

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

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

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS

**PATENT INFORMATION SUBMITTED WITH THE
FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT**
*For Each Patent That Claims a Drug Substance
(Active Ingredient), Drug Product (Formulation and
Composition) and/or Method of Use*

NDA NUMBER

21-818

NAME OF APPLICANT / NDA HOLDER

Romark Laboratories, L.C.

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME)

Alinia

ACTIVE INGREDIENT(S)

Nitazoxanide

STRENGTH(S)

500 mg

DOSAGE FORM

Tablet

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4). Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the *only* information relied upon by FDA for listing a patent in the Orange Book.

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FDA will not list patent information if you submit an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number

5,387,598

b. Issue Date of Patent

02/07/1995

c. Expiration Date of Patent

02/07/2012

d. Name of Patent Owner

Romark Laboratories, L.C.

Address (of Patent Owner)

3000 Bayport Drive, Suite 200

City/State

Tampa, FL

ZIP Code

33607

FAX Number (if available)

(813) 282-4910

Telephone Number

(813) 282-8544

E-Mail Address (if available)

marc.ayers@romark.com

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)

Address (of agent or representative named in 1.e.)

City/State

ZIP Code

FAX Number (if available)

Telephone Number

E-Mail Address (if available)

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above?

Yes

No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?

Yes

No

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement? Yes No

2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement? Yes No

2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b). Yes No

2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.

2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.) Yes No

2.6 Does the patent claim only an intermediate? Yes No

2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) Yes No

3. Drug Product (Composition/Formulation)

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement? Yes No

3.2 Does the patent claim only an intermediate? Yes No

3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) Yes No

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement? Yes No

4.2 Claim Number (as listed in the patent)	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
17		<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No

4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: (Submit indication or method of use information as identified specifically in the proposed labeling.) Diarrhea caused by Cryptosporidium parvum
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5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product. Yes

6. Declaration Certification

6.1 The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide Information below)



Date Signed

6/14/2005

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

NDA Applicant/Holder

NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official

Patent Owner

Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name

Marc S. Ayers, President and CEO of Romark Laboratories, L.C.

Address

3000 Bayport Drive, Suite 200

City/State

Tampa, FL

ZIP Code

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Telephone Number

(813) 282-8544

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Alinia

ACTIVE INGREDIENT(S)

Nitazoxanide

STRENGTH(S)

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1. GENERAL

a. United States Patent Number

5,578,621

b. Issue Date of Patent

11/26/1996

c. Expiration Date of Patent

11/26/2013

d. Name of Patent Owner

Romark Laboratories, L.C.

Address (of Patent Owner)

3000 Bayport Drive, Suite 200

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f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above?

Yes

No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?

Yes

No

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement? Yes No

2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement? Yes No

2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b). Yes No

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2.6 Does the patent claim only an intermediate? Yes No

2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) Yes No

3. Drug Product (Composition/Formulation)

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement? Yes No

3.2 Does the patent claim only an intermediate? Yes No

3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) Yes No

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement? Yes No

4.2 Claim Number (as listed in the patent) 4, 7 Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? Yes No

4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product. Use: (Submit indication or method of use information as identified specifically in the proposed labeling.)
Diarrhea caused by Cryptosporidium parvum

5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product. Yes

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Date Signed

6/14/2005

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NDA Applicant/Holder

NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official

Patent Owner

Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name

Marc S. Ayers, President and CEO of Romark Laboratories, L.C.

Address

3000 Bayport Drive, Suite 200

City/State

Tampa, FL

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Telephone Number

(813) 282-8544

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E-Mail Address (if available)

marc.ayers@romark.com

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NDA NUMBER

21-818

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Alinia

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Nitazoxanide

STRENGTH(S)

500 mg

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1. GENERAL

a. United States Patent Number

5,968,961

b. Issue Date of Patent

10/19/1999

c. Expiration Date of Patent

05/07/2017

d. Name of Patent Owner

Romark Laboratories, L.C.

Address (of Patent Owner)

3000 Bayport Drive, Suite 200

City/State

Tampa, FL

ZIP Code

33607

FAX Number (if available)

(813) 282-4910

Telephone Number

(813) 282-8544

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marc.ayers@romark.com

e. **Name of agent or representative** who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)

Address (of agent or representative named in 1.e.)

City/State

ZIP Code

FAX Number (if available)

Telephone Number

E-Mail Address (if available)

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above?

Yes

No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?

Yes

No

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement? Yes No

2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement? Yes No

2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b). Yes No

2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.

2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.) Yes No

2.6 Does the patent claim only an intermediate? Yes No

2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) Yes No

3. Drug Product (Composition/Formulation)

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement? Yes No

3.2 Does the patent claim only an intermediate? Yes No

3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) Yes No

4. Method of Use

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4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement? Yes No

4.2 Claim Number (as listed in the patent) Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? Yes No

4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product. Use: (Submit indication or method of use information as identified specifically in the proposed labeling.)

5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product. Yes

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Date Signed



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NDA Applicant/Holder

NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official

Patent Owner

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Name

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I. GENERAL

a. United States Patent Number

6,020,353

b. Issue Date of Patent

02/01/2000

c. Expiration Date of Patent

09/18/2014

d. Name of Patent Owner

Romark Laboratories, L.C.

Address (of Patent Owner)

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f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above?

Yes

No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?

Yes

No

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3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement? Yes No

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4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product. Use: (Submit indication or method of use information as identified specifically in the proposed labeling.)

5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product. Yes

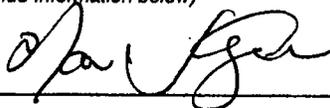
6. Declaration Certification

6.1 The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide Information below)

Date Signed



6/14/2005

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

NDA Applicant/Holder

NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official

Patent Owner

Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name

Marc S. Ayers, President and CEO of Romark Laboratories, L.C.

Address

3000 Bayport Drive, Suite 200

City/State

Tampa, FL

ZIP Code

33607

Telephone Number

(813) 282-8544

FAX Number (if available)

(813) 282-4910

E-Mail Address (if available)

marc.ayers@romark.com

The public reporting burden for this collection of information has been estimated to average 9 hours 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:

Food and Drug Administration
CDER (HFD-007)
5600 Fishers Lane
Rockville, MD 20857

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.

