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

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

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

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

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

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

Treatment Regimen:

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

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

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

Content and Review of Resubmission:

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

lamblia comparing the tablet, suspension and placebo, (2) [redacted] (3) a dissolution method for the tablet*. The resubmission was accepted for review.

* Per review by the clinical pharmacologist, Dr. Chilukuri, the dissolution method for the tablet, USP Apparatus 2, rotation speed of [redacted], dissolution medium of [redacted] is acceptable.

Evaluation of Efficacy and Resulting Labeling:

Giardia lamblia

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

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

Patients with diarrhea (mean duration = 5 days) were screened for the presence of cysts before enrollment and at enrollment using several procedures (unconcentrated stool stained with iodine or immunofluorescence, concentrated stool stained with iodine). Signs and symptoms were collected and patients were randomized into one of three treatment arms and treated with 500 mg BID PO x 3 days. Follow up clinical and parasitological evaluation was performed 4-7 day after the end of therapy (day 7-10 of study), parasitological outcome was assessed again at 11-14 days after the end of therapy (day 14-17 of study). The clinical outcome was judged as (a) wellness = no symptoms, no watery stools, no more than 2 soft stools, no hematochezia in 24 hours; no symptoms and no unformed stools in 48 hours, (b) continuing illness or (c) clinical treatment failure. Results are presented in the table below. In study 3011, it was noted that in some patients, the cyst count was reduced at the first visit but rebounded at the second; no clinical evaluation was done at that visit. The applicant indicated that Peru is hyperendemic for *Giardia* so patients may have ingested more cysts. While no clinical outcome was formally obtained, the applicant further wrote that investigators did no comment about complaints or relapsed symptoms at the last visit. [redacted] Meanwhile, the applicant's request for labeling [redacted] ' will again not be granted. The drug is effective clinically, so the labeling will reflect both the clinical and

parasitologic findings from these studies and advise that patients should be managed based on clinical findings.

RM01-3011 Peru, Egypt 3 arm study comparing tablet, suspension and placebo	**Adult patients , sole pathogen** (MOR p 64, 72)			
		Tablet	Placebo	
	Clinical *	46/54 (85%)	12/27 (44%)	P=0.0002
	Microbiology *	30/54 (56%)	5/27 (19%)	P=0.0019
	Microbiology **	22/45 (49%)	3/12 (25%)	P=0.1953
		Tablet	Suspension	95% C.I.
	Clinical *	46/54 (85%)	45/54 (83%)	-13.5, +17.1
	Microbiology *	30/54 (56%)	26/54 (48%)	-12.4, +26.4
	Microbiology **	22/45 (49%)	24/43 (56%)	-15.3, +26.3
98-001 Egypt	**Adult patients, sole pathogen** (original MOR p 49)			
		Tablet	Placebo	P value
	Clinical	8/8 (100%)	3/10 (30%	< .02
	Microbiology	6/8 (75%)	0/10 (0%)	< .008

* Evaluation done at 4-7 days after completing therapy (Day 7-10 of study), clinical outcome of "well" and parasitologic eradication of organism

** Evaluation done at 11-14 days after completing therapy (Day 14-17 of study), patients with negative cultures

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

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

> **Diarrhea caused by *Giardia lamblia:***
> Alinia for Oral Suspension (patients 1 year of age and older) and Alinia Tablets (patients 12 years and older) are indicated for the treatment of diarrhea caused by *Giardia lamblia.*

The CLINICAL STUDIES section will reflect the findings from the two studies of tablets (and already reflects the study results with the oral suspension):

CLINICAL STUDIES

Diarrhea caused by *Giardia lamblia* in adults and adolescents 12 years of age or older:

In a double-blind, controlled study (Study 1) conducted in Peru and Egypt in adults and adolescents with diarrhea caused by *Giardia lamblia*, a three-day course of treatment with Alinia Tablets administered 500 mg BID was compared with a placebo tablet and Alinia for Oral Suspension administered 500mg/25mL of suspension BID for 3 days. A second double-blind, controlled study (Study 2) conducted in Egypt in adults and adolescents with diarrhea caused by *Giardia lamblia* compared Alinia Tablets administered 500 mg BID for 3 days to a placebo. For both of these studies, clinical response was evaluated 4 to 7 days following the end of treatment. 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.' The following clinical response rates were obtained:

Adult and Adolescent Patients with Diarrhea Caused by *Giardia lamblia*

Clinical Response Rates* 4 to 7 Days Post-therapy

% (Number of Successes/Total)

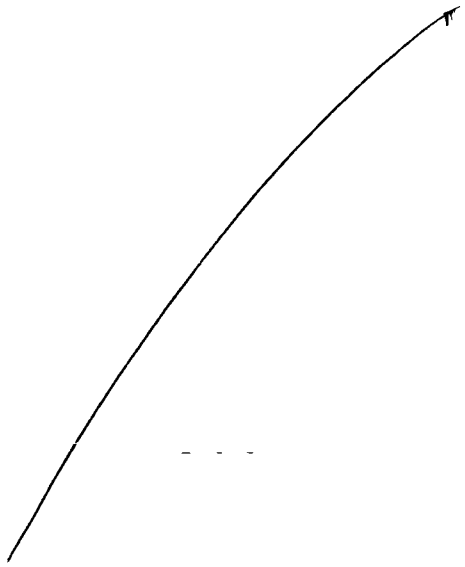
	Alinia Tablets	Alinia for Oral Suspension	Placebo Tablets
Study 1	85% (46/54)¶§	83% (45/54)¶§	44% (12/27)
Study 2	100% (8/8)	-	30% (3/10)

* Includes all patients randomized with *Giardia lamblia* as the sole pathogen. Patients failing to complete the studies were treated as failures.

¶ Clinical response rates statistically significantly higher when compared to placebo.

§ The 95% confidence interval of the difference in response rates for the tablet and suspension is (-14%, 17%).

Some of the patients with 'well' clinical responses had *Giardia lamblia* cysts in their stool samples 4 to 7 days following the end of treatment. The relevance of stool examination results in these patients is unknown. Patients should be managed based upon clinical response to treatment.



HIV-infected or Immunodeficient Patients

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

HIV-Infected or Immunodeficient Patients

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

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

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

Evaluation of Safety:

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

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

Alinia Tablets: In controlled and uncontrolled clinical studies of 1,628 HIV-uninfected patients age 12 years and older who received various dosage regimens of Alinia Tablets, the most common adverse events reported regardless of causality assessment were: abdominal pain (6.7%), diarrhea (4.3%), headache (3.1%) and nausea (3.1%). In placebo-controlled clinical trials using the recommended dose, the rates of occurrence of these events did not differ significantly from those of the placebo. In placebo-controlled trials of HIV-uninfected patients age 12 years and older who received Alinia Tablets for the treatment of diarrhea caused by *Giardia lamblia*, approximately 1% of patients discontinued therapy because of an adverse event.

