceptible organisms as in the case with metronidazole. The Applicant has also stated that studies in animals have also demonstrated activity of nitazoxanide against both *C. parvum* and *G. lamblia*. The activity of nitazoxanide has been demonstrated in a number of different animal models of Cryptosporidium infection. A single in vitro susceptibility study out of France was submitted that explored the activity of nitazoxanide against both asexual and sexual stages of *C. parvum*. Nitazoxanide and each of its metabolites (tizoxanide and tizoxanide glucuronide) inhibited the Nitazoxanide and each of its metabolites (tizoxanide and tizoxanide glucuronide) inhibited the sporozoites, asexual and sexual stages of the parasite's development after 46 hours.

> ***MO COMMENT:*** *Some new information has been added to understanding the biology and mechanism of nitazoxanide with these new NDAs. However, as is further discussed in the microbiology review (Please see Dr. Suvarna's Review), the PFOR mechanism of nitazoxanide was not studied with C. parvum. Furthermore, based on review of the animal studies data to these two NDAs, Dr. Suvarna's summarized that nitazoxanide efficacy against C. parvum in different animal studies taken together were inconclusive. The new study examining the effect of nitazoxanide on different life cycle stages was helpful, but this was just*

one single study. Hence, there still remains large gaps in understanding the biology and the mechanism of activity of nitazoxanide against C. parvum.

Giardia lamblia

Giardiasis caused by the protozoal parasite *Giardia lamblia* is one of the most common causes of intestinal disease and diarrhea worldwide. Ingestion of the hardy cysts starts the infection life cycle. There is excystation in the small intestine with release of trophozoites that multiply by binary fission. The trophozoites remain free in the lumen or attach to the mucosal epithelium by means of a ventral sucking disk. As a trophozoite encounters altered conditions, it forms a morphologically distinct cyst, which is the stage of the parasite usually found in the feces. Trophozoites may be present and even predominate in loose or watery stools, but it is the resistant cyst that survives outside the body and is responsible for transmission. Giardia remains a pathogen of the proximal small bowel and does not disseminate hematogenously. Cysts do not tolerate heating, desiccation, or continued exposure to feces but do remain viable for months in cold fresh water. The number of cysts excreted varies widely but can approach 10^7 per gram of stool.

The mechanisms by which *G. lamblia* causes alterations in small-bowel function are largely unknown. Although trophozoites adhere to the epithelium, they do not cause invasive or locally destructive alterations. The lactose intolerance and significant malabsorption that develop in a minority of infected adults and children are clinical signs of the loss of brush border enzyme activities. Disease manifestations of giardiasis range from asymptomatic carriage to fulminant diarrhea and malabsorption. Most infected persons are aymptomatic, but in epidemics, the proportion of symptomatic cases maybe higher. Symptoms may develop suddenly or gradually. In acute giardiasis, symptoms develop after an incubation period that lasts at least 5 to 6 days and usually 1 to 3 weeks. Symptoms include diarrhea, abdominal pain, bloating, belching, flatus, nausea, and vomiting. The duration of acute giardiasis is usually in excess of 1 week, although diarrhea often subsides. Chronic giardiasis may occur with or without antecedent acute episode. Increased flatus, loose stools, sulfurous burping, and weight loss are the predominant symptoms and can persist for years if untreated.

Infection can be diagnosed by examination and by testing of stool or duodenal fluid for the organism or Giardia antigen. Trophozoites and cysts can be identified in stool or duodenal fluid. Antigen can be detected by an enzyme-linked immunoassay. Three stool examination will permit reliable diagnosis in 95% of patients. Stool specimens should be concentrated. Antigen detection is more sensitive than examination for cysts/trophozoites.

Patients with symptoms or those at risk of spreading disease can be treated with quinacrine (cure rate, 85% to 95%; bitter tasting; available as tablets only), furazolidone (cure rate, 80%; liquid preparation but NO LONGER manufactured). Or metronidazole (high cure rates in adults – around 85% range; safety and efficacy in children or infants have not been defined; NOT APPROVED for giardiasis in the USA). Paromomycin can be used as a alternative treatment for pregnant women. Therapy should be given for 10 to 14 days and repeated if therapeutic failure is evident.