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:

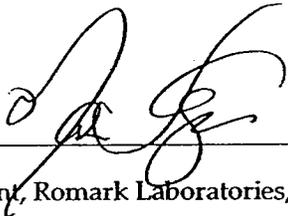
1. Patent number and expiration date: 5,387,598 expiring February 7, 2012
2. Type of patent: Drug product and method of use
3. Name of the patent owner: Romark Laboratories, L.C.
4. The owner of the patent and the NDA applicant are the same entity and have a place of business within the United States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

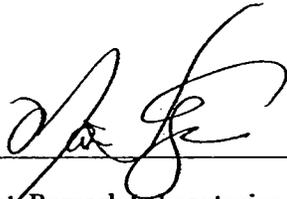
1. Patent number and expiration date: 5,859,038 expiring September 8, 2014
2. Type of patent: Method of use
3. Name of the patent owner: Romark Laboratories, L.C.
4. The owner of the patent and the NDA applicant are the same entity and have a place of business within the United States at the following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

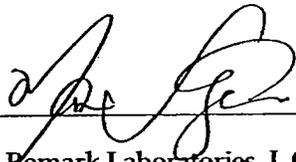
1. Patent number and expiration date: 5,886,013 expiring May 1, 2017
2. Type of patent: Drug product and method of use
3. Name of the patent owner: Romark Laboratories, L.C.
4. The owner of the patent and the NDA applicant are the same entity and have a place of business within the United States at the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

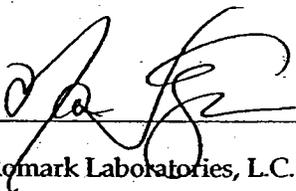
- 1. Patent number and expiration date: 5,935,591 expiring January 15, 2018
- 2. Type of patent: Method of use
- 3. Name of the patent owner: Romark Laboratories, L.C.
- 4. The owner of the patent and the NDA applicant are the same entity and have a place of business within the United States at the following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

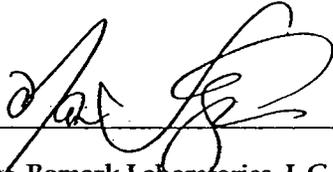
- 1. Patent number and expiration date: 5,968,961 expiring May 7, 2017
- 2. Type of patent: Drug product
- 3. Name of the patent owner: Romark Laboratories, L.C.
- 4. The owner of the patent and the NDA applicant are the same entity and have a place of business within the United States at the following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

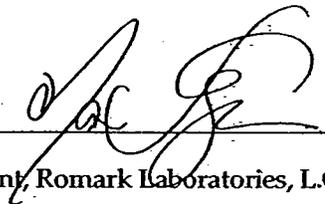
1. Patent number and expiration date: 6,020,353 expiring September 8, 2014
2. Type of patent: Drug and drug product
3. Name of the patent owner: Romark Laboratories, L.C.
4. The owner of the patent and the NDA applicant are the same entity and have a place of business within the United States at the 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 the Cryptaz® (nitazoxanide) tablets. 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 # 21-818 and 21-498/S-003

Trade Name Alinia Generic Name nitazoxanide

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

Approval Date If Known June 16, 2005

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following question about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?
YES /x/ NO /___/

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3, SE4, SE5, SE6, SE7, SE8

21-818 - 505(b)(1) and 21-498/S-003 - SE5

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.

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:

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?

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

YES /___/ NO /_X_/

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

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

YES /___/ NO /_X_/

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (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 /_X_/ NO /___/

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

NDA# 21-498 Alinia (nitazoxanide) for Oral Suspension

NDA# 21-497 Alinia (nitazoxanide) Tablets

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 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.) IF "YES" GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

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 8.

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.

(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 8:

(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 /_X_/

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:

Study RM01-3010: Multicenter, Double-Blind, Placebo-Controlled Study of Nitazoxanide Tablets in the Treatment of Cryptosporidium in Adults and Adolescents

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

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 /_X_/

Investigation #2 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:

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

/s/

Renata Albrecht
6/15/05 05:43:19 PM

17.0 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.



Marc S. Ayers, President



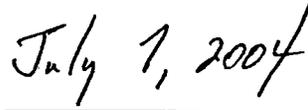
Date

17.0 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.



Marc S. Ayers, President



Date

- 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. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ 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: _____

Date studies are due (mm/dd/yy): 7/22/09

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. 16 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}

Regulatory Project Manager

cc: NDA 21-818
NDA 21-498/S-003
HFD-960/ Grace Carmouze

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/

Kristen Miller
6/15/05 02:26:56 PM

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}

Regulatory Project Manager

cc: NDA 21-498
HFD-960/ Grace Carmouze

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/

Kristen Miller

7/9/04 12:41:45 PM

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information

Romark submitted NDA 21-497 and 21-498 for **Alinia (nitazoxanide) Tablets and Oral Suspension**, respectively on May 29, 2002. On November 22, 2002, 21-498 was approved for treatment of diarrhea caused by *Cryptosporidium parvum* and *Giardia lamblia* in patients 1- 11 years of age, and 21-497 was issued an approvable letter. On January 28, 2004, NDA 21-497 was resubmitted and 21-498/S-001 was submitted and on July 21, 2004, NDA 21-497 and 21-498/S-001 were approved for treatment of diarrhea caused by *Giardia lamblia* in patients 12 years of age and older. On July 21, 2004, NDA 21-497 was administratively split into **21-818**, and this was issued an approvable letter for treatment of diarrhea caused by *Cryptosporidium parvum* in patients 12 years of age and older. On December 17, 2004, Romark resubmitted 21-818 and submitted 21-498/S-003 for the treatment of diarrhea caused by *Cryptosporidium parvum* in patients 12 years of age and older.

NDA: 21-498/S-003 21-818	Efficacy Supplement Type- SE5	Supplement Number: 003
Drug: Alinia (nitazoxanide) for Oral Suspension- 21-498/S-003 Tablets- 21-818		Applicant: Romark Laboratories, L.C.
RPM: Kristen Miller		HFD-590 Phone #: (301) 827-2127
Application Type: <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)		Reference Listed Drug (NDA #, Drug name): N/A
❖ Application Classifications:		
• Review priority		<input type="checkbox"/> Standard <input checked="" type="checkbox"/> Priority
• Chem class (NDAs only)		Class 3
• Other (e.g., orphan, OTC)		Orphan
❖ User Fee Goal Dates		June 20, 2005
Special programs (indicate all that apply)		<input checked="" type="checkbox"/> None Subpart H <input type="checkbox"/> 21 CFR 314.510 (accelerated approval) <input type="checkbox"/> 21 CFR 314.520 (restricted distribution) <input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review
❖ User Fee Information-		
• User Fee		<input type="checkbox"/> Paid N/A
• User Fee waiver		<input type="checkbox"/> Small business <input type="checkbox"/> Public health N/A <input type="checkbox"/> Barrier-to-Innovation <input type="checkbox"/> Other
• User Fee exception -		<input checked="" type="checkbox"/> Orphan designation <input type="checkbox"/> No-fee 505(b)(2) <input type="checkbox"/> Other
❖ Application Integrity Policy (AIP)		
• Applicant is on the AIP		<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
• This application is on the AIP		<input type="checkbox"/> Yes <input checked="" type="checkbox"/> 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.		<input checked="" type="checkbox"/> Verified
❖ Patent-		
• Information: Verify that patent information was submitted		<input checked="" type="checkbox"/> Verified
• Patent certification [505(b)(2) applications]: Verify type of certifications submitted		21 CFR 314.50(i)(1)(i)(A) <input type="checkbox"/> I <input type="checkbox"/> II <input type="checkbox"/> III <input type="checkbox"/> IV