Adverse events occurring in less than 1% of the patients age 12 years and older participating in clinical trials of Alinia Tablets are listed below:
Body as a Whole: asthenia, fever, pain, allergic reaction, pelvic pain, chills, chills and fever, flu syndrome.
Nervous System: dizziness, somnolence, insomnia, tremor, hypesthesia.
Digestive System: vomiting, dyspepsia, anorexia, flatulence, constipation, dry mouth, thirst.
Urogenital System: discolored urine, dysuria, amenorrhea, metrorrhagia, kidney pain, edema labia.
Metabolic & Nutrition: increased SGPT.
Hemic & Lymphatic Systems: anemia, leukocytosis.
Skin: rash, pruritus.
Special Senses: eye discoloration, ear ache.
Respiratory System: epistaxis, lung disease, pharyngitis.
Cardiovascular System: tachycardia, syncope, hypertension.
Muscular System: myalgia, leg cramps, spontaneous bone fracture.

Recommendations:

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

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

/S/

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

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/s/

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

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

NDA REGULATORY FILING REVIEW

NDA # **21-497** Supplement # **N/A** SE1 SE2 SE3 SE4 SE5 SE6 SE7 SE8

Trade Name: **Alinia**
Generic Name: **nitazoxanide**
Strengths: **500 mg**

Applicant: **Romark Laboratories, L.C.**

Date of Application: **May 29, 2002 (resubmission: January 28, 2004)**

Date of Receipt: **May 29, 2002 (resubmission: January 29, 2004)**
Date clock started after UN: **N/A**
Date of Filing Meeting: **Complete response meeting: March 3, 2004**
Filing Date: **July 28, 2002**
Action Goal Date (optional): **July 14, 2004** User Fee Goal Date: **July 29, 2004**

Indication(s) requested: **Treatment of diarrhea caused by Giardia lamblia**

Type of Original NDA: (b)(1) **X** (b)(2) _____
OR
Type of Supplement: (b)(1) _____ (b)(2) _____
NOTE: A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). If the application is a (b)(2) application, complete the (b)(2) section at the end of this review.

Therapeutic Classification: S _____ P **X**
Resubmission after withdrawal? **No** Resubmission after refuse to file? **No**
Chemical Classification: (1,2,3 etc.) _ original submission = **type 1 (NME); now class 3 (new formulation)**_
Other (orphan, OTC, etc.) **Orphan**

User Fee Status: Paid _____ Exempt (orphan, government) **X**
Waived (e.g., small business, public health) _____

Form 3397 (User Fee Cover Sheet) submitted: YES NO
User Fee ID # **N/A**
Clinical data? YES **X** NO, Referenced to NDA # _____

Is there any 5-year or 3-year exclusivity on this active moiety in either a (b)(1) or a (b)(2) application?

YES NO

If yes, explain:
At the original time of filing, there was no exclusivity, but now, at resubmission of the approvabled application, there is (on the suspension). Romark's nitazoxanide suspension was approved on 11/22/02, so it has exclusivity through 11/22/07 (NCE) and 11/22/09 (ODS).

Does another drug have orphan drug exclusivity for the same indication? YES NO

If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]?

YES [NO]

At the original time of filing, there was no exclusivity, but now, at resubmission of an approvabled application, there is (on the suspension). This is the same product in a different form (both submitted at the same time by Romark).

Is the application affected by the Application Integrity Policy (AIP)? YES [NO]
If yes, explain.

If yes, has OC/DMPQ been notified of the submission? N/A YES NO

- Does the submission contain an accurate comprehensive index? [YES] NO
- Was form 356h included with an authorized signature? [YES] NO
  If foreign applicant, both the applicant and the U.S. agent must sign.
- Submission complete as required under 21 CFR 314.50? [YES] NO
  If no, explain:
- If an electronic NDA, does it follow the Guidance? [N/A] YES NO
  If an electronic NDA, all certifications must be in paper and require a signature.
  Which parts of the application were submitted in electronic format?

  Additional comments:
- If in Common Technical Document format, does it follow the guidance? [N/A] YES NO
- Is it an electronic CTD? [N/A] YES NO
  If an electronic CTD, all certifications must be in paper and require a signature.
  Which parts of the application were submitted in electronic format?

  Additional comments:
- Patent information submitted on Form 3542a? [YES] NO
- Exclusivity requested? YES, _____years [NO]
  Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.
- Correctly worded Debarment Certification included with authorized signature? [YES] NO
  If foreign applicant, both the applicant and the U.S. Agent must sign the certification.

  NOTE: Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e.,

"[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as "To the best of my knowledge . . . ."

- Financial Disclosure forms included with authorized signature? [YES] NO
  (Forms 3454 and 3455 must be used and must be signed by the APPLICANT.)

- Field Copy Certification (that it is a true copy of the CMC technical section)? [YES] NO

Refer to 21 CFR 314.101(d) for Filing Requirements

- PDUFA and Action Goal dates correct in COMIS? [YES] NO
  If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.

- Drug name/Applicant name correct in COMIS? [YES] NO
  If not, have the Document Room make the corrections.

- List referenced IND numbers: —

- End-of-Phase 2 Meeting(s)? Date(s) _____ [NO]
  If yes, distribute minutes before filing meeting.

- Pre-NDA Meeting(s)? Date **9/19/01** NO
  If yes, distribute minutes before filing meeting.

Project Management

- All labeling (PI, PPI, MedGuide, carton and immediate container labels) consulted to DDMAC?
  [YES] NO

- Trade name (plus PI and all labels and labeling) consulted to ODS/DMETS? [YES] NO

- MedGuide and/or PPI (plus PI) consulted to ODS/DSRCS? [N/A] YES NO

- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling, submitted?
  [N/A] YES NO

If Rx-to-OTC Switch application:

- OTC label comprehension studies, all OTC labeling, and current approved PI consulted to ODS/DSRCS?
  [N/A] YES NO

- Has DOTCDP been notified of the OTC switch application? [N/A] YES NO

Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff?
  [N/A] YES NO

Chemistry

- Did applicant request categorical exclusion for environmental assessment? [YES- in 2002] NO
  If no, did applicant submit a complete environmental assessment? YES NO
  If EA submitted, consulted to Nancy Sager (HFD-357)? YES NO
- Establishment Evaluation Request (EER) submitted to DMPQ? [YES- in 2002] NO
- If a parenteral product, consulted to Microbiology Team (HFD-805)? [N/A] YES NO

If 505(b)(2) application, complete the following section: N/A

- Name of listed drug(s) and NDA/ANDA #:
- Describe the change from the listed drug(s) provided for in this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsules to solution").
- Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? (Normally, FDA will refuse-to-file such NDAs.) YES NO
- Is the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (See 314.54(b)(1)). If yes, the application should be refused for filing under 314.101(d)(9). YES NO
- Is the rate at which the product's active ingredient(s) is absorbed or otherwise made available to the site of action unintentionally less than that of the RLD? (See 314.54(b)(2)). If yes, the application should be refused for filing under 314.101(d)(9). YES NO
- Which of the following patent certifications does the application contain? Note that a patent certification must contain an authorized signature.

