CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-498

Administrative Documents

PATENT INFORMATION

United States Patent Number 5,387,598

As required under section 505(b)(1)(F) of the Federal Food, Drug, and Cosmetic Act, and as specified in 21 CFR 314.53(c)(1), Romark Laboratories, L.C. reports the following patent information:

1. Patent number and expiration date: 5,387,598 expiring February 7, 2012
2. Type of patent: Drug product and method of use
3. Name of the patent owner: Romark Laboratories, L.C.
4. The owner of the patent and the NDA applicant are the same entity and have a place of business within the United States at the following address:

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

PATENT DECLARATION

The undersigned declares that Patent No. 5,387,598 covers the formulation, composition, and/or method of use of Cryptaz® (nitazoxanide) for Oral Suspension. This product is the subject of this application for which approval is being sought.

Signature: _____

Title: President, Romark Laboratories, L.C.

PATENT INFORMATION AND DECLARATION

United States Patent Number 5,578,621

As required under section 505(b)(1)(F) of the Federal Food, Drug, and Cosmetic Act, and as specified in 21 CFR 314.53(c)(1), Romark Laboratories, L.C. reports the following patent information:

1. Patent number and expiration date: 5,578,621 expiring September 8, 2014
2. Type of patent: Drug product and method of use
3. Name of the patent owner: Romark Laboratories, L.C.
4. The owner of the patent and the NDA applicant are the same entity and have a place of business within the United States at the following address:

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

PATENT DECLARATION

The undersigned declares that Patent No. 5,578,621 covers the formulation, composition, and/or method of use of Cryptaz® (nitazoxanide) for Oral Suspension. This product is the subject of this application for which approval is being sought.

Signature: _____

Title: President, Romark Laboratories, L.C.

PATENT INFORMATION

United States Patent Number 5,856,348

As required under section 505(b)(1)(F) of the Federal Food, Drug, and Cosmetic Act, and as specified in 21 CFR 314.53(c)(1), Romark Laboratories, L.C. reports the following patent information:

1. Patent number and expiration date: 5,856,348 expiring September 8, 2014
2. Type of patent: Method of use
3. Name of the patent owner: Romark Laboratories, L.C.
4. The owner of the patent and the NDA applicant are the same entity and have a place of business within the United States at the following address:

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

PATENT DECLARATION

The undersigned declares that Patent No. 5,856,348 covers the formulation, composition, and/or method of use of Cryptaz® (nitazoxanide) for Oral Suspension. This product is the subject of this application for which approval is being sought.

Signature: _____

Title: President, Romark Laboratories, L.C.

PATENT INFORMATION

United States Patent Number 5,859,038

As required under section 505(b)(1)(F) of the Federal Food, Drug, and Cosmetic Act, and as specified in 21 CFR 314.53(c)(1), Romark Laboratories, L.C. reports the following patent information:

1. Patent number and expiration date: 5,859,038 expiring September 8, 2014
2. Type of patent: Method of use
3. Name of the patent owner: Romark Laboratories, L.C.
4. The owner of the patent and the NDA applicant are the same entity and have a place of business within the United States at the following address:

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

PATENT DECLARATION

The undersigned declares that Patent No. 5,859,038 covers the formulation, composition, and/or method of use of Cryptaz® (nitazoxanide) for Oral Suspension. This product is the subject of this application for which approval is being sought.

Signature: _____

Title: President, Romark Laboratories, L.C.

PATENT INFORMATION

United States Patent Number 5,886,013

As required under section 505(b)(1)(F) of the Federal Food, Drug, and Cosmetic Act, and as specified in 21 CFR 314.53(c)(1), Romark Laboratories, L.C. reports the following patent information:

1. Patent number and expiration date: 5,886,013 expiring May 1, 2017
2. Type of patent: Drug product and method of use
3. Name of the patent owner: Romark Laboratories, L.C.
4. The owner of the patent and the NDA applicant are the same entity and have a place of business within the United States at the following address:

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

PATENT DECLARATION

The undersigned declares that Patent No. 5,886,013 covers the formulation, composition, and/or method of use of Cryptaz® (nitazoxanide) for Oral Suspension. This product is the subject of this application for which approval is being sought.

Signature: _____

Title: President, Romark Laboratories, L.C.

PATENT INFORMATION

United States Patent Number 5,935,591

As required under section 505(b)(1)(F) of the Federal Food, Drug, and Cosmetic Act, and as specified in 21 CFR 314.53(c)(1), Romark Laboratories, L.C. reports the following patent information:

1. Patent number and expiration date: 5,935,591 expiring January 15, 2018
2. Type of patent: Method of use
3. Name of the patent owner: Romark Laboratories, L.C.
4. The owner of the patent and the NDA applicant are the same entity and have a place of business within the United States at the following address:

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

PATENT DECLARATION

The undersigned declares that Patent No. 5,935,591 covers the formulation, composition, and/or method of use of Cryptaz® (nitazoxanide) for Oral Suspension. This product is the subject of this application for which approval is being sought.

Signature: _____

Title: President, Romark Laboratories, L.C.

PATENT INFORMATION AND DECLARATION

United States Patent Number 5,965,590

As required under section 505(b)(1)(F) of the Federal Food, Drug, and Cosmetic Act, and as specified in 21 CFR 314.53(c)(1), Romark Laboratories, L.C. reports the following patent information:

1. The patent number and expiration date: 5,965,590 expiring July 3, 2017
2. Type of patent: Method of use
3. Name of the patent owner: Romark Laboratories, L.C.
4. The owner of the patent and the NDA applicant are the same entity and have a place of business within the United States at the following address:

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

PATENT DECLARATION

The undersigned declares that Patent No. 5,965,590 covers the formulation, composition, and/or method of use of Cryptaz® (nitazoxanide) for Oral Suspension. This product is the subject of this application for which approval is being sought.