	21 CFR 314.50(i)(1) () (ii) () (iii)	N/A
<ul style="list-style-type: none"> 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)		
<ul style="list-style-type: none"> Exclusivity summary 	X- (6/15/05)	
<ul style="list-style-type: none"> 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)	X- 6/15/05	
General Information		
❖ Actions		
<ul style="list-style-type: none"> Proposed action 	(X) AP () TA () AE () NA	
<ul style="list-style-type: none"> Previous actions (specify type and date for each action taken) 	AE (21-818) – 7/21/04	
<ul style="list-style-type: none"> Status of advertising (approvals only) 	() Materials requested in AP letter () Reviewed for Subpart H	
❖ Public communications		
<ul style="list-style-type: none"> Press Office notified of action (approval only): 	(X) Yes () Not applicable	
<ul style="list-style-type: none"> Indicate what types (if any) of information dissemination are anticipated 	() None (X) Press Release- by sponsor () Talk Paper () Dear Health Care Professional Letter	
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable))		
<ul style="list-style-type: none"> Division's proposed labeling (only if generated after latest applicant submission of labeling) 	N/A	
<ul style="list-style-type: none"> Most recent applicant-proposed labeling 	X- 6/14/05	
<ul style="list-style-type: none"> Original applicant-proposed labeling 	X	
<ul style="list-style-type: none"> Labeling reviews (including DDMAC, Office of Drug Safety trade name review, nomenclature reviews) and minutes of labeling meetings (indicate dates of reviews and meetings) 	N/A	
<ul style="list-style-type: none"> Other relevant labeling (e.g., most recent 3 in class, class labeling) 	N/A	
❖ Labels (immediate container & carton labels)		
<ul style="list-style-type: none"> Division proposed (only if generated after latest applicant submission) 	N/A	
<ul style="list-style-type: none"> Applicant proposed 	X	
<ul style="list-style-type: none"> Reviews 	N/A	
❖ Post-marketing commitments		
<ul style="list-style-type: none"> Agency request for post-marketing commitments 	N/A	
<ul style="list-style-type: none"> Documentation of discussions and/or agreements relating to post-marketing commitments 	N/A	
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	N/A	
Memoranda and Telecons	Division Requests for Information included: 1/14/05, 5/17/05	
❖ Minutes of Meetings		
<ul style="list-style-type: none"> EOP2 meeting (indicate date) 	N/A- no meeting occurred as all of the information was gathered	

	under Unimed (previous sponsor) for NDA 20-871 (NA in 1998).
• Pre-NDA meeting (indicate date)	Meeting held on 9/19/01, but no minutes available
• Pre-Approval Safety Conference (indicate date; approvals only)	N/A
• 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 – 6/15/05
Clinical Information	
❖ Clinical review(s) (indicate date for each review)	X- Executive Summary (6/15/05) X- Clinical Review (6/14/05)
❖ Microbiology (efficacy) review(s) (indicate date for each review)	X- (6/3/05)
❖ Safety Update review(s) (indicate date or location if incorporated in another review)	See Clinical Review (6/14/05)
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	X- (6/15/05)
❖ Demographic Worksheet (NME approvals only)	N/A
❖ Statistical review(s) (indicate date for each review)	X- (6/15/05)
❖ Biopharmaceutical review(s) (indicate date for each review)	X- (6/15/05)
Controlled Substance Staff review(s) and recommendation for scheduling (indicate date for each review)	N/A
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	N/A
• Bioequivalence studies	N/A
CMC Information	
❖ CMC review(s) (indicate date for each review)	X- (6/10/05)
❖ 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)	N/A
❖ Facilities inspection (provide EER report)	Date completed: N/A (X) Acceptable () Withhold recommendation
❖ Methods validation	This is not required for approval () Completed () Requested () Not yet requested
Nonclinical Pharm/Tox Information	
❖ Pharm/tox review(s), including referenced IND reviews (indicate date for each review)	X- (6/15/05)
❖ Nonclinical inspection review summary	N/A
Statistical review(s) of carcinogenicity studies (indicate date for each review)	N/A
❖ CAC/ECAC report	N/A

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information		
NDA: 21-818	Efficacy Supplement Type SE- N/A	Supplement Number: N/A
Drug: Alinia (nitazoxanide) Tablets		Applicant: Romark Laboratories, L.C.
RPM: Kristen Miller		HFD-590 Phone #: (301) 827-2127
Application Type: <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)		Reference Listed Drug (NDA #, Drug name): N/A
❖ Application Classifications:		
• Review priority		<input type="checkbox"/> Standard <input checked="" type="checkbox"/> Priority (Resubmission)
• Chem class (NDAs only)		Class 3 (new formulation)
• Other (e.g., orphan, OTC)		Orphan
❖ User Fee Goal Dates		
		July 29, 2004
❖ Special programs (indicate all that apply)		
		<input checked="" type="checkbox"/> None Subpart H <input type="checkbox"/> 21 CFR 314.510 (accelerated approval) <input type="checkbox"/> 21 CFR 314.520 (restricted distribution) <input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review
User Fee Information-		
• User Fee		<input type="checkbox"/> Paid N/A
• User Fee waiver		<input type="checkbox"/> Small business <input type="checkbox"/> Public health N/A <input type="checkbox"/> Barrier-to-Innovation <input type="checkbox"/> Other
• User Fee exception -		<input checked="" type="checkbox"/> Orphan designation <input type="checkbox"/> No-fee 505(b)(2) <input type="checkbox"/> Other
❖ Application Integrity Policy (AIP)		
• Applicant is on the AIP		<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
• This application is on the AIP		<input type="checkbox"/> Yes <input checked="" type="checkbox"/> 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.		
		<input checked="" type="checkbox"/> Verified
❖ Patent-		
• Information: Verify that patent information was submitted		<input checked="" type="checkbox"/> Verified
• Patent certification [505(b)(2) applications]: Verify type of certifications submitted		21 CFR 314.50(i)(1)(i)(A) <input type="checkbox"/> I <input type="checkbox"/> II <input type="checkbox"/> III <input type="checkbox"/> IV N/A 21 CFR 314.50(i)(1) <input type="checkbox"/> (ii) <input type="checkbox"/> (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).		<input type="checkbox"/> Verified N/A

❖ Exclusivity (approvals only)	
<ul style="list-style-type: none"> Exclusivity summary 	N/A
<ul style="list-style-type: none"> 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)	Filing Checklist- 7/9/04 (under Summary Review)
General Information	
❖ Actions	
<ul style="list-style-type: none"> Proposed action 	() AP () TA (X) AE () NA
<ul style="list-style-type: none"> Previous actions (specify type and date for each action taken) 	AE- November 22, 2002
<ul style="list-style-type: none"> Status of advertising (approvals only) 	N/A () Materials requested in AP letter () Reviewed for Subpart H
❖ Public communications	
<ul style="list-style-type: none"> Press Office notified of action (approval only) 	() Yes (X) Not applicable
<ul style="list-style-type: none"> Indicate what types (if any) of information dissemination are anticipated 	(X) None () Press Release () Talk Paper () Dear Health Care Professional Letter
^ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable))	
<ul style="list-style-type: none"> Division's proposed labeling (only if generated after latest applicant submission of labeling) 	N/A: Discuss when comes back in
<ul style="list-style-type: none"> Most recent applicant-proposed labeling 	N/A: Discuss when comes back in
<ul style="list-style-type: none"> Original applicant-proposed labeling 	X
<ul style="list-style-type: none"> 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 review- 5/13/04 Trade name review- 11/22/02
<ul style="list-style-type: none"> Other relevant labeling (e.g., most recent 3 in class, class labeling) 	N/A
❖ Labels (immediate container & carton labels)	
<ul style="list-style-type: none"> Division proposed (only if generated after latest applicant submission) 	N/A
<ul style="list-style-type: none"> Applicant proposed 	X
<ul style="list-style-type: none"> Reviews 	Under Label/Labeling Consults: DMETS review: 7/2/04
❖ Post-marketing commitments	
<ul style="list-style-type: none"> Agency request for post-marketing commitments 	N/A
<ul style="list-style-type: none"> Documentation of discussions and/or agreements relating to post-marketing commitments 	N/A
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	N/A – No issues arose that required letters/ faxes/ etc.
❖ Memoranda and Telecons	N/A
❖ Minutes of Meetings	
<ul style="list-style-type: none"> 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).
<ul style="list-style-type: none"> Pre-NDA meeting (indicate date) 	No minutes available (9/19/01)