  ____ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA.

  ____ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired.

  ____ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire.

  ____ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted.

  IF FILED, and if the applicant made a "Paragraph IV" certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must submit a signed certification that the patent holder

was notified the NDA was filed [21 CFR 314.52(b)]. Subsequently, the applicant must submit documentation that the patent holder(s) received the notification ([21 CFR 314.52(e)].

____ 21 CFR 314.50(i)(1)(ii): No relevant patents.

____ 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications.

____ 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above.)
____ Written statement from patent owner that it consents to an immediate effective date upon approval of the application.

- Did the applicant:
  - Identify which parts of the application rely on information the applicant does not own or to which the applicant does not have a right of reference? YES NO
  - Submit a statement as to whether the listed drug(s) identified has received a period of marketing exclusivity? YES NO
  - Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug? N/A YES NO
  - Certify that it is seeking approval only for a new indication and not for the indications approved for the listed drug if the listed drug has patent protection for the approved indications and the applicant is requesting only the new indication (21 CFR 314.54(a)(1)(iv).? N/A YES NO
- If the (b)(2) applicant is requesting exclusivity, did the applicant submit the following information required by 21 CFR 314.50(j)(4):
  - Certification that each of the investigations included meets the definition of "new clinical investigation" as set forth at 314.108(a). YES NO
  - A list of all published studies or publicly available reports that are relevant to the conditions for which the applicant is seeking approval. YES NO
  - EITHER
    The number of the applicant's IND under which the studies essential to approval were conducted.

    IND # _____ NO

    OR
    A certification that it provided substantial support of the clinical investigation(s) essential to approval if it was not the sponsor of the IND under which those clinical studies were conducted?

    N/A YES NO
- Has the Director, Div. of Regulatory Policy II, HFD-007, been notified of the existence of the (b)(2) application?

  YES NO

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/s/

Kristen Miller
7/9/04 09:13:29 AM
CSO

Teleconference Minutes

Teleconference Date: June 23, 2004

Application Numbers: NDA 21-497 - Alinia (nitazoxanide)

Sponsor: Romark Laboratories, L.C.

Attendees:

Romark Laboratories, L.C.

Marc Ayers, Ph.D.	President

FDA- Division of Special Pathogen and Immunologic Drug Products

Steve Gitterman, M.D.	Deputy Director, Division of Special Pathogen and Immunologic Drug Products (DSPIDP)
Joette Meyer, Pharm.D.	Clinical Reviewer
Kristen Miller, Pharm.D.	Regulatory Project Manager

Background

On January 28, 2004, Romark submitted a complete response to the November 22, 2002 approvable letter for NDA 21-497 Alinia® (nitazoxanide) Tablets. Study RM01-3011 was included in this submission. The Review Team requested a telecon with Romark to receive clarification on the parasitological and clinic response at the follow-up visit (i.e., Day 14) for this study. *(Romark's comments are in italics)*

Discussion

The study of *Giardia lamblia* in adult and adolescent patients (Study RM01-3011) had a test of cure visit at Day 7 during which both clinical and parasitological response was assessed. Parasitological response was assessed again at the follow-up visit on Day 14, but clinical response was not recorded at this visit. During the clinical review of the study it was noted that the number of cysts in concentrated stool samples decreased between baseline and Day 7, but tended to rebound by Day 14, especially at the Peru study site. The Clinical Reviewer also noted that most published studies evaluating treatment of diarrhea caused by *Giardia lamblia* do not include a follow-up visit, so it is unclear if the finding of relapse/reinfection at Day 14 is particular to nitazoxanide or if it occurs with other drugs as well. Romark was asked to please provide their thoughts on the significance of the parasitological findings at Day 14. *There are many possibilities:*

1. *Peru is hyperendemic for Giardia, so patients may have ingested additional cysts.*
2. *All cysts may not have been eradicated by drug treatment.*

Are the patients clinically relapsing? *Clinical response was not measured at Day 14, but Romark would check to see if any additional data were recorded at the study sites. Additionally, giardiasis is often asymptomatic, and is not treated.*

The Division stressed that our interest in this issue is mainly academic and we are not questioning the design of the study; we just wanted to discuss this issue that has come up during the review of the NDA. If the application is approved, this issue could be handled in a few ways:

1. A sentence included in the labeling to state what the studies showed at both Day 7 and Day 14.
2.

Romark will discuss these options and respond. They thanked the Review Team for bringing this to their attention.

Action Items

1. Romark will submit a preferred plan of action regarding the parasitological findings on Day 14.

Addendum:

On June 30, 2004, Romark sent an email to the Division which stated that they believe the results of the post-treatment stool examinations obtained at the Peruvian site were attributable to the use of sensitive microbiological techniques in a population where *Giardia* is hyperendemic. Evaluation of clinical response was not performed again after the Day 7 visit, but the investigator did not report any complaints from patients with recurrent symptoms at Day 14.

Romark went on to say given (1) the proposed indication is "diarrhea caused by ...", (2) treatment of asymptomatic persons is not recommended, and (3) the interpretation of results of post-treatment stool examinations in asymptomatic patients can be difficult, they do not believe a discussion in the product's labeling of results of post-treatment stool examinations would be meaningful.

Minutes Preparer: Kristen Miller, Pharm.D.; Project Manager
Concur: Steve Gitterman, M.D., Ph.D., Deputy Director

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/s/

Kristen Miller
7/6/04 12:39:48 PM
CSO

Steven Gitterman
7/9/04 12:03:23 PM
MEDICAL OFFICER

Office of Drug Safety

Memo

To: Renata Albrect, M.D.
Director, Division of Special Pathogen and Immunologic Drug Products, HFD-590

From: Alina R. Mahmud, R.Ph.
Team Leader, Division of Medication Errors and Technical Support, Office of Drug Safety
HFD-420

Through: Carol Holquist, R.Ph.
Director, Division of Medication Errors and Technical Support, Office of Drug Safety
HFD-420

CC: Kristen Miller
Project Manager, HFD-590

Date: June 28, 2004

Re: ODS Consult 02-0186-2; Alinia (Nitazoxanide) Tablets 500 mg; NDA 21-497.

In response to a consult from the Division of Special Pathogen and Immunologic Drug Products (HFD-590), DMETS reviewed the proposed blister and container label as well as the carton and insert labeling for Alinia tablets (NDA 21-497). According to the Division, Alinia tablets will be approved for Giardia lambia indication. — — Alinia Oral Suspension, subject to NDA 21-498, was approved on November 22, 2002 for the treatment of diarrhea caused by Cryptosporidium parvum and Giardia lambia. Additionally, the Division is requesting that a combined package insert be devised for Alinia Oral Suspension and Tablets. To date, no medication error reports pertaining to the nomenclature, labeling and packaging have been submitted to the Agency.

In reviewing the labels and labeling for Alinia, DMETS identified areas of possible improvement in minimizing the potential for medication errors. DMETS notes that we were not given the opportunity to comment on the draft labels and labeling for Alinia Oral Suspension at the time of approval.