Signature: _____

Title: President, Romark Laboratories, L.C.

PATENT INFORMATION

United States Patent Number 5,968,961

As required under section 505(b)(1)(F) of the Federal Food, Drug, and Cosmetic Act, and as specified in 21 CFR 314.53(c)(1), Romark Laboratories, L.C. reports the following patent information:

1. Patent number and expiration date: 5,968,961 expiring May 7, 2017
2. Type of patent: Drug product
3. Name of the patent owner: Romark Laboratories, L.C.
4. The owner of the patent and the NDA applicant are the same entity and have a place of business within the United States at the following address:

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

PATENT DECLARATION

The undersigned declares that Patent No. 5,968,961 covers the formulation, composition, and/or method of use of Cryptaz® (nitazoxanide) for Oral Suspension. This product is the subject of this application for which approval is being sought.

Signature: _____

Title: President, Romark Laboratories, L.C.

PATENT INFORMATION

United States Patent Number 6,020,353

As required under section 505(b)(1)(F) of the Federal Food, Drug, and Cosmetic Act, and as specified in 21 CFR 314.53(c)(1), Romark Laboratories, L.C. reports the following patent information:

1. Patent number and expiration date: 6,020,353 expiring September 8, 2014
2. Type of patent: Drug and drug product
3. Name of the patent owner: Romark Laboratories, L.C.
4. The owner of the patent and the NDA applicant are the same entity and have a place of business within the United States at the following address:

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

PATENT DECLARATION

The undersigned declares that Patent No. 6,020,353 covers the formulation, composition, and/or method of use of Cryptaz® (nitazoxanide) for Oral Suspension. This product is the subject of this application for which approval is being sought.

Signature: _____

Title: President, Romark Laboratories, L.C.

PATENT INFORMATION

United States Patent Number 6,117,894

As required under section 505(b)(1)(F) of the Federal Food, Drug, and Cosmetic Act, and as specified in 21 CFR 314.53(c)(1), Romark Laboratories, L.C. reports the following patent information:

1. Patent number and expiration date: 6,117,894 expiring May 7, 2017
2. Type of patent: Drug product
3. Name of the patent owner: Romark Laboratories, L.C.
4. The owner of the patent and the NDA applicant are the same entity and have a place of business within the United States at the following address:

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

PATENT DECLARATION

The undersigned declares that Patent No. 6,117,894 covers the formulation, composition, and/or method of use of Cryptaz® (nitazoxanide) for Oral Suspension. This product is the subject of this application for which approval is being sought.

Signature: _____

Title: President, Romark Laboratories, L.C.

EXCLUSIVITY SUMMARY for NDA # 21-498 SUPPL # N/A

Trade Name Alinia Generic Name nitazoxanide

Applicant Name Romark Laboratories, L.C. HFD-590

Approval Date November 22, 2002

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "YES" to one or more of the following questions about the submission.

   a) Is it an original NDA? YES/_X_/ NO /___/

   b) Is it an effectiveness supplement? YES /__/ NO /_X_/

   If yes, what type(SE1, SE2, etc.)? N/A

   c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "NO.")

   YES /_X_/ NO /___/

   If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

   N/A

   If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

   N/A

d) Did the applicant request exclusivity?

YES /___/ NO /_X_/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

N/A

e) Has pediatric exclusivity been granted for this Active Moiety?

YES /___/ NO /_X_/

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use? (Rx to OTC Switches should be answered No - Please indicate as such).

YES /___/ NO /_X_/

If yes, NDA # _____ Drug Name

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /_X_/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (even if a study was required for the upgrade).

PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /___/ NO /_X_/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA #

NDA #

NDA #

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /_X_/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA #

NDA #

NDA #

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9. IF "YES," GO TO PART III.

PART III: <u>THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS</u> N/A

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /___/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as

bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /___/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON Page 9:**

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /___/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /___/

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /___/

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study #

Investigation #2, Study #

Investigation #3, Study #

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

(a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1	YES /___/	NO /___/
Investigation #2	YES /___/	NO /___/
Investigation #3	YES /___/	NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # _____ Study #
NDA # _____ Study #
NDA # _____ Study #

(b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _____ Study #

NDA # _____ Study #

NDA # _____ Study #

(c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #__, Study #

Investigation #__, Study #

Investigation #__, Study #

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

(a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1	
IND # _____ YES /___/	NO /___/ Explain:
Investigation #2	
IND # _____ YES /___/	NO /___/ Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1	
YES /___/ Explain _____	NO /___/ Explain _____
_____	_____
_____	_____
Investigation #2	
YES /___/ Explain _____	NO /___/ Explain _____
_____	_____
_____	_____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /___/

If yes, explain: _____

_____

_____

_____

Signature of Preparer Date

Title:

Signature of Office or Division Director Date

CC:
Archival NDA
HFD-590/Division File
HFD-590/RPM
HFD-093/Mary Ann Holovac
HFD-104/PEDS/T.Crescenzi

Form OGD-011347
Revised 8/7/95; edited 8/8/95; revised 8/25/98, edited 3/6/00

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

/s/

Mark Goldberger
12/3/02 03:21:18 PM

PEDIATRIC PAGE

(Complete for all APPROVED original applications and efficacy supplements)

NDA/BLA # : 21-498 Supplement Type (e.g. SE5): N/A Supplement Number: N/A

Stamp Date: May 29, 2002 Action Date: November 22, 2002

HFD-590___ Trade and generic names/dosage form: Alinia (nitazoxanide) for Oral Suspension

Applicant: Romark Laboratories, L.C. Therapeutic Class: Antiparasitic (7030600)

Indication(s) previously approved: N/A

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): 1

Indication #1: Treatment of diarrhea caused by *Cryptosporidium parvum* and *Giardia lamblia*

Is there a full waiver for this indication (check one)?

☐ Yes: Please proceed to Section A.