***MO COMMENT**: There are available therapies for the treatment of Giardiasis in the United States. However, the only drug available in suspension form for young children (furazolidone) is no longer manufactured. Thus, the availability of a safe and effective new drug (which is available in formulation suitable for young children) for the*

treatment of giardiasis would be a notable advance in the therapeutic armamentarium. Note the known metronidazole cure rates (in the mid-80% range) for treatment of giardiasis. We would expect to see clinical cure rates in this range in study RM-NTZ-99-010, the metronidazole-controlled study in children with diarrhea caused by G. lamblia from Peru.

Literature cited for the above Scientific Background

Tzipori S. Cryptosporidiosis: current trends and challenges. *Microbes and Infection 2002; 4: 1045*

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Dillingham RA, Lima AA, Guerrant RL. Cryptosporidiosis: epidemiology and impact. *Microbes and Infection 2002; 4: 1059-1066*

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Cooperstock M, DuPomt HL, Corrado ML, Fekety R, Murray DM. Evaluation of New Anti-Infective Drugs for the Treatment of Diarrhea Caused by Giardia lamblia. *Clinical Infectious Diseases 1992; 15(Suppl 1): S244-5*

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REGULATORY GUIDANCE
For Diarrhea Caused by *C. Parvum* or *G. Lamblia*

The FDA did not deal with traveler's, parasitic, or infectious diarrhea in the 1997 ODE IV Evaluability Criteria and 1992 Points-to-Consider documents.

Guidelines for the development of anti-infective drugs for treatment of diarrhea including diarrhea caused by *Giardia lamblia* were published in Clinical Infectious Diseases 1992; 15 (Suppl 1): S244-8. There are no guidelines for development of anti-infective drugs for treatment of diarrhea caused by *C. parvum*.

The following are relevant excerpts taken from the above guideline since this is the document that the Applicant has relied on to conduct the clinical trials of the current NDAs under review.

Clinical Definitions of the Disease

General Definitions: Diarrhea is defined as the passage of three or more unformed stools per day. Diarrhea stools may be categorized as soft (takes the shape of the container) or watery (can be poured or soaks into a diaper).

Minimal Diagnostic Criteria for Inclusion into Study: Enrolled patients must have diarrhea (as defined above) and must have *G. lamblia* as **the sole identifiable pathogen**. Up to three

stool samples or a single small-bowel sample may be needed for diagnosis. Stool specimens should be mixed, placed in fixative, concentrated, and examined by both wet mount and permanent stain according to accepted techniques. Giardia (in cyst and/or trophozoite form) must be only the intestinal pathogen identified in stools, intestinal fluid, or biopsy specimens.

Study Elements

Inclusion Criteria: The patients enrolled should have diarrhea and should have Giardia organisms demonstrated in appropriate samples of the intestinal contents. Adults must also have one or more of the following enteric symptoms: abdominal pain or cramps, nausea, vomiting, tenesmus, or malabsorption.

Exclusion Criteria: Patients are to be excluded if the following conditions exist: the presence of an additional intestinal pathogen that might contribute to the presenting symptoms; chronic gastro-intestinal illness: the receipt of drug(s) known to affect intestinal motility or diarrhea: and/or the receipt of antimicrobial drugs other than the study drugs during the clinical trial.

Selection of the Comparison Drug: For symptomatic patients, an active control drug should be used. Quinacrine hydrochloride and furazolidone are currently approved for this purpose. After consultation with and review by the FDA, metronidazole may also be considered as the active control drug. From the existing literature, it is expected that the cure rate would be 85-95% for quinacrine, 70-80% for furazolidone, and 80-90% for metronidazole.

Study Design and Stratification: A randomized, double-blind, prospective study design with an active (or placebo) control should be employed whenever possible. For active control studies, the sample size should be adequate to show a 20% difference in outcomes with 80% statistical power. Before treatment, all symptoms should be quantified by severity, frequency, and duration and methods of scoring should be clearly stated. Stratification may be by age, epidemiological circumstances and immune status.