• Pre-Approval Safety Conference (indicate date; approvals only)	N/A
• 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- July 21, 2004
Clinical Information	
❖ Clinical review(s) (indicate date for each review)	X- Executive Summary (7/21/04) X- Clinical Review - (7/21/04)
❖ Microbiology (efficacy) review(s) (indicate date for each review)	X- 7/19/04
❖ Safety Update review(s) (indicate date or location if incorporated in another review)	See Clinical Review (7/21/04)
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	X- (7/9/04)
❖ Demographic Worksheet (NME approvals only)	N/A
❖ Statistical review(s) (indicate date for each review)	X- (7/6/04)
❖ Biopharmaceutical review(s) (indicate date for each review)	X- (7/15/04)
❖ Controlled Substance Staff review(s) and recommendation for scheduling (indicate date for each review)	N/A
Clinical Inspection Review Summary (DSI)	
• Clinical studies	N/A
• Bioequivalence studies	N/A
CMC Information	
❖ CMC review(s) (indicate date for each review)	X- (7/9/04)
❖ 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 (7/19/04)
❖ Facilities inspection (provide EER report)	Date completed: (7/9/04) (X) Acceptable () Withhold recommendation
❖ Methods validation	This is not required for approval. () Completed () Requested () Not yet requested
Nonclinical Pharm/Tox Information	
❖ Pharm/tox review(s), including referenced IND reviews (indicate date for each review)	X- (7/9/04)
❖ Nonclinical inspection review summary	N/A
❖ Statistical review(s) of carcinogenicity studies (indicate date for each review)	N/A
CAC/ECAC report	N/A



Teleconference Minutes

Teleconference Date: June 13, 2005

Application Numbers: NDA 21-818 Alinia® (nitazoxanide) Tablets
NDA 21-498/S-003 Alinia® (nitazoxanide) Oral Suspension

Sponsor: Romark Laboratories

Attendees:

Romark Laboratories

Marc Ayers President and CEO
Heidi Ano Director of Regulatory Affairs

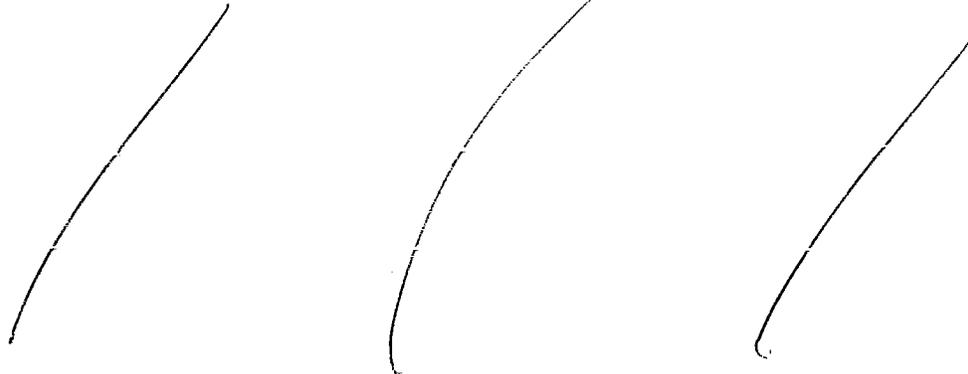
Division of Special Pathogen and Immunologic Drug Products

Eileen Navarro, M.D. Medical Team Leader
Joette Meyer, Pharm.D. Medical Reviewer
Karen Higgins, Sc.D. Statistical Team Leader
Ruthanna Davi, Ph.D. Statistical Reviewer
Shukal Bala, Ph.D. Microbiology Team Leader
Kalavati Suvarna, Ph.D. Microbiology Reviewer
Sheetal Patel Pharmacy Intern
Kristen Miller, Pharm.D. Regulatory Project Manager

BACKGROUND: On May 29, 2002, Romark submitted NDA 21-497 and 21-498 for Alinia (nitazoxanide) Tablets and Oral Suspension, respectively. On November 22, 2002, 21-498 was approved for treatment of diarrhea caused by *Cryptosporidium parvum* and *Giardia lamblia* in patients 1- 11 years of age, and 21-497 was issued an approvable letter. On January 28, 2004, NDA 21-497 was resubmitted and 21-498/S-001 was submitted and on July 21, 2004, NDA 21-497 and 21-498/S-001 were approved for treatment of diarrhea caused by *Giardia lamblia* in patients 12 years of age and older. On July 21, 2004, NDA 21-497 was administratively split into 21-818, and this was issued an approvable letter for treatment of diarrhea caused by *Cryptosporidium parvum* in patients 12 years of age and older. On December 17, 2004, Romark resubmitted 21-818 and submitted 21-498/S-003 for the treatment of diarrhea caused by *Cryptosporidium parvum* in patients 12 years of age and older. The Division requested a telecon to discuss the labeling for this application.

DISCUSSION POINTS:

Following introductions, the Review Team proposed the following changes to the CLINICAL STUDIES section:



The Review Team asked Romark to provide a chart comparing Studies RM-NTZ-98-002 and RM01-3010, including the similarities and differences of the patient population, demographics, design, endpoints, and evaluation. Romark agreed to submit the table and the labeling with the discussed changes by the close of business on June 13, 2005.

Addendum: The table comparing the studies and the labeling with the changes accepted was submitted to the Division electronically on June 13 and submitted formally on June 14, 2005.

ACTION ITEMS

1. Romark will submit labeling with the discussed changes on June 13, 2005.
2. Romark will submit a chart comparing Studies RM-NTZ-98-002 and RM01-3010 on June 13, 2005.