X No: Please check all that apply: ____Partial Waiver __X__Deferred __X__Completed
NOTE: More than one may apply
Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies- *N/A*

Reason(s) for full waiver:

☐ Products in this class for this indication have been studied/labeled for pediatric population
☐ Disease/condition does not exist in children
☐ Too few children with disease to study
☐ There are safety concerns
☐ Other:_____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies- *N/A*

Age/weight range being partially waived:

Min_____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Reason(s) for partial waiver:

☐ Products in this class for this indication have been studied/labeled for pediatric population
☐ Disease/condition does not exist in children
☐ Too few children with disease to study
☐ There are safety concerns
☐ Adult studies ready for approval
☐ Formulation needed
☐ Other:_____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

'First' age/weight range being deferred:

Min _____	**kg**_____	**mo.** 0	**yr.**_____	**Tanner Stage**_____
Max_____	**kg**_____	**mo.** <12	**yr.**_____	**Tanner Stage**_____

'Second' age/weight range being deferred:

Min _____	**kg**_____	**mo.**_____	**yr.** 12	**Tanner Stage**_____
Max_____	**kg**_____	**mo.**_____	**yr.** 16	**Tanner Stage**_____

Reason(s) for deferral:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**

Other: Sponsor has plans to complete studies for this age range

Date studies are due (mm/dd/yy): 11/22/07

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____	**kg**_____	**mo.**_____	**yr.** 1	**Tanner Stage**_____
Max_____	**kg**_____	**mo.**_____	**yr.** 11	**Tanner Stage**_____

Comments: Studies were performed in foreign sites. The population includes significant numbers of malnourished children.

This page was completed by:

{See appended electronic signature page}

Medical Officer and
Regulatory Project Manager

cc: NDA 21-498
HFD-950/ Terrie Crescenzi
HFD-960/ Grace Carmouze
(revised 9-24-02)

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, PEDIATRIC TEAM, HFD-960
301-594-7337

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

/s/

Rosemary Johann-Liang
11/27/02 11:19:49 AM

DEBARMENT CERTIFICATION

Pursuant to 306(k) of the Federal Food Drug and Cosmetic Act, Romark Laboratories, L.C. certifies that it did not employ or otherwise use in any capacity the services of any person debarred under subsection (a) or (b), in connection with this application.

APPEARS THIS WAY
ON ORIGINAL

DIVISION DIRECTOR REVIEW

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

Drugs:

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 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

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 — ' 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.

Nitazoxanide is approved for marketing in multiple Central and South American countries. A reported — 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)
—	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 -ITT	**Pediatric patients , sole pathogen** (MOR p52)			
		Suspension	Metronidazole	95% C.I.
	Clinical	47/55 (85%)	44/55 (80%)	-9%, +20%
	Microbiology	39/55 (71%)	41/55 (75%)	-20%, +13%
-Per protocol				
	Clinical	43/48 (90%)	39/47 (83%)	-8%, +21%
	Microbiology	39/47 (83%)	37/46 (80%)	-15%, +17%
	Adult patients, sole pathogen (			
		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 21-498 (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,

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),

- The pediatric patients in clinical trials received the oral suspension at 100 mg BID for patients 1-2 years of age and 200 mg BID for patients > 2-11 years of age. The correct dose of oral suspension in adults is unknown, and cannot be derived from pediatrics because of the following unanswered issues.

    - The tablet is not bioequivalent to the oral suspension. The oral suspension formulation is less bioavailable compared to the tablet, therefore the oral suspension provides relatively lower systemic levels and higher gastrointestinal lumenal levels compared to the tablet. Both *C. parvum* and *G. lamblia* are pathogens found in the gastrointestinal lumen. It is unknown whether the systemic drug levels or the lumenal drug levels are more important for efficacy, therefore it is not possible to determine a therapeutically bioequivalent dose.

-
-

- The safety profile of the tablet formulation in non-HIV infected adult patients is also quite limited, although this should not be considered a major deficiency, because a large safety database is available from HIV infected adults and did not shown a safety signal. Animal data and pediatric patient safety data are also encouraging.

In summary,

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.

/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

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

Teleconference Minutes

Teleconference Date: November 4, 2002

Application Numbers: NDA 21-498
Nitazoxanide Suspension

Sponsor: Romark Laboratories, L.C.

Attendees:

Romark Laboratories, L.C.

Marc Ayers	President
Heidi Ano	Regulatory Affairs Director

FDA- Division of Special Pathogen and Immunologic Drug Products

Renata Albrecht, M.D.	Division Director
Rigoberto Roca, M.D.	Medical Team Leader
Rosemary Johann-Liang M.D.	Medical Reviewer
Shukal Bala, Ph.D.	Microbiology Team Leader
Kalavati Suvarna Ph.D.	Microbiology Reviewer
Steven Kunder Ph.D.	Pharmacology Reviewer
Dakshina Chilukuri Ph.D.	Clinical Pharmacology/Biopharmaceutics Reviewer
Barbara Davit, Ph.D.	Clinical Pharmacology & Biopharmaceutics Team Leader
Kristen Miller, PharmD	Regulatory Project Manager

Background

Romark submitted NDA 21-498 on May 29, 2002 for the use of Nitazoxanide for Oral Suspension in the treatment of diarrhea caused by *Cryptosporidium parvum* and *Giardia lamblia* in pediatric patients 1- 11 years of age who are HIV negative. This teleconference was requested by the Division to discuss the proposed nitazoxanide labeling.