A. GENERAL COMMENTS

1. The — is distracting and should be deleted.

1 pages redacted from this section of the approval package consisted of draft labeling

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/s/

Alina Mahmud
7/2/04 09:57:37 AM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
7/2/04 10:04:01 AM
DRUG SAFETY OFFICE REVIEWER

2 Page(s) Withheld

1/28/04

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

PRESCRIPTION DRUG USER FEE COVER SHEET

Form Approved: OMB No. 0910-0297
Expiration Date: December 31, 2006.

See Instructions on Reverse Side Before Completing This Form

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. See exceptions on the reverse side. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment. Payment instructions and fee rates can be found on CDER's website: http://www.fda.gov/cder/pdufa/default.htm

1. APPLICANT'S NAME AND ADDRESS

Romark Laboratories, L.C.
6200 Courtney Campbell Causeway
Suite 200
Tampa, FL 33607

2. TELEPHONE NUMBER *(Include Area Code)*

(813) 282-8544

3. PRODUCT NAME

Alinia (nitazoxanide) Tablets, 500 mg

4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER

21-497

5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL?

☑ YES ☐ NO

IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM.

IF RESPONSE IS 'YES', CHECK THE APPROPRIATE RESPONSE BELOW:

☐ THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION.

☑ THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO:

NDA 21-497
(APPLICATION NO. CONTAINING THE DATA).

6. USER FEE I.D. NUMBER

N/A

7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.

☐ A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 *(Self Explanatory)*

☐ A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE *(See item 7, reverse side before checking box.)*

☑ THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act *(See item 7, reverse side before checking box.)*

☐ THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALLY *(Self Explanatory)*

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION? ☐ YES ☑ NO *(See item 8, reverse side if answered YES)*

Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
CBER, HFM-99
1401 Rockville Pike
Rockville, MD 20852-1448

and

Food and Drug Administration
CDER, HFD-94
12420 Parklawn Drive, Room 3046
Rockville, MD 20852

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SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE	TITLE	DATE
	President	1/28/2004

FORM FDA 3397 (12/03)

PSC Media Arts (301) 443-1090 EF

DIVISION DIRECTOR REVIEW

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

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

Date of Submission: May 29, 2002 (User Fee due date November 29, 2002)

Proposed Indications:

- Treatment of diarrhea caused by *Cryptosporidium parvum*
- Treatment of diarrhea caused by *Giardia lamblia*

Proposed Age Groups and Dosage Regimens:

- Age 12 years and above: 500 mg Tablets PO every twelve hours for 3 days
- 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

Purpose of Memorandum:

The purpose of this memorandum is to provide a brief summary of the Division's recommendations on these applications, including the scientific and regulatory issues surrounding the approval of nitazoxanide for oral suspension; and the deficiencies with the tablet formulation.

Background:

Nitazoxanide was first submitted to the Agency as IND on August 10, 1995, and on December 26, 1997, the NDA 20-871 for oral tablets was submitted for the proposed treatment of diarrhea caused by *Cryptosporidium parvum* in HIV positive patients. This application was taken to advisory committee, the committee voted that the studies did not show efficacy of the product in the proposed indication, and the application received a non-approvable letter on June 30, 1998. On August 31, 1999, IND was submitted to the Agency to evaluate nitazoxanide for oral suspension in children.

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

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

Most recently, on September 25, 2002, Romark submitted a complete response to NDA 20-871; the resubmission is currently under review.

Nitazoxanide is approved for marketing in multiple Central and South American countries. A reported — courses of therapy have been sold in Latin America.

Evaluation of Efficacy:

The applications contained results from 5 controlled clinical studies

RM-NTZ-98-002	A double-blind placebo-controlled study in adults and children with diarrhea caused by *C. parvum* (n=50 adults and n=49 children in Egypt)
RM02-3007	A double-blind placebo-controlled study in HIV-seronegative children with diarrhea caused by *C. parvum* (n=50 children in Zambia)
RM02-3008	A double-blind placebo-controlled study in HIV-seropositive children with diarrhea caused by *C. parvum* (n=50 children in Zambia)
RM-NTZ-98-001	A double-blind placebo-controlled study in adults with diarrhea caused by *G. lamblia* or *E. histolytica* (n=93 adults in Egypt)
RM-NTZ-99-010	A single-blind metronidazole-controlled study in children with diarrhea caused by *G. lamblia* (n=110 children in Peru)

The following factors were among those evaluated:

- Clinical outcome - clinical response from ≥ 3 unformed stools to no unformed stools by 7 ± 2 days after completing therapy, clinical response by patient
- Microbiological outcome - outcome in patients with *C. parvum* or *G. lamblia* as single pathogen, microbiology response by patient, culture at 7 ± 2 days and 10 ± 2 days after completing therapy
- Intra-patient clinical and microbiological correlation
- Safety

The results of the comparative clinical trials that evaluated the efficacy of NTZ in the treatment of these intestinal infections are provided in the tables below.

Results of Clinical Studies of *CRYPTOSPORIDIUM PARVUM*

Study & Site	Population	NTZ	Placebo	P value
98-002 Egypt	**HIV(-) pediatric patients** (MOR p 38)			
	Clinical	21/24 (88%)	9/24 (38%)	.0004
	Parasitological	18/24 (75%)	6/25 (24%)	.0001
	OTLUS*	3.5 days	> 6 days	.0001
3007 Zambia	**HIV(-) pediatric patients** (MOR p 41)			
	Clinical	14/25 (56%)	5/22 (23%)	.037
	Parasitological	13/25 (52%)	3/22 (14%)	.007
3008 Zambia	**HIV(+) pediatric patients treated for 3 days** (MOR p 44)			
	Clinical	2/25 (8%)	6/24 (25%)	.14
	Parasitological	4/25 (16%)	5/25 (20%)	1.0
	Mortality	5/25 (20%)	4/24 (17%)	1.0
98-002 Egypt	**HIV (-) adult patients** with single pathogen (MOR p36)			
	Clinical	15/21 (71%)	9/21 (43%)	.118
	Parasitological	12/21 (57%)	6/21 (29%)	.118

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

Results of Clinical Studies of *GIARDIA LAMBLIA*

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

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

Results of Safety Analyses

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

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

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

Recommendations for Regulatory Action [excepts from Dr. Rosemary Johann-Liang's Medical Officer Review]

- NDA 21-497 (nitazoxanide tablets) should receive an APPROVABLE action. Although NTZ treatment effect for diarrhea due to *G. lamblia* is suggested from studies RM-NTZ-98-002 and RM-NTZ-98-001, substantial evidence of efficacy has not yet been shown through these trials. , and the number of non-AIDS adult patients with *G. lamblia* as sole pathogens for study were too small to provide substantial evidence at this time. The applicant will need to demonstrate substantial efficacy in this population with adequate number of patients having the sole pathogen under study. It is further recommended that in future efficacy studies to garner this indication, the contribution of formulation-effect (the tablet and suspension formulations should be compared to each other and to placebo) as well as food-effect (fed-state versus fasting-state) be elucidated.