Definitions of Responses to Therapy: At a minimum, all patients must be seen before treatment and at follow-up 48 hours to 7 days after completing a course of therapy. Participants will furnish follow-up stool samples 48 hours to 7 days after completing therapy. Test of Clinical Cure *Wellness* may be defined as the first 24-hour period during which the patient experiences no symptoms and passes no watery stools and no more than two soft stools or as the first 48-hour period during which the patient experiences no symptoms and passes no unformed stools. *Continuing illness* is defined as the passage of any number of watery stools, the passage of more than two soft stools per 24 hours, or the presence of enteric symptoms plus the passage of any number of soft or watery stools during a 48-hour observation period. *Clinical treatment failure* is defined as clinical deterioration or worsening of symptoms after at least 24 hours of treatment or as continuing illness after 5 full days of treatment with the study medication or the control drug. Test of Microbiological Cure Two stool samples collected at least 48 hours after the last dose of medication must be free of both Giardia cysts and Giardia trophozoites.

Timetable for microbiological and clinical procedures (guideline's Table 1, S248):

Time frame	Microbiological procedure	Clinical procedures
Before treatment (-48 to 0 Hours)	Detect Giardia in stool or small-bowel fluid	Take history: perform physical examination: begin diary: do blood counts, chemistry profile: obtain informed consent

During treatment	None	Administer study or control drug Maintain daily diary; monitor for potential toxicity
After treatment (48 h to 7 days)	Collect follow-up stool samples	Maintain diary: perform follow-up examination

Methods of Presenting and Analyzing Data: The outcome variables to be compared are mean number of unformed stools per day of study, mean number of unformed stools for the treatment period, mean number of days the patients were symptomatic (passage of any number of unformed stools plus-for-adults-a symptom): median time from treatment to passage of last unformed stool; and numbers of overall microbiological eradications, microbiological eradications/clinical failures, and clinical cures. Criteria for clinical and microbiological efficacy may be determined in four ways. 1) Symptoms of diarrhea abate. 2) The duration of diarrhea is shortened (clinical cure). 3) Stool form improves. 4) The infectious organism is eradicated (microbiological cure). G. lamblia should be the only infectious organism sought in post-treatment stools. For final assessment, microbiological outcome is paramount.

CONSULTS FOR THE NDA

Consult for Trade Name

Consults were requested for review of sponsor's trade name and proposed labeling for Cryptaz (nitazoxanide). In the consult request, it was noted that this drug was submitted for the treatment of diarrhea caused by Cryptosporidium parvum in patients with AIDS and a CD4+ count of < or equal to 200/mm^3 in December 1997 (NDA 20-871). The Labeling and Nomenclature Committee reviewed the name at that time and thought the proposed name was acceptable. A second name was also reviewed — around the same time and also deemed acceptable. However, this application was given a non-approvable.

The following Divisions within FDA were consulted **at this time** for review of the trade name "Cryptaz" from marketing and safety perspective.

Division of Drug Marketing, Advertising, and Communications (DDMAC)

DDMAC's review summary (dated October 11, 2002) was as follows:

> **The name Cryptaz is problematic because it suggests indications for Cryptaz, such as cryptosporidium and cryptococcus. I do not have any suggestions or objections to the alternate name —**

Division of Medication Errors and Technical Support (DMETS)

DMETS' review summary (dated October 16, 2002) was as follows:

> **DMETS does not recommend the use of the proprietary name "Cryptaz". In reviewing the proprietary name "Cryptaz", the primary concern raised was related to a look-alike and sound-alike name that already exists in the US marketplace. The product considered having the greatest potential for name confusion was Ceptaz. The DMETS Expert Panel expressed**

concern that Ceptaz and the proposed name Cryptaz sound and look similar, which could result in confusion between the two products. Both names contain two syllables, and the letter combination at the beginning of each name ("cep" vs. "cry") looks similar when scripted. Additionally, the endings of each name contain identical letter combinations ("ptaz"). In cases of complicated urinary tract infections, the recommended adult dose for Ceptaz is 500 mg, administered every 8 to 12 hours, which overlaps with the recommended Ceptaz and Cryptaz are available in powder form, requiring reconstitution before administration. Although the products differ in route of administration (oral vs. intravenous or intramuscular) and dosage forms (tablets or oral suspension vs. injection), the similarities in the look-alike and sound-alike properties of the name, in addition to the overlap in dosing strength and dosing regimen increase the risk of confusion between Ceptaz and Cryptaz.