Minutes Preparer: Kristen Miller, Pharm.D., Project Manager
Chair Concurrence: Eileen Navarro, M.D., Clinical Team Leader

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

/s/

Kristen Miller
6/22/05 09:25:02 AM
CSO

Eileen Navarro
7/5/05 09:24:58 AM
MEDICAL OFFICER

NDA REGULATORY FILING REVIEW

NDA # **21-498/S-003** and **21-818** Supplement # **003** SE5

Trade Name: **Alinia**
Generic Name: **nitazoxanide**
Strengths: **500 mg Tablets and 100mg/5mL Oral Suspension**

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

Date of Application: **21-818: May 29, 2002 (resubmission: December 17, 2004)**
21-498/S-003: December 17, 2004

Date of Receipt: **21-818: May 29, 2002 (resubmission: December 20, 2004)**
21-498/S-003: December 20, 2004

Date clock started after UN: **N/A**
Date of Filing Meeting: **Complete response determined on January 13, 2004**
Filing Date: **February 18, 2005**
Action Goal Date (optional): **June 15, 2005** User Fee Goal Date: **June 20, 2005**

Indication(s) requested: **Treatment of diarrhea caused by Cryptosporidium parvum in patients age 12 years of age and older**

Type of Original NDA: (b)(1) (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
Resubmission after withdrawal? No Resubmission after refuse to file? No

Chemical Classification: (1,2,3 etc.) **NDA: class 3 (new formulation)**

Other (orphan, OTC, etc.) Orphan _____

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

Form 3397 (User Fee Cover Sheet) submitted: YES NO

User Fee ID # N/A _____

Clinical data? YES 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:

Nitazoxanide 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

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: 48,620
- 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

ATTACHMENT

MEMO OF FILING MEETING

BACKGROUND:

Romark submitted NDA 21-497 and 21-498 for Alinia (nitazoxanide) Tablets and Oral Suspension, respectively on May 29, 2002. On November 22, 2002, 21-498 was approved for treatment of diarrhea caused by *Cryptosporidium parvum* and *Giardia lamblia* in patients 1- 11 years of age, and 21-497 was issued an approvable letter. On January 28, 2004, NDA 21-497 was resubmitted and 21-498/S-001 was submitted and on July 21, 2004, NDA 21-497 and 21-498/S-001 were approved for treatment of diarrhea caused by *Giardia lamblia* in patients 12 years of age and older. On July 21, 2004, NDA 21-497 was administratively split into 21-818, and this was issued an approvable letter for treatment of diarrhea caused by *Cryptosporidium parvum* in patients 12 years of age and older. On December 17, 2004, Romark resubmitted 21-818 and submitted 21-498/S-003 for the treatment of diarrhea caused by *Cryptosporidium parvum* in patients 12 years of age and older.

ASSIGNED REVIEWERS:

<u>Discipline</u>	<u>Reviewer</u>
Medical:	Joette Meyer, M.D.
Statistical:	Ruthanna Davi, Ph.D.
Pharmacology:	Steven Kunder, Ph.D.
Chemistry:	Gene Holbert, Ph.D.
Biopharmaceutical:	Dakshina Chilukuri, Ph.D.
Microbiology, clinical:	Kalavati Suvarna, Ph.D.
Regulatory Project Management:	Kristen Miller, Pharm.D.

Per reviewers, are all parts in English or English translation? YES NO

If no, explain:

CLINICAL FILE REFUSE TO FILE

• Clinical site inspection needed: YES NO

• Advisory Committee Meeting needed? YES, date if known _____ NO

• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? N/A YES NO

CLINICAL MICROBIOLOGY NA _____ FILE REFUSE TO FILE

STATISTICS FILE REFUSE TO FILE

BIOPHARMACEUTICS FILE REFUSE TO FILE

• Biopharm. inspection needed: YES NO

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/s/

Kristen Miller
6/15/05 05:52:45 PM
CSO



**Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation IV**

FACSIMILE TRANSMITTAL SHEET

DATE: May 17, 2005

To: Marc Ayers	From: Kristen Miller
Company: Romark Laboratories, L.C.	Division of Special Pathogen and Immunologic Drug Products
Fax Number: (813) 282-4910	Fax Number: 301-827-2475
Phone Number: (813) 282-8544	Phone Number: 301-827-2127

Subject: Requests for information

Total no. of pages including cover: 3

Comments: Concur:

Joette Meyer, Pharm.D.; Clinical Reviewer
Eileen Navarro, M.D.; Clinical Team Leader

Document to be mailed: • YES NO

**THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS
ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND
PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.**

If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at 301-827-2127. Thank you.

We acknowledge receipt on December 20, 2004 of your December 17, 2004 resubmission to your new drug application (21-818) for Alinia ® (nitazoxanide) Tablets, 500 mg and your new supplement to your new drug application (21-498/S-003), Alinia ® (nitazoxanide) for Oral Suspension, 100 mg/ 5 mL. To facilitate labeling discussions scheduled for June 3, 2005, please provide the following information:

Please clarify how the placebo rate in the population studied in Egypt correlates to the natural history of cryptosporidium in normal hosts in the United States. Specifically, please address the following:

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

We are providing the above information via telephone facsimile for your convenience. Please feel free to contact me at 301-827-2127 if you have any questions regarding the contents of this transmission.

Kristen Miller, Pharm.D.
Regulatory Project Manager

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/s/

Kristen Miller
5/17/05 09:24:14 AM
CSO



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-818

Romark Laboratories, L.C.
Attention: Mr. Marc S. Ayers
President & C.E.O.
3000 Bayport Drive
Suite 200
Tampa, Florida 33607

Dear Mr. Ayers:

We acknowledge receipt on December 20, 2004 of your December 17, 2004 resubmission to your new drug application for Alinia ® (nitazoxanide) Tablets, 500 mg.

We consider this to be a complete, class 2 response to our July 21, 2004 action letter. Therefore, the user fee goal date is June 20, 2005.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred.

The November 22, 2002 approval letter for NDA 21-498 stated the following:

For the treatment of diarrhea caused by Cryptosporidium parvum and Giardia lamblia,

- *We are deferring submission of pediatric studies for patients less than one year of age until November 22, 2007.*
- *We are deferring submission of pediatric studies for patients twelve through sixteen years of age until November 22, 2007.*
- *You have fulfilled the pediatric study requirement at this time for patients one through eleven years of age.*

If you have any questions, please call Kristen Miller, Pharm.D., Regulatory Project Manager, at (301) 827-2127.

Sincerely,

{See appended electronic signature page}

Diana Willard
Chief, Project Management Staff
Division of Special Pathogen and Immunologic
Drug Products, HFD-590
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

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/s/

Diana Willard

1/18/05 08:08:25 AM

NDA 21-818 Acknowledgement of a Class 2 Complete Response



**Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation IV**

FACSIMILE TRANSMITTAL SHEET

DATE: January 14, 2005

To: Marc Ayers	From: Kristen Miller
Company: Romark Laboratories, L.C.	Division of Special Pathogen and Immunologic Drug Products
Fax Number: (813) 282-4910	Fax Number: 301-827-2475
Phone Number: (813) 282-8544	Phone Number: 301-827-2127

Subject: Requests for information

Total no. of pages including cover: 3

Comments: Concur:

Joette Meyer, Pharm.D.; Clinical
Eileen Navarro, M.D.; Clinical Team Leader
Jyoti Zalkikar, Ph.D.; Statistics

Document to be mailed:

YES

NO

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We acknowledge receipt on December 20, 2004 of your December 17, 2004 resubmission to your new drug application (21-818) for Alinia ® (nitazoxanide) Tablets, 500 mg and your new supplement to your new drug application (21-498/S-003), Alinia ® (nitazoxanide) for Oral Suspension, 100 mg/ 5 mL.