Meeting Objectives

The meeting objectives are to discuss:

- the content of the labeling proposed by the Division
- any issues regarding the proposed trade name Cryptaz and
-

Discussion

Acceptability of the name "Cryptaz"

Following introductions, Romark questioned why the name Cryptaz had been removed from the labeling. *The Division stated that the name Cryptaz, although it had been submitted to the Labeling and Nomenclature Committee in 1998, was resubmitted to the Division of Medication Errors and Technical Support (DMETS) and to the Division of Drug Marketing, Advertising and Communication (DDMAC) for review to evaluate if other issue had arisen in the interim. These divisions found Cryptaz to be unadvisable.* Romark asked how the decision of 'unadvisable' was reached. *DDMAC felt that Cryptaz implied an indication for cryptosporidium or cryptococcus, and DMETS felt that it could be confused with the name Ceptaz.* Romark commented that Ceptaz has a very different indication, and a different route. *The Division agreed, but still felt that there was the potential for drug errors. As an aside, the Division also pointed out that if nitazoxanide was going to come in for different indications, that it may be beneficial not to imply only one indication.* Romark agreed to think about possibilities for a new name.

Nitazoxanide's Indication

After reasoning for other revisions were discussed, Romark questioned the deletion of the [redacted] ' from the indication. *The Division stated that using a Kappa statistical method, the confidence interval is not met to show correlation between parasitological and clinical response, so we can not accept that as part of the indication.* Romark said that they would think about this.

Effectiveness of Nitazoxanide Tablets

The Division stated that we are currently only negotiating the labeling for the suspension because the outstanding issues are minor.

Absorption of Suspension vs. Tablets

The Division stated that it would be interesting to see the clinical significance of the higher absorption reported for tablets compared to the suspension (to help to determine where nitazoxanide exerts its activity).

Post-marketing Commitments

Finally, suggestions for post-marketing commitments included the following:

- *Food effects on the suspension*
- *In vitro drug interaction studies repeated with tizoxanide and tizoxanide glucuronide (the major moieties found in plasma)*
- *In vitro absorption studies with tizoxanide to see amount absorbed in intestines*

Action Items

Romark agree to submit their counterproposal for the package insert, a new name, and post-marketing commitments within the week.

/S/

Minutes Preparer: Kristen Miller, PharmD; Project Manager

/S/

Concur: Renata Albrecht, M.D.; Division Director, DSPIDP

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/s/

Kristen Miller
11/12/02 12:37:40 PM
CSO

Renata Albrecht
11/21/02 05:04:13 PM
MEDICAL OFFICER

MEMORANDUM OF TELECON

DATE: October 31, 2002 at 9:00

APPLICATION #: NDA —— 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 —— 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 —— —— 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 —— *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 —— 21-498 (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 100 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 100 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 100 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

MEMORANDUM OF MEETING MINUTES

MEETING DATE:	November 4, 2002
TIME:	12:00 PM
APPLICATION:	NDA 21-498 (Nitazoxanide for Oral Suspension)
TYPE OF MEETING:	Pre-Approval Safety Conference Meeting
MEETING CHAIR:	Mark J. Goldberger, M.D., M.P.H.: Director, ODE IV
MEETING RECORDER:	Kristen Miller, PharmD: Regulatory Project Manager

FDA ATTENDEES, TITLES, AND OFFICE/DIVISION

Mark Goldberger, MD, MPH	Office Director [Office of Drug Evaluation (ODE) IV]
Renata Albrecht, M.D.	Division Director [Division of Special Pathogen and Immunologic Drug Products (DSPIDP)]
Julie Beitz, M.D.	Division Director (ODS/DDRE)
Mark Avigan, M.D.	Deputy Director (ODS/DDRE)
Allen Brinker, M.D., M.S.	Epidemiology Team Leader (ODS/DDRE)
Sarah Singer, R.Ph.	Safety Evaluator (ODS/DDRE)
Quynh Nguyen, Pharm.D.	Regulatory Health Project Manager (ODS/DDRE)
Rigoberto Roca, M.D.	Medical Team Leader (DSPIDP)
Rosemary Johann-Liang M.D.	Medical Reviewer (DSPIDP)
Shukal Bala, Ph.D.	Microbiology Team Leader (DSPIDP)
Kalavati Suvarna Ph.D.	Microbiology Reviewer (DSPIDP)
Steven Kunder Ph.D.	Pharmacology Reviewer (DSPIDP)
Gene Holbert, Ph.D.	Chemistry Reviewer (Division of New Drug Chemistry III)
Dakshina Chilukuri Ph.D.	Clinical Pharmacology/Biopharmaceutics Reviewer (OCPB III)
Ellen Frank, R.Ph.	Chief, Project Management Staff (DSPIDP)
Kristen Miller, PharmD	Regulatory Project Manager (DSPIDP)

BACKGROUND: Romark's application 21-498 (nitazoxanide for Oral Suspension) has a priority review goal date of November 29, 2002. Since this will be approved, and it is a new molecular entity, a pre-approval safety conference (PSC) is required.

MEETING OBJECTIVES: The purpose of the PSC is to:

- Ensure the Office of Drug Safety's (ODS) Division of Drug Risk Evaluation (DDRE) is aware of potential postmarketing safety problems in NTZ
- Consider the need for any special postmarketing analyses/safety studies or evaluations to be agreed to by Romark prior to approval
- Determine if there is any specific info/feedback that we would like from ODS

DISCUSSION POINTS:

Following introductions, a regulatory summary of the nitazoxanide NDAs was provided. Nitazoxanide (tablet formulation) was originally submitted in 1997 under NDA 20-871 for treatment of diarrhea caused by *Cryptosporidium parvum* in HIV positive patients. This application received a non-approvable letter in 1998.

In May, 2002, NDA — 21-498, (nitazoxanide for oral suspension) indicated for treatment of diarrhea caused by *Cryptosporidium parvum* and *Giardia lamblia* in immunocompetent patients, were submitted and granted priority reviews. This meeting focused on 21-498, nitazoxanide powder for suspension for pediatric patients, one to eleven years of age because the application is expected to be approved during this review cycle.