MO COMMENT: The Applicant rebutted the above recommendations from our consults stating that "in selecting the name Cryptaz, we did not intend to imply that use of the product be limited to treatment of Cryptosporidium infections, nor did we intend to imply activity against Cryptococcus spp. The Latin root crypt means hidden. Our intent would be to associate Cryptaz with activity against pathogenic organisms such as Cryptosporidium parvum and Giardia lamblia that are hidden in the intestinal tracts of humans." The Applicant further commented that "There are a number of significant differences between Ceptaz® for Injection and Nitazoxinide for Oral Suspension (route of administration, packaging, indications, primary setting for use, primary distribution) that would mitigate any potential for confusion of the two products."

The Applicant has certainly presented valid reasons for proceeding with the trade name "Cryptaz". However, based upon the analysis by DMETS, there are enough safety concerns (similarities in the look-alike and sound-alike properties of the name) to warrant consideration of an alternative trade name. The Applicant was then asked to submit alternative candidate names to be reviewed by DDMAC and DMETS.

Following the above recommendation, the Applicant submitted an alternative candidate name: "ALINIA". This candidate name was posed to DDMAC and DMETS and was found to be acceptable by both Divisions. Hence, it is recommended that the trade name "Alinia" be used for nitazoxanide suspension.

Consults for Foreign Studies

Because all the controlled trials submitted as evidence for safety and efficacy of nitazoxanide were performed in foreign sites, the FDA DSI team (Drs. Antoine El Hage and Robert Shibuya) inspected the following three centers in three countries which performed the 5 trials reviewed in this NDA.

DSI Inspections: PERU
Juan Jave Ortiz, Cajamarca, September 2-6
DSI Reviewer Note (10/23/02) to the Division Re: Protocol #RM-NTZ-99-010 entitled "Randomized Comparative Study of Nitazoxanide and Metronidazole in the Treatment of Giardiasis in Children"

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

DSI Inspections: EGYPT
Samir Kabil, Cairo, October 28-November 1
DSI Clinical Inspections Summary (11/13/02) to the Division Re: protocols RM- & RM-NTZ-98-002

- It appears that the data from this site is acceptable for review.
- Screened in excess of 800 patients to randomize a total of 200 subjects
- Two contract labs performed the stool examinations (both of Cairo, Egypt.)
- The Egyptian Ministry of Health initailly grants a license to a laboratory when it commences operations and does not inspect unless it hears of complaints. Both labls had not had any problems and thus, had not been inspected since its initiation. lab is not and has not been accredited by College of American Pathologists.

DSI Inspections: ZAMBIA
M. Paul Kelly, Lusaka, November 4-8
DSI Clinical Inspections Summary (11/13/02) to the Division Re: protocols RM-3007 and RM-3008

- Screened 1538 patients to enroll a total of 100 subjects
- Records for all 50 subjects in protocol 3007 (HIV-negative) and about 30/50 subjects in protocol 3008 (HIV-positive) were reviewed in detail.
- All subjects were consented for the trial
- Deaths were adequately documented and were due to a sepsis-like picture.
- It appears that data from this site is acceptable for review
- While enrolled subjects met the inclusion and exclusion criteria, the study population used does not seem to be representative of the U.S. pediatric population. Subjects rended to be severely underweight and many had significant anemia and hepatic abnormalities. All subjects were hospitalized and placed on an alimentation program for the duration of the trial.
- The lab is not CAP accredited and dropped Extended Quality Assessment accreditation in 1997 due to a lack of funding, not an inability to meet the accreditation requirements. The laboratory equipment appeared antiquated although serviceable and the lab appeared well organized.

DSI Overall Conclusions

- With regard to the regulatory inspections, no significant violations were noted. Study subjects appeared to have been properly consented and protocol procedures had been followed.
- Data appear acceptable.

- Laboratories used to perform the stool examinations, my assessment is that the facilities and personnel were probably adequate although not to US standards.
- Subjects enrolled in protocol 3007 (Zambian children, HIV-negative) might not be reflective of the US population in that they tended to be severely malnourished and anemic.

CHEMISTRY/MANUFACTURING AND CONTROLS

Please see Dr. Gene Holbert's Chemist's Review of — NDA 21-498. According to Dr. Holbert, the chemistry issues specified in the non-approval letter to NDA 20-871 was adequately addressed for the current NDA submissions.

ANIMAL PHARMACOLOGY/TOXICOLOGY

Please see Dr. Steven Kunder's Pharmacology/Toxicology Review of NDA — 21-498. Due to the short duration course proposed in these applications, carcinogenesis studies were not submitted.