- NDA 21-498 (nitazoxanide oral suspension) should receive an APPROVAL action for the treatment of diarrhea due to *C. parvum* and *G. lamblia.* Clinical efficacy and safety of the product were adequately demonstrated for children 1 year to less than 12 years of age. Two adequate and well-controlled studies demonstrating that nitazoxanide oral suspension was superior to placebo were submitted for *C. parvum.* One adequate and well-controlled study was submitted demonstrating efficacy in *G. lamblia*; the results of these study were corroborated by evidence of superiority of

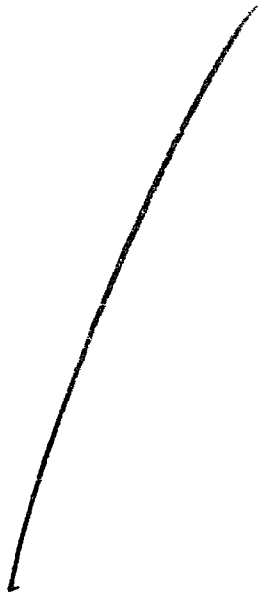
nitazoxanide tablets compared to placebo in a limited number of adults treated with diarrhea where *G. lambia* was the sole pathogen —

- The proposed trade name, Cryptaz, was unacceptable (see DMETS and DDMAC consults) and the company has chosen Alinia. This name was considered acceptable by the consultants.

Summary and Recommendations:

The Applicant has submitted two NDA's requesting approval of the indications listed above. Specifically, nitazoxanide for oral suspension has been evaluated in pediatric patients between the ages of 1 and 11 years, inclusive, while the oral tablet formulation has been evaluated in adult patients (ages > 12). The review team's recommendations are that the data for the oral suspension are adequate to recommend approval for this use (see package insert for oral suspension), while the information on the oral tablet is at present inadequate for approval. The latter, while inadequate for approval, are encouraging and do support further investigation of the tablet formulation (outlined in the approvable letter).

As presented in more detail above, the data are adequate to support the approval of the oral suspension in the treatment of the two indications in pediatric patients 1 through 11 years in age who are HIV negative and who do not have an immunodeficiency. The question was raised



In summary, while the data on the oral tablet and evidence of limited efficacy in adults is encouraging, the current data do not support approval of the tablet formulation or of the adult population. On note, the applicant has not requested that we consider approval based on extrapolation from pediatric patient and oral suspension data, and continues plans to develop the tablet formulation in adults.

In the approval letter for the oral suspension, the applicant has been asked to further characterize the pharmacokinetic profile of the oral suspension, and to monitor patient use or the product, specifically whether off label use and long-term use may occur.

In the approvable letter for the tablets, the applicant has been asked to further evaluate the efficacy of NTZ in adults with , *G. lamblia* as a single pathogen in adequate and well-controlled studies. Specifically, the applicant has been asked in these studies to address the microbiological response in each patient and correlate this with the clinical response in that patient. A request was made to consider evaluating the efficacy of the tablet as well as the oral suspension in adults.

/S/

Renata Albrecht, M.D.
Director
DSPIDP

/S/

Rigoberto Roca, M.D.
Medical Team Leader
DSPIDP

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/s/

Renata Albrecht
1/7/03 06:00:13 PM
MEDICAL OFFICER

Rigoberto Roca
1/7/03 06:02:56 PM
MEDICAL OFFICER

CONSULTATION RESPONSE

DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT
OFFICE OF DRUG SAFETY
(DMETS; HFD-420)

DATE RECEIVED: Sept. 20, 2002	**DUE DATE:** Nov. 29, 2002	**ODS CONSULT #:** 02-0186-1

TO: Renata Albrecht, M.D.
Director, Division of Special Pathogen and Immunologic Drug Products
HFD-590

THROUGH: Kristen Miller
Project Manager
HFD-590

PRODUCT NAME: **Alinia** (Nitazoxanide Tablets) 500 mg and (Nitazoxanide Oral Suspension) 100 mg/5 mL **NDA#: 21-497 and 21-498**	**NDA SPONSOR:** Romark Laboratories, L.C.

SAFETY EVALUATOR: Alina R. Mahmud, R.Ph.

SUMMARY: In response to a consult from the Division of Special Pathogen and Immunologic Drug Products (HFD-590), the Division of Medication Errors and Technical Support (DMETS) conducted a review of the proposed proprietary name "Alinia" to determine the potential for confusion with approved proprietary and established names as well as pending names.

NOTE: This review contains proprietary and confidential information that should not be released to the public.

DMETS RECOMMENDATION: DMETS has no objections to the use of the proposed proprietary name Alinia.

/S/

Carol Holquist, R.Ph.
Deputy Director
Division of Medication Errors and Technical Support
Office of Drug Safety
Phone: (301) 827-3242 Fax: (301) 443-9664

/S/

Jerry Phillips, R.Ph.
Associate Director
Office of Drug Safety
Center for Drug Evaluation and Research
Food and Drug Administration

Division of Medication Errors and Technical Support (DMETS)
Office of Drug Safety
HFD-420; Parklawn Rm. 6-34
Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: November 14, 2002

NDA# 21-497 and 21-498

NAME OF DRUG: **Alinia**
(Nitazoxanide Tablets)
500 mg
and
(Nitazoxanide Oral Suspension)
100 mg/5 mL

NDA HOLDER: **Romark Laboratories, L.C.**

*****NOTE: This review contains proprietary and confidential information that should not be released to the public.*****

I. INTRODUCTION:

This consult is written in response to a request from the Division of Special Pathogen and Immunologic Drug Products, for an assessment of the proposed proprietary name, Alinia. This is the second submission for the proprietary name review.

Cryptaz was previously reviewed by the CDER Labeling and Nomenclature Committee (LNC) on May 14, 1998 and found acceptable. However, on October 16, 2002, DMETS conducted a review and did not recommend to the use of the proposed proprietary name, Cryptaz.

PRODUCT INFORMATION

Alinia contains the active ingredient nitazoxanide, and is indicated for the treatment if diarrhea caused by *Cryptosporidium parvum* and *Giardia lamblia*, — — Clinical experience with nitazoxanide for — — — Therefore, Alinia is not indicated in these patients. Alinia will be available as a 500 mg tablet, and an oral suspension with a concentration of
100 mg/5 mL. The recommended dose in adults and adolescents 12 years of age and older is 500 mg every 12 hours for 3 days. In children ages 4 – 11 years old, the recommended dose is 10 mL (200 mg nitazoxanide suspension) every 12 hours for 3 days. In children 12 – 47 months of age, the recommended dose is 5 mL (100 mg nitazoxanide suspension) every 12 hours for 3 days. Both the tablets and the oral suspension should be taken with food.

II. RISK ASSESSMENT:

The medication error staff of DMETS conducted a search of several standard published drug product reference texts[1,2] as well as several FDA databases[3] for existing drug names which sound-alike or look-alike to Alinia to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's Text and Image Database[4] and the Saegis[5] Pharma-In-Use database were also conducted. An expert panel discussion was conducted to review all findings from the searches. In addition, DMETS conducted three prescription analysis studies consisting of two written prescription studies (inpatient and outpatient) and one verbal prescription study, involving health care practitioners within FDA. This exercise was conducted to simulate the prescription ordering process in order to evaluate potential errors in handwriting and verbal communication of the name.