Next, a summary of nitazoxanide's safety was provided. DDRE concurred with the review team's assessment that nitazoxanide is safe for short term use, but raised concerns regarding the following circumstances:

- Off-label use
- Duration of use (repeat and prolonged dosing)
- Use in children with different characteristics than those studied
- Use in immunodeficient children (other than HIV positive)

The review team acknowledged these concerns and suggested establishing post-marketing commitments to determine actual use. Discussion resulted in the following suggested vehicles to address this concern:

- Insurance companies (best for high volume products)
- Voluntary patient evaluations attached to the product
- Voluntary physician evaluations
- Romark's help to track distribution

ACTION ITEMS:

1. Labeling will be adjusted to address the concern of nitazoxanide use in children with immunodeficiencies (along with HIV positive)
2. The sponsor will be asked for assistance with tracking actual use after approval through post-marketing commitments.

Minutes Preparer: Kristen Miller, PharmD; Regulatory Project Manager

Chair Concurrence: Mark Goldberger, MD, MPH; Director, Office of Drug Evaluation IV

Drafted by: KEM: 11/4/02
Edited by: ss: 11/5/02; qn: 11/5/02; ef: 11/6/02; rr: 11/7/02; ra: 11/13/02
Concur: jb: 11/7/02

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/s/

Mark Goldberger
11/22/02 11:41:00 AM

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information		
NDA: 21-498	Efficacy Supplement Type SE- N/A	Supplement Number: N/A
Drug: Cryptaz (nitazoxanide) Tablets/ for Oral Suspension	Applicant: Romark Laboratories, L.C.	
RPM: Kristen Miller	HFD-590	Phone # : (301) 827-2127
Application Type: (X) 505(b)(1) ( ) 505(b)(2)	Reference Listed Drug (NDA #, Drug name): N/A	

❖ Application Classifications:	
• Review priority	( ) Standard (X) Priority
• Chem class (NDAs only)	Class 1 (NME)
• Other (e.g.. orphan, OTC)	Orphan
❖ User Fee Goal Dates	November 29, 2002
❖ Special programs (indicate all that apply)	(X) None Subpart H ( ) 21 CFR 314.510 (accelerated approval) ( ) 21 CFR 314.520 (restricted distribution) ( ) Fast Track ( ) Rolling Review
❖ User Fee Information-	
• User Fee	( ) Paid N/A
• User Fee waiver	( ) Small business ( ) Public health N/A ( ) Barrier-to-Innovation ( ) Other
• User Fee exception -	(X) Orphan designation ( ) No-fee 505(b)(2) ( ) Other
❖ Application Integrity Policy (AIP)	
• Applicant is on the AIP	( ) Yes (X) No
• This application is on the AIP	( ) Yes (X) No
• Exception for review (Center Director's memo)	N/A
• OC clearance for approval	N/A
❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification and certifications from foreign applicants are co-signed by U.S. agent.	(X) Verified
❖ Patent-	
• Information: Verify that patent information was submitted	(X) Verified
• Patent certification [505(b)(2) applications]: Verify type of certifications submitted	21 CFR 314.50(i)(1)(*i*)(A) ( ) I ( ) II ( ) III ( ) IV N/A 21 CFR 314.50(i)(1) ( ) (ii) ( ) (iii)
• For paragraph IV certification, verify that the applicant notified the patent holder(s) of their certification that the patent(s) is invalid, unenforceable, or will not be infringed (certification of notification and documentation of receipt of notice).	( ) Verified N/A

❖ Exclusivity (approvals only)	
• Exclusivity summary	**X- (12/3/02)**
• Is there an existing orphan drug exclusivity protection for the active moiety for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of sameness for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification!*	( ) Yes, Application #_____ (X) No
❖ Administrative Reviews (Project Manager, ADRA) *(indicate date of each review)*	**N/A**
General Information	
❖ Actions	
• Proposed action	(X) AP ( ) TA ( ) AE ( ) NA
• Previous actions (specify type and date for each action taken)	**N/A**
• Status of advertising (approvals only)	(X) Materials requested in AP letter ( ) Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only): **By Jason Brodsky & email**	(X) Yes ( ) Not applicable
• Indicate what types (if any) of information dissemination are anticipated	( ) None (X) Press Release (X) Talk Paper **(Jason Brodsky)** ( ) Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable)	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	**11/4/02-Our first (Many changes)**
• Most recent applicant-proposed labeling	**11/6 and 11/22/02 version included**
• Original applicant-proposed labeling	**X**
• Labeling reviews (including DDMAC, Office of Drug Safety trade name review, nomenclature reviews) and minutes of labeling meetings *(indicate dates of reviews and meetings)*	**DDMAC reviews- email (10/11/02 and 11/18/02)** **DMETS reviews: 11/1 & 11/22/02** **Minutes of labeling telecon under 'Telecons/Memos'**
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	**N/A**
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	**N/A**
• Applicant proposed	**X- (for Cryptaz and Alinia)**
• Reviews	**Under Label/Labeling Consults:** **DDMAC emails : 10/11& 11/18/02** **DMETS reviews: 11/1 & 11/22/02**
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	**Under Telecons/Memos: (In labeling telecon minutes)**
• Documentation of discussions and/or agreements relating to post-marketing commitments	**Romark's letter included, and discussion in Telecons/Memos: (In labeling telecon minutes)**
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	**N/A – No issues arose that required letters/ faxes/ etc.**
❖ Memoranda and Telecons	**Telecons included: Dissolution and labeling (including post-marketing, indication deficiencies)**
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	**N/A- no meeting occurred as all of the information was gathered**