MICROBIOLOGY

Please see Dr. Kalavati Suvarna's Microbiologist's Review.
In brief, she presented the following to the Division's NTZ team on NDA day.

C. parvum in vitro studies

NDA 20-871 (previous study)	NDA — 21-498 (new)
• • •	• 1 study with MDBK cell line: >90%inhibition • No toxicity to cell line- reason not known. • 2 new studies w/ different cell line (A-549) • 40-50% inhibition • <11.2% toxicity • Azithromycin and Rifabutin used as comparators • Activity of NTZ in combo w/ azithromycin or rifabutin better than each of drug alone

Effect on different stages - 1 study

- No comparators were used
- Polyclonal antibodies to sporozoites that reacts with all stages
- based on the time of addition of drug when different stages would be observed in cell line
- Immunofluorescence
  Enzyme linked immunoassay
  Electron microscopy
- Some effect on the stages - **first time such an experiment was done.**

Stage	Inhibition by IF			Inhibition by EIA		
	NTZ	TZ	TZg	NTZ	TZ	TZg
Trophozoites 0 - 2 hours	74 %	46%	0%	60-75%	45 - 55%	10%

Type I meronts (8N) 2 - 6 hours	96%	63%	0%	50-75%	5%	35 - 45%
Type II meronts (4N)-Low	96%	75%	18%	-	-	-
Sexual stages 18-22 hours (gametocytes, gametes, oocysts)	92%	60%	0%	30%	50 - 55%	100%
All stages 2 - 46 hours	88%	58%	0%	75 - 80%	25%	70%

NTZ = Nitazoxanide; TZ = Tizoxanide; TZg = Tizoxanide glucuronide

C. parvum animal studies

NDA 20-871 (previous)	NDA — 21-498 (new)
• s	• **Suckling mice** - vehicle treated control - results of control ? Calculated results. (publication) tissue activity was not determined
•	• **Immunosuppressed rats**- decrease in oocyst counts in control animals with time-spontaneously cured Decrease in oocyst counts Decrease in mucosal infection
•	• **Gnotobiotic piglets** - no decrease in oocyst counts (publication) NTZ causes diarrhea

MO COMMENT: She summarized that some new information was added for the in vitro studies but the extent of the studies and the resultant data were underwhelming. In addition, she found the C. parvum animal studies to be inconclusive for definitive efficacy of nitazoxanide.

Microbiologic Assessments in Clinical Studies

C. parvum

- Oocysts are shed intermittently
- The optimum number of negative stool samples to confirm absence of protozoa has not been determined.

What is Recommended for micro studies of *C. parvum*

- 3 or more stool samples within 5 days be examined for clinical evaluation of new drugs
- concentrated stool samples
- examination of concentration of stool samples - 2 or more methods (staining, immunofluorescence assays, EIA)
- Staining:
  -Variation: due to thickness of smear, young oocysts less acid fast, older oocysts may be easily decolorized

-Misidentification
-Oocyst ghost unstained
-Auramine staining: less specific than acid fast; should be confirmed with acid-fast staining

- Immunoassays are more sensitive (Ag detection by immunofluorescence and EIA) compared to acid fast staining
  -can detect ghosts oocysts
  -background fluorescence due to particles in stool sample observed with IF

What was done for micro examination in the NDA's clinical studies
Parasitological examination - mainly by microscopic examination of stools and concentrated stools not used in the some studies.

***C. parvum* studies**	**Parasitological examination methods**	
RM-NTZ-98-002 (Non-AIDS) (n =100)	Ziehl Neelson acid-fast stained smears with **one drop of stool sample**	[redacted] immunoassay (11 patients)
RM-02-3007 (Non-AIDS) (n =50)	Auramine-phenol stained smears Unconcentrated and Concentrated stool samples	
RM-02-3008 (AIDS) (n = 50)	Same as RM-02-3007	

Giardia
Examination of 3 or more stool samples and staining of smear recommended. What was done?

***Giardia* studies**	**Parasitological examination methods**	
[redacted] (adults) (n =100; 22 with Giardiasis)	Direct microscopic examination of unconcentrated and concentrated stool	[redacted] immunoassay (16 patients)
RM-99-010 (children) (n =110)	Direct microscopic examination of unconcentrated and concentrated stool- **NO quantitative results**	

MO COMMENT: *She summarized that the microbiological assessments throughout the 5 studies were sub-optimal for both C. parvum and G. lamblia examinations in light of the current laboratory methodologies and the usual recommended procedures.*

HUMAN PHARMACOKINETICS/PHARMACODYNAMICS

Please see Dr. Dakshina Chilukuri's Biopharmaceutics Review. The following is his executive summary and recommendations.