A. EXPERT PANEL DISCUSSION

An Expert Panel discussion was held by DMETS to gather professional opinions on the safety of the proprietary name Alinia. Potential concerns regarding drug marketing and promotion related to the proposed name were also discussed. This group is composed of DMETS Medication Errors Prevention Staff and representation from the Division of Drug Marketing, Advertising, and Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

1. The Expert Panel identified three proprietary names that were thought to have the potential for confusion with Alinia. These products are listed in table 1 (see page 4), along with the usual dosage and available dosage forms.

2. DDMAC did not have concerns about the name Alinia with regard to promotional claims.

[1]MICROMEDEX Healthcare Intranet Series, 2000, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes the following published texts: DrugDex, Poisindex, Martindale (Parfitt K (Ed), Martindale: The Complete Drug Reference. London: Pharmaceutical Press. Electronic version.), Index Nominum, and PDR/Physician's Desk Reference (Medical Economics Company Inc, 2000).

[2] Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO.

[3] The Established Evaluation System [EES], the Division of Medication Errors and Technical Support [DMETS] database of Proprietary name consultation requests, New Drug Approvals 98-00, and the electronic online version of the FDA Orange Book.

[4]WWW location http://www.uspto.gov/tmdb/index.html.

[5] Data provided by Thomson & Thomson's SAEGIS ™ Online Service, available at www.thomson-thomson.com

Table 1: Potential Sound-Alike/Look-Alike Names Identified by DMETS Expert Panel

Product Name	Dosage form(s), Established name	Usual adult dose*	Other**
Alinia	Nitazoxanide Tablets: 500mg Suspension: 100 mg/5 mL	**500 mg every 12 hours for 3 days.**	
Alimta***	Premetrexed Disodium for Injection 500 mg/vial	500 mg/m^2 over 10 minutes once every 21 days	**L/A
Climara	Estradiol Transdermal System 0.025 mg/24 hr, 0.05 mg/24 hr, 0.75 mg/24 hr, 0.1 mg/24hr	Apply once a week.	**L/A

*Frequently used, not all-inclusive.
**L/A (look-alike), S/A (sound-alike)
NOTE: This review contains proprietary and confidential information that should not be released to the public.

B. PRESCRIPTION ANALYSIS STUDIES

1. Methodology:

Three separate studies were conducted within FDA for the proposed proprietary name to determine the degree of confusion of Alinia with other U.S. drug names due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. These studies employed a total of 106 health care professionals (pharmacists, physicians, and nurses). This exercise was conducted in an attempt to simulate the prescription ordering process. An inpatient order and outpatient prescriptions were written, each consisting of a combination of marketed and unapproved drug products and a prescription for Alinia (below). These prescriptions were optically scanned and one prescription was delivered to a random sample of the participating health professionals via e-mail. In addition, the outpatient orders were recorded on voice mail. The voice mail messages were then sent to a random sample of the participating health professionals for their interpretations and review. After receiving either the written or verbal prescription orders, the participants sent their interpretations of the orders via e-mail to the medication error staff.

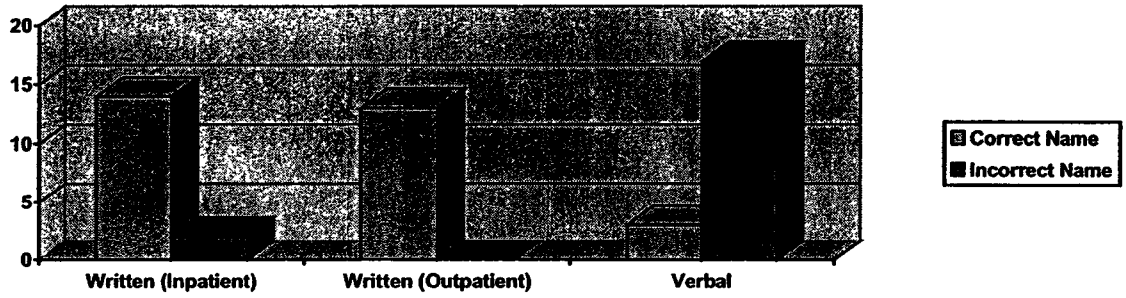
HANDWRITTEN PRESCRIPTION	VERBAL PRESCRIPTION
Outpatient RX: Alinia 100 mg/5mL	Alinia, 5 tsp. every 12 hours for 3 days, dispense 60 mL.
Inpatient RX: Alinia 100mg/5ml	

2. Results:

The results are summarized in Table 2.

Table 2

Study	# of Participants	# of Responses (%)	Correctly Interpreted (%)	Incorrectly Interpreted (%)
Written Inpatient	39	16 (41%)	14 (88%)	2 (12%)
Written Outpatient	35	13 (37%)	13 (100%)	0 (0%)
Verbal	32	20 (63%)	3 (15%)	17 (85%)
Total	106	49 (46%)	30 (61%)	19 (39%)



Among the verbal prescription study participants for Alinia, 17 of 20 (85%) of the participants interpreted the name incorrectly. The majority of the responses were misspelled variations of "Alinia". The incorrect responses were *Alenia (9), Valenia, Allena, Alemia, Alevia, Elinia, Aleenea, Aleanea,* and *Zaleenia.*

Among the written prescription study participants for Alinia, 2 of 29 (7%) of the participants interpreted the name incorrectly. The incorrect responses were *Alivia* and *Alima.*

C. SAFETY EVALUATOR RISK ASSESSMENT:

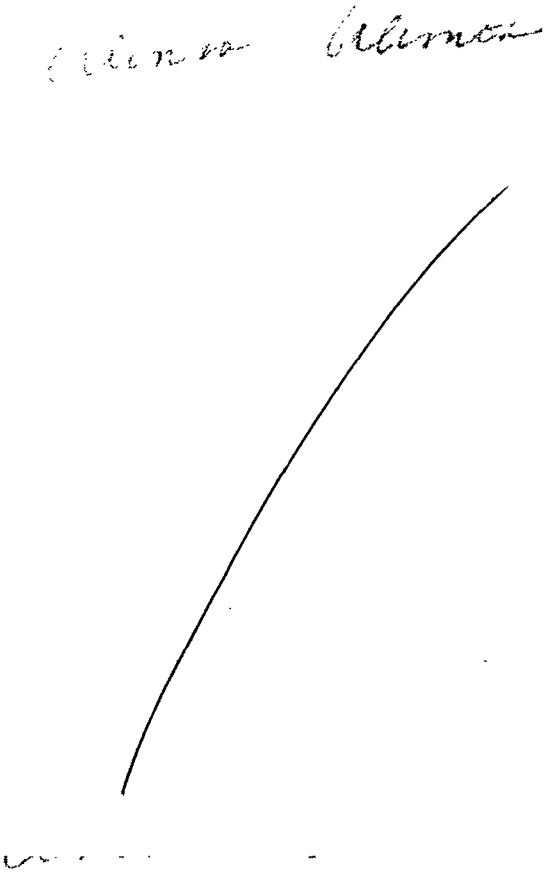
*****NOTE: This review contains proprietary and confidential information that should not be released to the public.*****

In reviewing the proposed proprietary name "Alinia", the primary concerns raised were related to three look-alike and/or sound-alike names. The products considered to have potential for name confusion with Alinia were Alimta, — , and Climara.