	under Unimed for NDA 20-871 (NA in 1998).
• Pre-NDA meeting (indicate date)	No minutes available (9/19/01)
• Pre-Approval Safety Conference (indicate date; approvals only)	X- (11/4/02)
• Other	N/A
❖ Advisory Committee Meeting	
• Date of Meeting	N/A
• 48-hour alert	N/A
❖ Federal Register Notices, DESI documents, NAS, NRC (if any are applicable)	N/A
Summary Application Review	
❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) *(indicate date for each review)*	X – 1/7/03
Clinical Information	
❖ Clinical review(s) *(indicate date for each review)*	X- Executive Summary (1/7/03) X- Clinical Review (1/7/03)
❖ Microbiology (efficacy) review(s) *(indicate date for each review)*	X- (11/20/02)
❖ Safety Update review(s) *(indicate date or location if incorporated in another review)*	See Clinical Review (1/7/03)
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	X- (11/27/02)
❖ Demographic Worksheet *(NME approvals only)*	X
❖ Statistical review(s) *(indicate date for each review)*	X- (12/2/02)
❖ Biopharmaceutical review(s) *(indicate date for each review)*	X- (11/22/02)
❖ Controlled Substance Staff review(s) and recommendation for scheduling *(indicate date for each review)*	N/A
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	X- Consult requests X- Clinical Inspections Summary
• Bioequivalence studies	N/A
CMC Information	
❖ CMC review(s) *(indicate date for each review)*	X- (11/26/02)
❖ Environmental Assessment	
• Categorical Exclusion *(indicate review date)*	X
• Review & FONSI *(indicate date of review)*	N/A
• Review & Environmental Impact Statement *(indicate date of each review)*	N/A
❖ Micro (validation of sterilization & product sterility) review(s) *(indicate date for each review)*	See Micro Review (11/20/02)
❖ Facilities inspection (provide EER report))	Date completed: 11/18/02 (X) Acceptable ( ) Withhold recommendation
❖ Methods validation **This is not required for approval**	( ) Completed ( ) Requested ( ) Not yet requested
Pharm/Tox Information	
❖ Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	X- (11/8/02)
❖ Nonclinical inspection review summary	N/A
Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	N/A
❖ CAC/ECAC report	N/A

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® for Oral Suspension (nitazoxanide 100 mg/5mL)

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

N021-498

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 and .
(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)

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

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

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

19-2

USER FEE VALIDATION SHEET

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?

S 9/10/02
PM Signature / Date

S 10 Sep 02
CPMS Concurrence Signature / Date

2/14/00

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 and (Nitazoxanide Oral Suspension) 100 mg/5 mL NDA#: —— 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# — 21-498

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 — an oral suspension with a concentration of
100 mg/5 mL. The recommended dose —
— 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. —
— 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 Suspension: 100 mg/5 mL		
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.

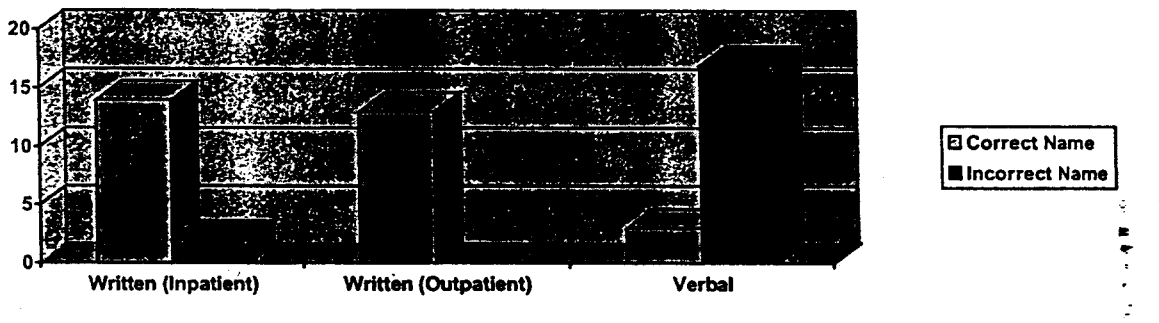
HANDWRITTEN PRESCRIPTION	VERBAL PRESCRIPTION
Outpatient RX: Alinia 100 mg/5mL	Alinia, 5 tsp. every 12 hours for 3 days, dispense 60 mL.
Inpatient RX: Alinia 100mg/5ml	

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 .

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 [redacted] and Climara.

We conducted prescription studies to simulate the prescription ordering process. Our study did not confirm confusion between Alinia and [redacted] 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.

Redacted 1

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secret and/or

confidential

commercial

information

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

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: October 16, 2002

NDA# [redacted] 21-498

NAME OF DRUG: **Cryptaz**

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, Cryptaz. The draft container labels and labeling for Cryptaz were reviewed for possible interventions in minimizing medication errors. The proprietary name was previously reviewed by the CDER Labeling and Nomenclature Committee (LNC) on May 14, 1998 and found acceptable.

PRODUCT INFORMATION

Cryptaz contains the active ingredient nitazoxanide, and is indicated for the treatment if diarrhea caused by *Cryptosporidium parvum* and *Giardia lamblia*, [redacted] [redacted] clinical experience with nitazoxanide for [redacted] Therefore, Cryptaz is not indicated in these patients. Cryptaz will be available [redacted] an oral suspension with a concentration of 100 mg/5 mL. [redacted] 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. [redacted] 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 Cryptaz 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 Cryptaz. 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 two proprietary names that were thought to have the potential for confusion with Cryptaz. 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 Cryptaz with regard to promotional claims if the drug is approved for a Cryptosporidium indication.