Executive Summary

The applicant is seeking approval of Cryptaz® (Nitazoxanide) — for Oral Suspension in — 21-498, respectively. The proposed indications are treatment of chronic diarrhea pediatric patients due to *Cryptosporidium parvum* (*C. parvum*) and *Giardia lamblia* (*G.lamblia*). The drug is to be taken with food.

Nitazoxanide is a salicylamide acetate ester, which has demonstrated in vitro activity against the intracellular parasite C. parvum. The pharmacokinetics of the drug has been characterized in healthy normal subjects and in AIDS patients. Pharmacokinetic studies in humans and experimental animals have failed to detect parent nitazoxanide in plasma, urine, or fecal samples. Nitazoxanide is rapidly desacetylated to tizoxanide (desacetylnitazoxanide) in biological fluids, most likely by a combination of nonspecific esterase activity and spontaneous hydrolysis. Thus, the plasma concentration-time curves of tizoxanide have been monitored in clinical and preclinical pharmacokinetic studies.

The applicant previously submitted an NDA 20-871 in 1997 for the approval of nitazoxanide to treat AIDS patients with chronic diarrhea due to C. parvum. Following recommendations of the Anti-Infectives Advisory Committee, the applicant was issued a non-approvable letter indicating deficiencies in the application. The applicant has since submitted these new NDA — 21-498 for nitazoxanide suspension respectively with additional data. — The powder for suspension in NDA 21-498 is targeted for pediatric patients of ages 12 months to 11 years.

To support the approval of Cryptaz®, the applicant conducted studies B099597, RM01/02-1015 and 198.637; a bioequivalence study of a suspension and tablet formulations of nitazoxanide, a PK study in pediatric patients and a multiple dose study in healthy volunteers. Additional in vitro studies to evaluate intestinal permeability and the potential for interaction of nitazoxanide with cytochrome P450 enzymes were performed.

NDA 21-498 will be approved.

Thus, Cryptaz®will be approved for use in children to be administered as an oral suspension.

Recommendations

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation III has reviewed the information included in original — 21-498 for Nitazoxanide and suspension. The Human Pharmacokinetics and Bioavailability Section of — 21-498 has met the requirements of the 21 CFR 320 and the clinical pharmacology labeling requirements of 21 CFR 201.56.

Administration with food: The bioequivalence data, when viewed together with the food-effect data and the efficacy data indicate that the drug should not be administered with food. This is required to achieve high local concentrations in the gastrointestinal tract where the site of action resides.

Drug Interaction Studies: Nitazoxanide showed potential to inhibit cytochrome P450 2C9. However, since only tizoxanide can be determined in the systemic circulation, the clinical relevance of this study is not clear. It is recommended that the applicant repeat the in vitro drug-drug interaction studies with tizoxanide.

In Vitro Transfer across the Epithelial Barrier: It is recommended that the applicant investigate in vitro transfer of tizoxanide across the digestive epithelium. This is because it is not known to what extent conversion of nitazoxanide to tizoxanide occurs prior to absorption through the gut wall.

Dissolution: Based on the review of the submitted dissolution data, OCPB considers that the proposed dissolution method for both the tablet and suspension (i.e., USP Apparatus 2, rotation speed of 100 rpm, and dissolution medium of phosphate buffer at pH 7.5 with 6% hexadecyltrimethyl ammonium bromide), is acceptable. Specifications should be as follows

- For the suspension, NLT —% (Q) of the labeled amount dissolved as nitazoxanide and tizoxanide combined at 30 minutes
- For the tablet, NLT — % (Q) of the labeled amount dissolved as nitazoxanide and tizoxanide combined at — minutes

The applicant is being contacted to determine if dissolution studies have been performed at lower agitation speeds. If dissolution data at lower speeds are not available, then a recommendation to perform the studies will be made.

Labeling: Please note that the additional labeling information could be based on the applicant studies or on information published in the literature.