We conducted prescription studies to simulate the prescription ordering process. Our study did not confirm confusion between Alinia and Alimta, — or Climara. The majority of the incorrect interpretations of the written and verbal studies were misspelled/phonetic variations of the proposed name, Alinia. However, a negative finding does not discount the potential for name confusion given the limited predictive value of these studies, primarily due to the sample size.

Alimta (Premetrexed Disodium) is a folate antagonist proposed for the treatment of malignant pleural mesothelioma in combination with cisplatin. The recommended dose is 500 mg/m^2 over 10 minutes once every 21 days followed approximately 30 minutes later by a 2 hour infusion of 75 mg/m^2 cisplatin. The product is reconstituted by adding 20 mL of 0.9% sodium chloride injection to a solution containing 25 mg/mL premetrexed. The reconstituted solution is further diluted for IV infusion. Alimta will be marketed as a 500 mg lyophilized powder for injection. The DMETS Expert Panel expressed concern that Alimta and Alinia look similar (see below), which could result in confusion between the two products. The first four letters of the names, "Alim" vs. "Alin" look almost identical when scripted. Additionally, both names end with the letter "a". The letter "t" in Alimta can look similar to the second letter "i" in Alinia if the "t" is not clearly crossed. Alimta and Alinia share a similar strength (500 mg/vial vs. 500 mg tablet) and both are available in powder form, requiring reconstitution before administration. However, Alimta and Alinia differ in dosage form (tablets or oral suspension vs. injection), route of administration (oral vs. intravenous or intramuscular), usual dose (varies according to body surface area vs. 500 mg), dosing regimen (once every 21 days vs. every 12 hours) and storage (Alimta stored with chemotherapy agents). Additionally, the products differ in that a dose of Alimta is followed by a 2 hour infusion of cisplatin. Therefore, the use of Alimta will be carefully monitored by a healthcare practitioner. Due to the differences between Alimta and Alinia, the potential for confusion should be minimal.

ALINIA ALIMTA



Climara (Estradiol) is indicated for moderate-to-severe vasomotor symptoms associated with menopause, female hypogonadism, female castration, primary ovarian failure, atrophic conditions caused by deficient endogenous estrogen production, atrophic urethritis, prevention of osteoporosis, abnormal uterine bleeding due to hormonal imbalance in the absence of organic pathology and only when associated with a hypoplastic or atrophic endometrium. Climara and Alinia look similar when the "Al" in Alinia and the "Cl" in Climara is scripted. Additionally, the remaining letters in the names look almost identical when scripted (see writing sample below). However, the products differ in strength (500 mg and 100 mg/mL vs. 0.025 mg, 0.05 mg, 0.75 mg, 0.1 mg), dosing regimen (every 12 hours vs. once weekly), dosage form (tablets and suspension vs. transdermal patches), route of administration (orally vs. transdermally) and duration of use (acute vs. chronic). Given these differences, the likelihood for confusion between Climara and Alinia is minimal.

ALINIA CLIMARA

III. RECOMMENDATIONS:

DMETS has no objections to the use of the proposed proprietary name Alinia.

DMETS would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Sammie Beam, Project Manager, at 301-827-3242.

/S/

Alina Mahmud, R.Ph.
Team Leader
Division of Medication Errors and Technical Support
Office of Drug Safety

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Alina Mahmud
11/21/02 08:46:42 AM
PHARMACIST

Carol Holquist
11/21/02 08:50:45 AM
PHARMACIST

Jerry Phillips
11/23/02 02:49:12 PM
DIRECTOR

6 Page(s) Withheld

MEMORANDUM OF TELECON

DATE: October 31, 2002 at 9:00

APPLICATION #: NDA 21-497 and 21-498 (nitazoxanide)

BETWEEN:

Name: Marc Ayers, President of Romark Laboratories, L.C.

Phone: (813) 282-8544

AND

Name: Kofi Kumi, Ph.D.- Clinical Pharmacology/ Biopharmaceutics Acting Team Leader
Dakshina Chilukuri, Ph.D.- Clinical Pharmacology/ Biopharmaceutics Reviewer
Kristen Miller, PharmD- Regulatory Project Manager

SUBJECT: Dissolution Methods

BACKGROUND: On October 30, 2002, the Division requested a brief teleconference with Romark to discuss Romark's dissolution methods data submitted in response to the Division's October 8th request.

TELECONFERENCE

Following introductions, the Division stated that the data on — RPM had been received, but there were a few issues that needed to be clarified. Only one unit with no mean or range was submitted, and the Division wanted to see six units/test. Once a specific speed is agreed on, then twelve units would be requested, but for now, only one batch with six units needs to be seen. Romark said that they were clear on the request, so they would clarify to see what was actually submitted to us. *Additionally, the Division requested dissolution data for the individual tablets.*

Second, the Division said that the original NDA stated that sample trays were run at —
— and they just wanted to clarify that the methods submitted were done at — as well. Romark replied that they were done at —

Romark asked if the Division would suggest only doing a run at — RPM. *The Division deferred responding until data for all six individual units had been submitted.*

Romark agreed to call back to let the Division know about the data provided and to supply dissolution data for the individual tablets.

/S/

Kofi Kumi, Ph.D.

Drafted by: kem: 10/31/02
Concurrence and edited by: kk and dc: 11/5/02

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/s/

Kristen Miller
11/5/02 01:00:26 PM
CSO

MEMORANDUM OF TELECON

DATE: October 8, 2002 at 2:30

APPLICATION #: NDA 21-497 and 21-498 (nitazoxanide)

BETWEEN:

Name: Marc Ayers, President of Romark Laboratories, L.C.

Phone: (813) 282-8544

AND

Name: Barbara Davit, Ph.D.- Clinical Pharmacology & Biopharmaceutics Team Leader (DSPIDP)
Dakshina Chilukuri, Ph.D.- Clinical Pharmacology & Biopharmaceutics Reviewer (DSPIDP)
Gene W. Holbert, Ph.D.- Chemistry Reviewer
Kristen Miller, PharmD- Regulatory Project Manager (DSPIDP)

SUBJECT: Dissolution Methods

BACKGROUND: On October 8, 2002, the Division requested a brief teleconference with Romark to discuss dissolution methods for nitazoxanide.

TELECONFERENCE

Following introductions, the Division asked if Romark had any data for the tablets and suspension (powder) using a paddle speed lower than — RPM. Romark replied that they would find out, but if it was not provided, they probably did not have any. Early on there were difficulties, but he was not positive of their rationale for not trying any lower rotation speeds.