To facilitate our review of these applications, please provide the following information:

1. An electronic table of adverse event data from the 1657 HIV-negative patients (ages 12 years and older) who received NTZ tablets in controlled and uncontrolled clinical trials. In addition, please indicate how many of the 1657 patients came from each study (including the study number), the duration of therapy (did they all receive 3 day treatment regimens?), and the type of infection being treated (e.g., Cryptosporidium, Giardia). For the controlled studies, please include the adverse events reported for the placebo and/or comparator arms, as well.
2. A similar adverse event tables where the patients (i.e., the 1657 patients treated with NTZ plus the additional placebo and comparator-treated patients) are grouped by:
 - age (i.e., one table for patients aged 12 to less than 18 years, and another for 18 years and older)
 - sex
 - race
3. Electronic tables of the deaths, drop-outs due to adverse events or other serious or potentially serious adverse events, and adverse events related to laboratory abnormalities for the 1657 treated with NTZ plus the additional placebo and comparator-treated patients.
4. The CRFs for the following patients:

Pat #	Grt #
4	4255
7	4258
20	4271
29	4280
70	4306
94	4318
101	4325
109	4333
115	4339
116	4340

We are providing the above information via telephone facsimile for your convenience. Please feel free to contact me at 301-827-2127 if you have any questions regarding the contents of this transmission.

Kristen Miller, Pharm.D.
Regulatory Project Manager

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/s/

Kristen Miller
1/14/05 01:36:48 PM
CSO



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-498/S-003

Romark Laboratories, L.C.
Attention: Mr. Marc S. Ayers
President & C.E.O.
3000 Bayport Drive
Suite 200
Tampa, Florida 33607

Dear Mr. Ayers:

We have received your supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product:	Alinia® (nitazoxanide) for Oral Suspension, 100 mg/ 5 mL
NDA Number:	21-498
Supplement number:	003
Review Priority Classification:	Priority (P)
Date of supplement:	December 17, 2004
Date of receipt:	December 20, 2004

This supplemental application proposes the following change

- extension of the indication of Alinia® for Oral Suspension to include the treatment of diarrhea caused by *Cryptosporidium parvum* in patients 12 years and older.

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on February 18, 2005 in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be June 20, 2005.

Under 21 CFR 314.102(c), you may request an informal conference with this Division (to be held approximately 90 days from the above receipt date) for a brief report on the status of the review but not on the ultimate approvability of the application. Alternatively, you may choose to receive a report by telephone.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and

effectiveness of the product in pediatric patients unless this requirement is waived or deferred.

The November 22, 2002 approval letter for NDA 21-498 stated the following:

For the treatment of diarrhea caused by Cryptosporidium parvum and Giardia lamblia,

- *We are deferring submission of pediatric studies for patients less than one year of age until November 22, 2007.*
- *We are deferring submission of pediatric studies for patients twelve through sixteen years of age until November 22, 2007.*
- *You have fulfilled the pediatric study requirement at this time for patients one through eleven years of age.*

The July 21, 2004 approval letter for NDA 21-497 (Alinia® {nitazoxanide} Tablets, 500 mg) and NDA 21-498/S-002 was for the treatment of diarrhea caused by Giardia lamblia in patients 12 years of age and older. This letter stated the following:

For the treatment of diarrhea caused by Giardia lamblia,

- *We are deferring submission of pediatric studies for patients zero months to twelve months of age until July 22, 2009.*
- *You have fulfilled the pediatric study requirement at this time for patients one through sixteen years of age.*

If you believe that this drug qualifies for a waiver of the pediatric study requirement, you should submit a request for a waiver with supporting information and documentation in accordance with the provisions of section 2 of the Pediatric Research Equity Act (PREA) within 60 days from the date of this letter. We will notify you within 120 days of receipt of your response whether a waiver is granted. If a waiver is not granted, we will ask you to submit your pediatric drug development plans within 120 days from the date of denial of the waiver.

Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products (pediatric exclusivity). You should refer to the Guidance for Industry on Qualifying for Pediatric Exclusivity (available on our web site at www.fda.gov/cder/pediatric) for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request" in addition to your plans for pediatric drug development described above. Please note that satisfaction of the requirements in section 2 of PREA alone may not qualify you for pediatric exclusivity.

All communications concerning this supplement should be addressed as follows:

U.S. Postal Service:

Food and Drug Administration

Center for Drug Evaluation and Research

Division of Special Pathogen and Immunologic Drug Products, HFD-590

Attention: Division Document Room

5600 Fishers Lane

Rockville, Maryland 20857

Courier/Overnight Mail:

Food and Drug Administration

Center for Drug Evaluation and Research

Division of Special Pathogen and Immunologic Drug Products, HFD-590

Attention: Division Document Room, N115

9201 Corporate Blvd.

Rockville, Maryland 20850

If you have any questions, please call Kristen Miller, Pharm.D., Regulatory Project Manager, at (301) 827-2127.

Sincerely,

{See appended electronic signature page}

Diana Willard

Chief, Project Management Staff

Division of Special Pathogen and Immunologic

Drug Products, HFD-590

Office of Drug Evaluation IV

Center for Drug Evaluation and Research

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/s/

Diana Willard
1/12/05 02:44:40 PM
NDA 21-498/S-003 Acknowledgement

Teleconference Minutes

Teleconference Date: July 19, 2004

Application Numbers: NDA 21-497
NDA 21-818
Alinia (nitazoxanide) Tablets

Sponsor: Romark Laboratories, L.C.

Attendees:

Romark Laboratories, L.C.

Marc Ayers President

FDA- Division of Special Pathogen and Immunologic Drug Products

Joette Meyer, Pharm.D. Clinical Reviewer
Kristen Miller, Pharm.D. Regulatory Project Manager

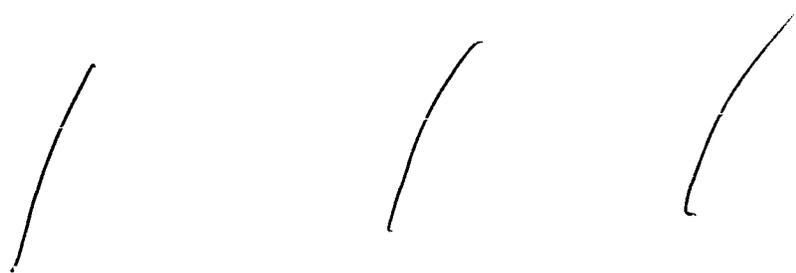
Background

On January 29, 2004, Romark submitted a complete response to our November 22, 2002, approvable letter for NDA 21-497 for the use of Alinia (nitazoxanide) Tablets in the treatment of diarrhea caused by *Cryptosporidium parvum* and *Giardia lamblia* in patients 12 years of age and older. NDA 21-497 was administratively split, and NDA 21-818 was created for the indication of Alinia® Tablets in the treatment of diarrhea caused by *Cryptosporidium parvum* in patients 12 years of age and older. The indication for NDA 21-497 is Alinia® Tablets in the treatment of diarrhea caused by *Giardia lamblia* in patients 12 years of age and older.