> ***MO COMMENT:*** *The dissolution issue was resolved satisfactority between the FDA's Biopharmaceutics Reviewers and Romark Laboratories Inc.*

FOREIGN EXPERIENCE

(taken directly from the Applicant's submission)

List of Countries in which Nitazoxanide Has Been Approved for Marketing

Country	Date Approved for Marketing
Mexico	July 19, 1996
Paraguay	May 22, 1997
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
Brazil	March 21, 2001

The product has been marketed in each of the countries listed above except for Brazil and Paraguay where marketing has not yet been initiated.

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.

The dose and duration of treatment used for the product in these Latin American countries is the same as that proposed in this application: — 200 mg twice daily for 3 days in children aged 4 to 11 years, and 100 mg twice daily for 3 days in children aged 12 to 47 months.

More than 6 million courses of the 3-day treatment regimen (about 2.5 million in children ≤ 11 years) have been sold in Latin America since 1996 with the large majority of these being sold in Mexico. The Applicant has stated in the NDA that no adverse experiences related to the use of nitazoxanide in Latin America have been reported to or otherwise come to the attention of Romark Laboratories.

Post Marketing Experience from Foreign Countries

The approvals for nitazoxanide are all foreign as discussed above. This is a new molecular entity seeking approval in the United States. Post-marketing experience is also as above with the most information from use in countries of Latin America.

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CLINICAL STUDIES

Integrated Review of Efficacy

Overview of Adequate and Well-Controlled Studies

The Applicant has submitted five controlled clinical studies to substantiate the efficacy of a three-day course of treatment with nitazoxanide in treating diarrhea caused by *Cryptosporidium parvum* and *Giardia lamblia*.

RM-NTZ-98-002	A double-blind placebo-controlled study in adults and children with diarrhea caused by *C. parvum* EGYPT (n=50 adults and n=49 children)
RM02-3007	A double-blind placebo-controlled study in HIV-seronegative children with diarrhea caused by *C. parvum* ZAMBIA (n=50 children)
RM02-3008	A double-blind placebo-controlled study in HIV-seropositive children with diarrhea caused by *C. parvum* ZAMBIA (n=50 children)
—	—
RM-NTZ-99-010	A single-blind metronidazole-controlled study in children with diarrhea caused by *G. lamblia* PERU (n=92 children)

One of these studies (RM-NTZ-98-002) evaluated the efficacy of both the 500 mg tablets and the pediatric suspension, another (—) evaluated the efficacy of the tablets, and the remaining three evaluated the efficacy of the pediatric suspension.

Each of the studies was designed based on guidelines published for evaluation of new drugs for treating diarrhea caused by *G. lamblia*. Each study evaluated clinical and parasitological response approximately 4 days after the end of treatment as well as time from initiation of treatment to passage of last unformed stool. Clinical responses were assigned as either "Well", "Continuing illness", or "Clinical treatment failure" based upon definitions provided in the guidelines (see Regulatory Guidance section above). Parasitological response was assessed based on two follow-up stool examinations collected 4 to 7 days after the end of treatment.

> ***MO COMMENT:*** *There are significant deviations from the guideline* ***(Cooperstock M et al. Evaluation of New Anti-Infective Drugs for the Treatment of Diarrhea Caused by Giardia lamblia. Clinical Infectious Diseases 1992; 15(Suppl 1): S244-8)*** *which are worthy of note.*

1) *The guideline states that the stool examinations used for enrollment should be within 48 hours prior to Day 0 of study. In three of the above 5 studies, the initial parasitological assessment that was used for enrollment into study was within 7 days (screening study). To further confuse the issue, the two Zambian studies repeated the stool examination at Day 0 and excluded patients (who had positive stool examinations from screening) from analysis if the stool examination from Day 0 was negative. This issue (and how it was resolved for data analysis) will be further discussed in later sections.*
2) *The guideline is very clear that studies should be conducted in patients with "sole pathogen". For both of the Egyptian studies in these NDAs, there were significant numbers of subjects who were not enrolled with "sole pathogen" under study.*
3) *As discussed under the brief summary of the microbiology review above (please see Dr. Suverna's complete microbiological review), the parasitological assessments in all 5 studies (for both C. parvum and G. lamblia) were sub-optimal (i.e. minimal verification by immunoflorescence for C. parvum; no quantification or verification by enzyme immunoassay for G. lamblia).*

The doses of nitazoxanide used were the same for each of the studies.