The Division suggested that Romark do a dissolution study with two lower speeds (— RPMs). It is assumed that — RPMs will be necessary because of the product's low solubility, but we would like to be sure. A slower rotation is generally chosen for suspensions, so in addition to the — RPM studies, please do a study at — RPM for the suspension if necessary.

Romark inquired whether another study should be performed using — RPM. *The Division replied that that would not be necessary, as historical data could be used. Finally, the medium is acceptable as well.* Romark agreed to start these immediately, and let the Division know if studies have already been completed within two days.

/S/

Barbara Davit, Ph.D.

Drafted by: kem:10/17/02
Concurrence and edited by: dc and bd: 11/5/02

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/s/

Kristen Miller
11/5/02 12:49:30 PM
CSO

1 Page(s) Withheld

9 Page(s) Withheld

USER FEE VALIDATION SHEET

21-497
NDA # 21-498 Supp. Type & # N000 UFID # N/A
(e.g., N000, SLR001, SE1001, etc.)

1. (YES) NO User Fee Cover Sheet Validated? MIS_Elements Screen Change(s):

Orphan exemption under Action 736 (a)(1)(E) of the FFDCAct

2. (YES) NO APPLICATION CONTAINS CLINICAL DATA?
(Circle YES if NDA contains study or literature reports of what are explicitly or implicitly represented by the application to be adequate and well-controlled trials. Clinical data do not include data used to modify the labeling to add a restriction that would improve the safe use of the drug (e.g., to add an adverse reaction, contraindication or warning to the labeling).

REF IF NO CLINICAL DATA IN SUBMISSION, INDICATE IF CLINICAL DATA ARE CROSS REFERENCED IN ANOTHER SUBMISSION.

3. YES (NO) SMALL BUSINESS EXEMPTION

4. YES (NO) WAIVER GRANTED

5. YES (NO) NDA BEING SPLIT FOR ADMINISTRATIVE CONVENIENCE (other then bundling).
If YES, list all NDA #s, review division(s) and those for which an application fee applies.

NDA #	Division		
N_____	HFD-_____	Fee	No Fee
N_____	HFD-_____	Fee	No Fee

6. (YES) NO BUNDLING POLICY APPLIED CORRECTLY? No Data Entry Required
(Circle YES if application is properly designated as one application or is properly submitted as a supplement instead of an original application. Circle NO if application should be split into more than one application or be submitted as an original instead of a supplement. If NO, list resulting NDA #s and review division(s).

NDA #	Division	NDA #	Division
N_____	HFD-_____	N_____	HFD-_____

7. (P) S PRIORITY or STANDARD APPLICATION?

151 9/10/02 151 10 Sep 02
PM Signature / Date CPMS Concurrence Signature / Date

2/14/00

6 Page(s) Withheld

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

Form Approved: OMB No. 0910-0297
Expiration Date: February 29, 2004.

USER FEE COVER SHEET

See Instructions on Reverse Side Before Completing This Form

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. See exceptions on the reverse side. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment. Payment instructions and fee rates can be found on CDER's website: http://www.fda.gov/cder/pdufa/default.htm

1. APPLICANT'S NAME AND ADDRESS

Romark Laboratories, L.C.
6200 Courtney Campbell Causeway
Suite 880
Tampa, FL 33607

2. TELEPHONE NUMBER *(Include Area Code)*

(813) 282-8544

3. PRODUCT NAME

Cryptaz (nitazoxanide) 500 mg tablets

4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER

N021-497

5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL?

☒ YES ☐ NO

IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM.

IF RESPONSE IS 'YES', CHECK THE APPROPRIATE RESPONSE BELOW:

☒ THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION.

☒ THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO:

NDA 20-871
(APPLICATION NO. CONTAINING THE DATA).

6. USER FEE I.D. NUMBER

N/A

7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.

☐ A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92
(Self Explanatory)

☐ A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE
(See item 7, reverse side before checking box.)

☒ THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act
(See item 7, reverse side before checking box.)

☐ THE APPLICATION IS A PEDIATRIC SUPPLEMENT THAT QUALIFIES FOR THE EXCEPTION UNDER SECTION 736(a)(1)(F) of the Federal Food, Drug, and Cosmetic Act
(See item 7, reverse side before checking box.)

☐ THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALLY
(Self Explanatory)

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION?

☐ YES ☒ NO

(See item 8, reverse side if answered YES)

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE	TITLE	DATE
[signature]	President	May 28, 2002

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Office of Orphan Products Development *(HF-35)*
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

February 14, 2002

Romark Laboratories, L.C.
6200 Courtney Campbell Causeway
Suite 880
Tampa, FL 33607

Attention: Marc S. Ayers
President

Dear Mr. Ayers:

Reference is made to your request for orphan-drug designation dated September 14, 2001, of nitazoxanide for the treatment of giardiasis (designation request # [redacted] submitted pursuant to Section 526 of the Federal Food, Drug, and Cosmetic Act (21 USC 360bb).

We have completed the review of this request and have determined that nitazoxanide qualifies for orphan designation for the treatment of **intestinal** giardiasis. Please note that it is nitazoxanide and not its formulation that has received orphan designation. You have notified us that you are currently developing nitazoxanide under the trade name Cryptaz™.

Please be advised that if nitazoxanide is approved for an indication broader than the orphan designation, your product might not be entitled to exclusive marketing rights pursuant to Section 527 of the FFDCA (21 U.S.C. 360cc). Therefore, prior to final marketing approval, sponsors of designated orphan drugs are requested to compare the designated orphan indication with the proposed marketing indication and to submit additional data to amend their orphan designation prior to marketing approval if warranted.

Finally, please notify this Office within 30 days of submission of a marketing application for the use of nitazoxanide as designated. Also an annual progress report must be submitted within 14 months after the designation date and annually thereafter until a marketing application is approved (21 CFR 316.30). If you need further assistance in the development of your product for marketing, please feel free to contact Henry Startzman, MD at (301) 827-3666.

Please refer to this letter as official notification of designation and congratulations on obtaining your orphan-drug designation.

Sincerely yours,

LSI

Marlene E. Haffner, MD, MPH
Rear Admiral, United States Public Health Service
Director, Office of Orphan Products Development

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

June 1, 2001

Romark Laboratories, LC
6200 Courtney Campbell Causeway
Suite 880
Tampa, FL 33607

Attention: Marc Ayers
President
Romark Laboratories, LC

Dear Mr. Ayers:

This is in reference to your request dated April 10, 2001, to amend the indication stated in the orphan drug-designation # — of nitazoxanide, i.e., from " — — to "treatment of cryptosporidiosis."

We have reviewed your request and found that the amended change in the indication does not result in exceeding the prevalence threshold upon which the drug was originally designated. Therefore, the amendment is granted. The orphan-drug designation of nitazoxanide now reads, "for the treatment of cryptosporidiosis."

Sincerely yours,

LSI

Marlene E. Haffner, MD, MPH
Rear Admiral, United States Public Health Service
Director, Office of Orphan Products Development

25 Draft Labeling Page(s) Withheld