The Review Team requested this teleconference to discuss the pediatric requirements and post marketing commitments for these applications.

Discussion

Pediatric Requirements and Post-Marketing Commitments



Post-Marketing Commitments

No post-marketing commitments will be required with this action. Interesting academic issues surrounding nitazoxanide still exist and the sponsor was encouraged to think about performing future studies to address these issues. The first issue is to understand whether patients relapse clinically 2 weeks following the end of treatment and, as a secondary endpoint, to compare the correlation between clinical and parasitological response for nitazoxanide and placebo. Twenty-five to 30 patients per arm would be needed to achieve statistical superiority of nitazoxanide over placebo in terms of the clinical endpoint.

Second, 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 in some patients 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. To more fully understand this, a third arm using a FDA-approved drug for *Giardia lamblia* could be added to the above mentioned study.

Four handwritten checkmarks are arranged horizontally across the page, indicating approval or completion of the preceding text.

Minutes Preparer: Kristen Miller, Pharm.D.; Project Manager

Concur: Joette Meyer, Pharm.D.; Clinical Reviewer

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/s/

Kristen Miller
7/21/04 09:50:50 AM
CSO

Joette Meyer
7/21/04 09:55:56 AM
MEDICAL OFFICER

Teleconference Minutes

Teleconference Date: July 16, 2004

Application Numbers: NDA 21-497
NDA 21-818
Alinia (nitazoxanide) Tablets

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

Steve Gitterman, M.D., Ph.D.	Deputy Director
Joette Meyer, Pharm.D.	Clinical Reviewer
Kristen Miller, Pharm.D.	Regulatory Project Manager

Background

On January 29, 2004, Romark submitted a complete response to our November 22, 2002, approvable letter for NDA 21-497 for the use of Alinia (nitazoxanide) Tablets in the treatment of diarrhea caused by *Cryptosporidium parvum* and *Giardia lamblia* in patients 12 years of age and older.

The Review Team requested this teleconference to discuss the pediatric requirements, potential post marketing commitments, the ongoing study in adults with diarrhea caused by *Cryptosporidium parvum*, and administrative items for this application.

Discussion

Following introductions, the Review Team noted that the action would most likely take place during the week of July 19, 2004. The following updates were then provided:

Cryptosporidium parvum

- The Review Team apologized for not responding to Romark's justification for extrapolating data from patients with *Giardia lamblia* and pediatric patients with *Cryptosporidium parvum* to adults with *Cryptosporidium parvum*, prior to labeling negotiations. Romark understands that this was an unlikely possibility from the beginning, but appreciates the opportunity to provide their rationale.

- Please amend the protocol for the ongoing study in adults with diarrhea caused by *Cryptosporidium parvum* to include an evaluation of clinical response at 14 days after the end of treatment (at the same time point that the parasitological response is evaluated).
Romark agreed to submit this protocol amendment.

Pediatric Requirements and Post-Marketing Commitments

Administrative Items

- NDA 21-497 was administratively split, and NDA 21-818 was created for the indication of Alinia® Tablets in the treatment of diarrhea caused by *Cryptosporidium parvum* in patients 12 years of age and older. The indication for NDA 21-497 is Alinia® Tablets in the treatment of diarrhea caused by *Giardia lamblia* in patients 12 years of age and older.
- Please submit an amendment to NDA 21-498 specifically asking for the indication of Alinia® for Oral Suspension in the treatment of diarrhea caused by *Giardia lamblia* in patients 12 years of age and older. The amendment should refer to the study submitted on January 29, 2004 to NDA 21-497 for all supportive data. Please also attach the proposed labeling to this amendment.
- Please submit the final carton and container labels for NDA 21-497.

Romark agreed to submit this information, and thanked the Review Team for the updates.

Action Items

1. Romark will submit an amendment to the protocol for the ongoing tablet study in adults with diarrhea caused by *Cryptosporidium parvum* to include an evaluation of clinical response at 14 days after the end of treatment.

2. Romark will submit an amendment to NDA 21-498 specifically asking for the indication of Alinia® for Oral Suspension in the treatment of diarrhea caused by *Giardia lamblia* in patients 12 years of age and older. The amendment will refer to the study submitted on January 29, 2004 to NDA 21-497, and will include proposed labeling.
3. Romark will submit the final carton and container labels for NDA 21-497.

Minutes Preparer: Kristen Miller, Pharm.D.; Project Manager

Concur: Joette Meyer, Pharm.D.; Clinical Reviewer
Steve Gitterman, M.D., Ph.D.; Deputy Director

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/s/

Kristen Miller
7/21/04 09:25:15 AM
CSO

Steven Gitterman
7/21/04 09:56:35 AM
MEDICAL OFFICER

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 lamblia* indication only rather than the indication of both *Giardia lamblia* and *Cryptosporidium parvum* as proposed by the sponsor. 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 lamblia*. 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 [redacted] is distracting and should be deleted.

2. The dosage form descriptor "Tablets" should appear immediately following the established name rather than the strength. Please revise accordingly.

B. CONTAINER LABEL (bottles of 60 tablets)

1. See GENERAL COMMENTS.
2. Relocate the net quantity statement so that it does not appear in conjunction with the product strength.

C. CARTON LABELING (bottles of 60 tablets)

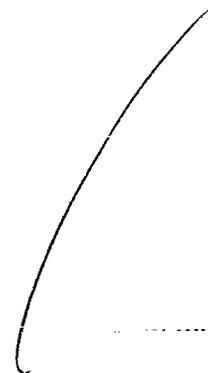
1. See GENERAL COMMENTS.
2. Decrease the prominence of the net quantity statement as it currently appears more prominent than the strength. Additionally, relocate the net quantity statement to appear away from the strength to avoid confusion.

D. CARTON LABELING (3-day therapy packs)

1. See GENERAL COMMENTS.

2.

3.



If you have any questions or need clarification, please contact Sammie Beam at 301-827-2102.

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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

NDA REGULATORY FILING REVIEW

NDA # **21-497 and 21-818** 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 Cryptosporidium parvum and Giardia lamblia**

Type of Original NDA: (b)(1) (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

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)
Waived (e.g., small business, public health)

Form 3397 (User Fee Cover Sheet) submitted: YES NO

User Fee ID # N/A

Clinical data? YES 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 approved 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 approvable 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)?
If yes, explain.

YES NO

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: 48,620
- 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

**PRESCRIPTION DRUG
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>

<p>1. APPLICANT'S NAME AND ADDRESS Romark Laboratories, L.C. 6200 Courtney Campbell Causeway Suite 200 Tampa, FL 33607</p>	<p>4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER 21-497</p>
<p>2. TELEPHONE NUMBER (Include Area Code) (813) 282-8544</p>	<p>5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL? <input checked="" type="checkbox"/> YES <input type="checkbox"/> 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: <input type="checkbox"/> THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION. <input checked="" type="checkbox"/> THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO: NDA 21-497 (APPLICATION NO. CONTAINING THE DATA).</p>
<p>3. PRODUCT NAME Alinia (nitazoxanide) Tablets, 500 mg</p>	<p>6. USER FEE I.D. NUMBER N/A</p>

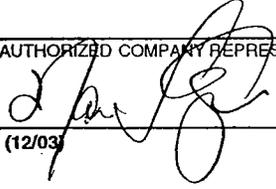
7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.