[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

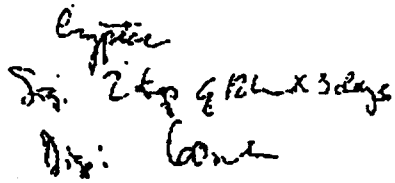
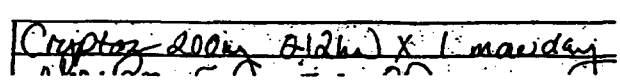
Product Name	Dosage form(s), Established name	Usual adult dose*	Other**
Cryptaz	Nitazoxanide Suspension: 100 mg/5 mL		
Ceptaz	Ceftazidime Powder for Injection: 1 and 2 gram vials Infusion Pack: 1 and 2 gram Pharmacy bulk package: 10 grams	1 gram IV or IM every 8 to 12 hours. Complicated Urinary Tract Infections: 500 mg every 8 to 12 hours.	**L/A, S/A
Cystospaz	Hycosamine Sulfate 0.15 mg Tablets	1 or 2 tablets four times daily or fewer, if needed.	**L/A, S/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 Cryptaz 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 Cryptaz (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.

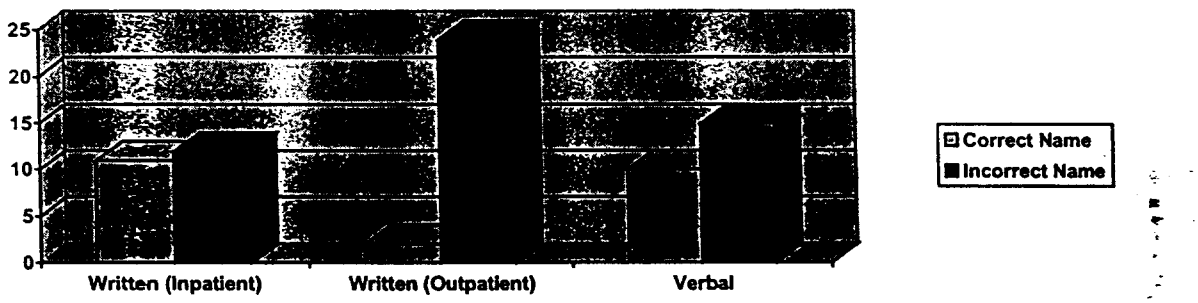
HANDWRITTEN PRESCRIPTION	VERBAL PRESCRIPTION
Outpatient RX: 	Cryptaz, 2 tsp. every 12 hours for 3 days, dispense 60 mL.
Inpatient RX: 	

2. Results:

The results are summarized in Table 2.

Table 2

Study	# of Participants	# of Responses (%)	Correctly Interpreted (%)	Incorrectly Interpreted (%)
Written Inpatient	32	23 (72%)	11 (48%)	12 (52%)
Written Outpatient	39	26 (67%)	2 (8%)	24 (92%)
Verbal	35	25 (71%)	10 (40%)	15 (60%)
Total	106	74 (70%)	23 (31%)	51 (69%)



Among the verbal prescription study participants for Cryptaz, 15 of 25 (60%) of the participants interpreted the name incorrectly. The majority of the responses were misspelled variations of "Cryptaz". The incorrect responses were *Criptaz (6), Kriptaz (3), Creptaz (1), Criptaze (1), Kruptaz (1), Kryptaz (2), and Protaz (1).*

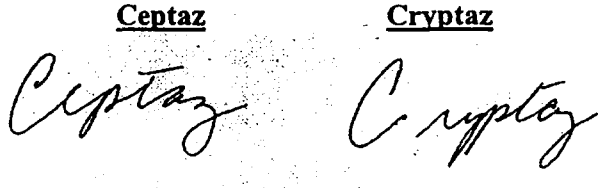
Among the written prescription study participants for Cryptaz, 36 of 49 (73%) of the participants interpreted the name incorrectly. The majority of the responses were misspelled variations of "Cryptaz". The incorrect responses were *Cryptor (6), Cryptoz (5) Cryptac (4), Cryptar (4), Cryptoc (3), Criptoz (2), Cruptaz (2), Emptor (2), Camptec (1), Comptor (1), Cozyptar (1), Cryptic (1), Cymptoc (1), Criptaz (1), Cruptoz (1), and Cryptax (1).*

C. SAFETY EVALUATOR RISK ASSESSMENT:

In reviewing the proposed proprietary name "Cryptaz", 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 Cryptaz were Ceptaz, Cystospaz, ——— Of these products, those considered to have the ***greatest*** potential for name confusion with Cryptaz were Ceptaz and Cystospaz.

We conducted prescription studies to simulate the prescription ordering process. Our study did not confirm confusion between Cryptaz and Ceptaz or Cystospaz. The majority of the incorrect interpretations of the written and verbal studies were misspelled/phonetic variations of the proposed name, Cryptaz. 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.

Ceptaz contains ceftazidime, a broad-spectrum cephalosporin antibiotic indicated for the treatment of patients with infections caused by susceptible strains of designated organisms. Ceptaz can be used alone or concomitantly with other antibiotics in cases of severe and life-threatening infections, and in immunocompromised patients. The recommended adult dose for Ceptaz is 1 gram administered intravenously or intramuscularly every 8 to 12 hours. However, the specific dosage and route of administration can vary depending on the condition being treated, the severity of the infection, and the renal function of the patient. The DMETS Expert Panel expressed concern that Ceptaz and the proposed name Cryptaz sound and look similar (see below), 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 adult dosing strength and dosing regimen for Cryptaz (500 mg taken every 12 hours). Furthermore, both 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.



Cystospaz contains hycosamine, a prescription only medication indicated in the management of disorders of the lower urinary tract associated with hypermotility. It is also effective as adjunctive therapy in the treatment of peptic ulcer and irritable bowel syndrome, acute enterocolitis, and other functional gastrointestinal disorders. The recommended adult dose of Cystospaz is one or two tablets taken by mouth four times daily. Fewer tablets may be taken if necessary. The DMETS Expert Panel expressed concern that Cystospaz and the proposed name Cryptaz may look and sound similar. The beginning of each name differ only by the addition of one letter ("cy" vs. "cry"), and the endings of the names contain the same letters ("az"). The names, however, differ in the number of syllables. Cystospaz contains three syllables, whereas Cryptaz contains two syllables. This helps to differentiate the drug names from each other when pronounced and written. Additionally, the medications differ in dosing regimen. The recommended dose of Cystospaz is 1 or 2 tablets four times daily or fewer, if needed. Whereas the recommended dose for Cryptaz will be one tablet every 12 hours for 3 days. These differences help to minimize the risk of confusion between the two drug products.