- Adults and adolescents (>11 years): one nitazoxanide 500 mg tablet every 12 hrs for 3 days with a meal.
- Children age 4 to 11 years: 10 mL of nitazoxanide suspension every 12 hrs for 3 days with a meal.
- Children age 12 months to 47 months: 5 mL of nitazoxanide suspension every 12 hrs for 3 days with a meal.

Each of the studies was conducted in foreign countries where these infections are endemic and conducted in three different populations in three different parts of the world by three different teams of investigators.

***MO COMMENT:** The MO reviewed a 15% random sample of the patients from Studies 98-002, 3007, 3008, [redacted] and 99-010, all the original case report forms of patients with serious adverse events from study 3007, and all the G. lamblia baseline pathogen positive patients from Study [redacted]. The MO reviewed the exclusion/inclusion criteria, dates of the visits, clinical signs and symptoms, concomitant medications and indications, microbiology findings, Evaluability determinations, and assignment outcomes. The MO agreed with the Applicant's determinations for the patients in the samples reviewed. Therefore the Applicant's analyses were accepted.*

In addition to these reviews, the MO also performed additional sensitivity analyses in conjunction with the team statistician (Dr. Jyoti Zalkikar).

These additional exploratory reviews and their associated analyses are described within the related sections of this review.

The Applicant has presented the integrated efficacy by each pathogen (three studies as evidence for efficacy for C. parvum and two studies as evidence for efficacy for G. lamblia). ***In this integrated efficacy review, I will present the efficacy evidence by pathogen AND by the NDA in the following order.*** *It is also important to bear in mind that the Applicant is seeking the indications for not only treating the clinical symptoms of diarrhea from these two pathogens,*

1)

2) NDA 21-498: Efficacy of NTZ for C. parvum diarrhea (clinical and microbiological claims) in patients taking the 100 mg/ 5 mL Oral Suspension (Children 1-11 years)

3)

4) NDA 21-498: Efficacy of NTZ for G. lamblia diarrhea (clinical and microbiological claims) in patients taking the 100 mg/ 5 mL Oral Suspension (Children 1-11 years)

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Diarrhea caused by C. *Parvum* in non-AIDS Children: NDA 21-498

Efficacy of NTZ for *C. parvum* diarrhea (clinical and microbiological claims) in patients taking the 100 mg/ 5 mL Oral Suspension (Children 1-11 years)

Efficacy evidence of NTZ for *C. parvum* diarrhea in children taking the Oral suspension is presented from two studies. The first study is the 98-002 study discussed above under the adult data. Of the one-hundred subjects enrolled in that study, half of the patients were children (1-11 years of age) and took the oral suspension. Data from one child was excluded from the analyses because his mother changed her mind about participation in the study and returned all of the child's study medication. According to the protocol, the clinical response of another child with a positive stool culture for *Salmonella* spp. was excluded from the analysis of clinical response (but not parasitological response).

Applicant's Table 3-1 from NDA —— Vol 1.61 gives the following summary efficacy data for children in study 98-002.

Table 7: Applicant's Summary Efficacy for Study 98-002, NDA 21-498

	Nitazoxanide	Placebo	P (Fisher's exact test; one-sided)
Clinical response			
All children	21/24 (88%)	9/24 (38%)	.0004
Age 1-3	10/11 (91%)	4/11 (36%)	.01187
Age 4-11	11/13 (85%)	5/13 (38%)	.0207
Parasitological response			
All children	18/24 (75%)	6/25 (24%)	.0001
Age 1-3	8/11 (73%)	2/14 (14%)	.0431
Age 4-11	10/13 (77%)	6/25 (24%)	.0016
Median time from ITPLUS*			
All children	3.5 days	>6 days	.0001

*initiation of treatment to passage of last unformed stool

The differences in response rates by treatment group was significant for children below the age of 12 for both primary endpoints as well as the differences in response rates for the secondary endpoint of median time from initiation of treatment to passage of last unformed stool.

The following is the FDA's statistical reviewer's analysis of response rates for children in this study. Shown alongside the response rates is the Kappa Statistic. As previously mentioned, this Kappa Coefficient is a quantitative measure of reproducibility of drug benefit measured in two ways. In this case, the Kappa Coefficient measures the correlation between the clinical response and the