<input type="checkbox"/> A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 (Self Explanatory)	<input type="checkbox"/> A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE (See item 7, reverse side before checking box.)
<input checked="" type="checkbox"/> 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.)	<input type="checkbox"/> THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALY (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 CDER, HFM-99 1401 Rockville Pike Rockville, MD 20852-1448	Food and Drug Administration CDER, HFD-94 and 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.
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SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE 	TITLE President	DATE 1/28/2004
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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 75 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 25° and then cooled to 10° C and they just wanted to clarify that the methods submitted were done at 25° C as well. Romark replied that they were done at 25° C.

Romark asked if the Division would suggest only doing a run at 50 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.

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 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 (50 and 75 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 50 and 75 RPM studies, please do a study at 25 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.

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

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
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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.
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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.

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	Jerry Phillips, R.Ph. Associate Director Office of Drug Safety Center for Drug Evaluation and Research Food and Drug Administration
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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 of diarrhea caused by *Cryptosporidium parvum* and *Giardia lamblia*,

— Clinical experience with nitazoxanide for the treatment of diarrhea caused by *C. parvum* in patients with AIDS has not been fully and systematically studied. 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 databases³ 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 Database⁴ and the Saegis⁵ 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.

¹MICROMEDEX 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).

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

³The 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.

⁴WWW location <http://www.uspto.gov/tmdb/index.html>.

⁵Data 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.

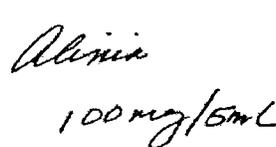
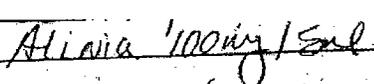
**L/A (look-alike), S/A (sound-alike)

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.

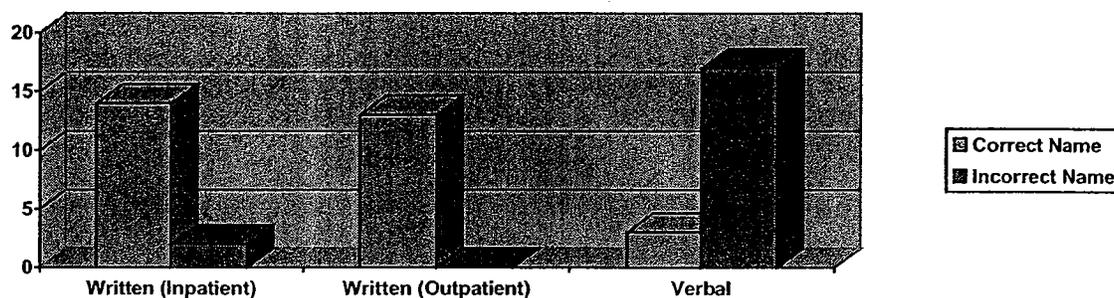
HANDWRITTEN PRESCRIPTION	VERBAL PRESCRIPTION
<p>Outpatient RX:</p> 	<p>Alinia, 5 tsp. every 12 hours for 3 days, dispense 60 mL.</p>
<p>Inpatient RX:</p> 	

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.

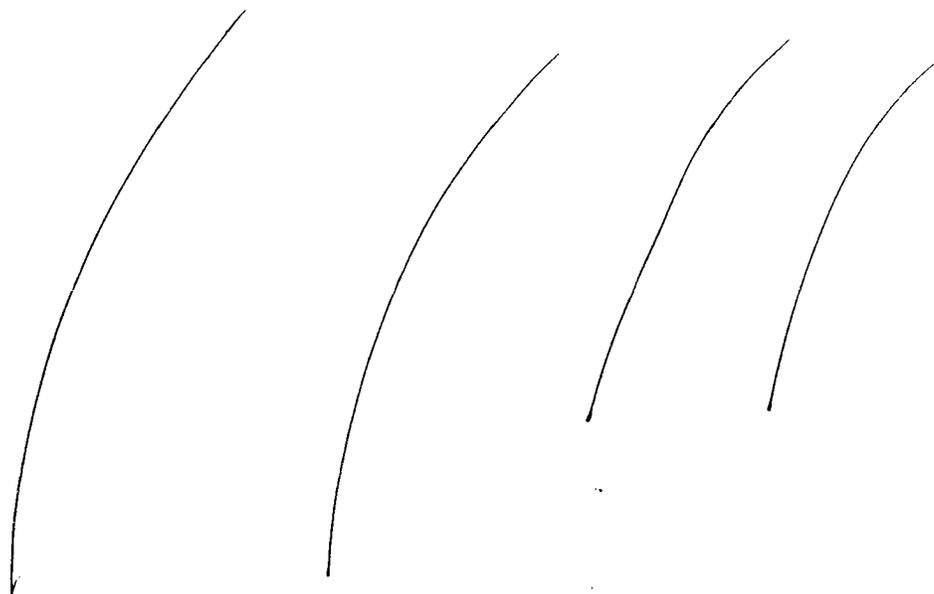
We conducted prescription studies to simulate the prescription ordering process. Our study did not confirm confusion between Alinia and Alimta, — or Climara. The majority of the incorrect interpretations of the written and verbal studies were misspelled/phonetic variations of the proposed name, Alinia. 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/m² over 10 minutes once every 21 days followed approximately 30 minutes later by a 2 hour infusion of 75 mg/m² 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

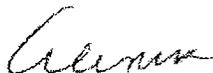
ALIMTA

Alinia Alimta

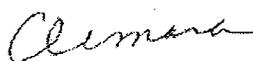


Climara (Estradiol) is indicated for moderate-to-severe vasomotor symptoms associated with menopause, female hypogonadism, female castration, primary ovarian failure, atrophic conditions caused by deficient endogenous estrogen production, atrophic urethritis, prevention of osteoporosis, abnormal uterine 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.

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

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/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

USER FEE VALIDATION SHEET

NDA # 21-498 ²¹⁻⁴⁹⁷ 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 FDCA

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 than bundling).
 If YES, list all NDA #s, review division(s) and those for which an application fee applies.

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

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?

Kushill 9/10/02
 PM Signature / Date

Ellen C. Frank 10 Sep 02
 CPMS Concurrence Signature / Date

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 COMMERCIALY (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
CDER, HFM-99
401 Rockville Pike
Rockville, MD 20852-1448

Food and Drug Administration
CDER, HFD-94
and 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

President

DATE

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 _____ (designation request # 01-1504), submitted pursuant to Section 526 of the Federal Food, Drug, and Cosmetic Act (21 USC 360bb).

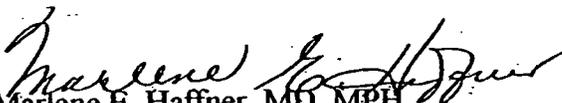
We have completed the review of this request and have determined that nitazoxanide qualifies for orphan designation for the treatment of _____. Please note that it is nitazoxanide and not its formulation that has received orphan designation. You have notified us that you are currently developing nitazoxanide 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,



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



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 # 95-0918 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,

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