III. COMMENTS TO THE SPONSOR:

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 U.S. marketplace. The product considered having the greatest potential for name confusion was Ceptaz.

Ceptaz contains ceftazidime, a broad-spectrum cephalosporin antibiotic indicated for the treatment of patients with infections caused by susceptible strains of designated organisms. Ceptaz can be used alone or concomitantly with other antibiotics in cases of severe and life-threatening infections, and in immunocompromised patients. The recommended adult dose for Ceptaz is 1 gram administered intravenously or intramuscularly every 8 to 12 hours. However, the specific dosage and route of administration can vary depending on the condition being treated, the severity of the infection, and the renal function of the patient. The DMETS Expert Panel expressed concern that Ceptaz and the proposed name Cryptaz sound and look similar (see below), 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 [redacted]. Furthermore, both 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.

Ceptaz	Cryptaz
	

In review of the container label, and package insert labeling, DMETS has focused on safety issues relating to possible medication errors. DMETS has identified the following, which might minimize potential user error:

A. [redacted]

B. CONTAINER LABEL (Oral Suspension)

1. We note that the dosage form appears separate from the established name. We recommend the inclusion of the words "oral suspension" in the established name, and likewise its removal from the portion of the label above the product strength.

2. Include a statement indicating how many milligrams of active ingredient are present in each 5 mL of liquid after reconstitution.

3. The Poison Prevention Act required the use of a child-resistant closure (CRC) cap on unit-of-use drug products. We note you propose to market Cryptaz oral suspension as a unit-of-use bottle. Please ensure the use of a child-resistant closure cap.

IV. RECOMMENDATIONS:

A. DMETS does not recommend the use of the proprietary name Cryptaz.

B. DMETS recommends implementation of the labeling revision as outlined in Section III of this review.

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 301-827-7847.

/S/

Tia M. Harper-Velazquez, Pharm.D.
Safety Evaluator
Division of Medication Errors and Technical Support
Office of Drug Safety

Concur:

/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/

Tia Harper-Velazquez
11/1/02 02:55:51 PM
PHARMACIST

Alina Mahmud
11/1/02 02:59:46 PM
PHARMACIST

Carol Holquist
11/1/02 03:50:32 PM
PHARMACIST

Jerry Phillips
11/1/02 03:57:55 PM
DIRECTOR

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

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:	NDA SPONSOR: Romark Laboratories, L.C.
Cryptaz (Nitazoxanide Tablets) 500 mg and (Nitazoxanide Oral Suspension) 100 mg/5 mL NDA#: [redacted] 21-498	

SAFETY EVALUATOR: Tia M. Harper-Velazquez, Pharm.D.

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 "Cryptaz" 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 does not recommend the use of the proprietary name "Cryptaz". DMETS recommends revising the labels and labeling as described in section III of this review.

/S/

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

Demographic Worksheet

ion Information *(Enter all identifying information for the submission pertaining to this summary)*

NDA Number: 21-498 **Submission Type:** N/A (pilot) **Serial Number:** N/A (pilot)

Populations Included In Application *(Please provide information for each category listed below from the primary safety database excluding PK studies)*

Category		Number Exposed To Study Drug		Number Exposed To Study Drug		Number Exposed To Study Drug
Gender	Males	67	All Females	62	Females >50	0
Age:	0-#1 Mo.	0	>1 Mo.-#2Year		>2-#12	
	12-16	0	17-64	0	365	0
Race:	White	24	Black	50	Asian	0
	Other	Hispanic 55				

Gender-Based Analyses *(Please provide information for each category listed below.)*

Category	Was Analysis Performed?		If no is checked, indicate which applies or provide comment below	
Efficacy	☒ Yes	☐ No	☐ Inadequate #'s	☐ Disease Absent
Safety	☒ Yes	☐ No	☐ Inadequate #'s	☐ Disease Absent

Was gender-based analysis included in labeling?	
Yes	No
☐	☒
☐	☒

Is a dosing modification based on gender recommended in the label? ☐ Yes ☒ No

If the analysis was completed, who performed the analysis ☒Sponsor ☒FDA

Age-Based Analyses *(Please provide information for each category listed below)*

Category	Was Analysis Performed?		If no is checked, indicate which applies or provide comment below	
Efficacy	☒ Yes	☐ No	☐ Inadequate #'s	☐ Disease Absent
Safety	☒ Yes	☐ No	☐ Inadequate #'s	☐ Disease Absent

Was age-based analysis included in labeling?	
Yes	No
☒	☐
☒	☐

Is a dosing modification based on age recommended in the label? ☒ Yes ☐ No

If the analysis was completed, who performed the analysis ☒Sponsor ☒FDA

Race-Based Analyses *(Please provide information for each category listed below)*

Category	Was Analysis Performed?		If no is checked, indicate which applies or provide comment below	
Efficacy	☒ Yes	☐ No	☐ Inadequate #'s	☐ Disease Absent
Safety	☒ Yes	☐ No	☐ Inadequate #'s	☐ Disease Absent

Was race-based analysis included in labeling?	
Yes	No
☐	☒
☐	☒

Is a dosing modification based on race recommended in the label? ☐ Yes ☒ No

If the analysis was completed, who performed the analysis ☒Sponsor ☒FDA

In the comment section below, indicate whether an alternate reason (other than "inadequate numbers" or "disease absent") was provided for why a subgroup analysis was NOT performed, and/or if other subgroups were studied for which the metabolism or excretion of the drug might be altered (including if labeling was modified).

Comment: