CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-497

21-498/S-001

ADMINISTRATIVE DOCUMENTS AND CORRESPONDENCE

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

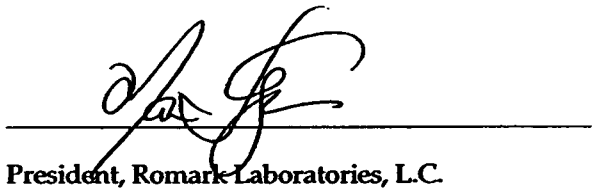
As required under section 505(b)(1)(F) of the Federal Food, Drug, and Cosmetic Act, and as specified in 21 CFR 314.53(c)(1), Romark Laboratories, L.C. reports the following patent information:

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

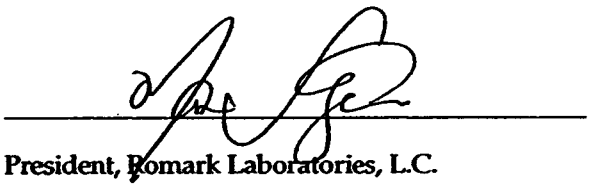
As required under section 505(b)(1)(F) of the Federal Food, Drug, and Cosmetic Act, and as specified in 21 CFR 314.53(c)(1), Romark Laboratories, L.C. reports the following patent information:

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

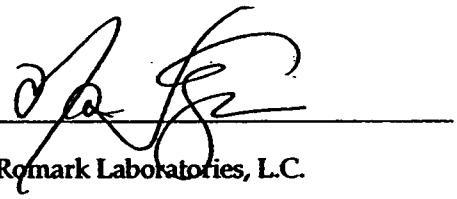
As required under section 505(b)(1)(F) of the Federal Food, Drug, and Cosmetic Act, and as specified in 21 CFR 314.53(c)(1), Romark Laboratories, L.C. reports the following patent information:

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

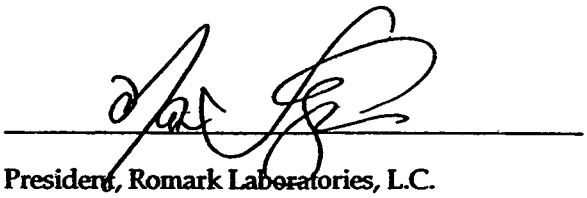
As required under section 505(b)(1)(F) of the Federal Food, Drug, and Cosmetic Act, and as specified in 21 CFR 314.53(c)(1), Romark Laboratories, L.C. reports the following patent information:

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.

Department of Health and Human Services
Food and Drug Administration

Form Approved: OMB No. 0910-0513
Expiration Date: 7/31/06
See OMB Statement on Page 3.

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
21-497

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)	STRENGTH(S)
Nitazoxanide	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.

For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

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	b. Issue Date of Patent	c. Expiration Date of Patent
5,387,598	02/07/1995	02/07/2012

d. Name of Patent Owner	Address *(of Patent Owner)*	
Romark Laboratories, L.C.	6200 Courtney Campbell Causeway, 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*) 17	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 Giardia lamblia		

5. No Relevant Patents

or 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
	July 7, 2004

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 6200 Courtney Campbell Causeway, 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

Department of Health and Human Services
Food and Drug Administration

Form Approved: OMB No. 0910-0513
Expiration Date: 7/31/06
See OMB Statement on Page 3.

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
21-497

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)	STRENGTH(S)
Nitazoxanide	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.

For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

DA 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	b. Issue Date of Patent	c. Expiration Date of Patent
5,578,621	11/26/1996	11/26/2013

d. Name of Patent Owner
Romark Laboratories, L.C.

Address *(of Patent Owner)*
6200 Courtney Campbell Causeway, Suite 200

City/State
Tampa, FL

ZIP Code	FAX Number *(if available)*
33607	(813) 282-4910
Telephone Number	E-Mail Address *(if available)*
(813) 282-8544	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)*

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?		
4, 7		☑ 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 Giardia lamblia

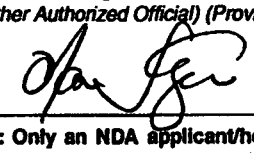
5. No Relevant Patents

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
	July 7, 2004

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 6200 Courtney Campbell Causeway, 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

Department of Health and Human Services
Food and Drug Administration

Form Approved: OMB No. 0910-0513
Expiration Date: 7/31/06
See OMB Statement on Page 3.

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
21-497

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)	STRENGTH(S)
Nitazoxanide	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.

For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

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	b. Issue Date of Patent	c. Expiration Date of Patent
5,968,961	10/19/1999	05/07/2017

d. Name of Patent Owner	Address *(of Patent Owner)*	
Romark Laboratories, L.C.	6200 Courtney Campbell Causeway, 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)*

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? ☐ 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

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
	July 7, 2004

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 6200 Courtney Campbell Causeway, 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

Department of Health and Human Services
Food and Drug Administration

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

Form Approved: OMB No. 0910-0513
Expiration Date: 7/31/06
See OMB Statement on Page 3.

NDA NUMBER
21-497

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)	STRENGTH(S)
Nitazoxanide	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.

For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

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	b. Issue Date of Patent	c. Expiration Date of Patent
6,020,353	02/01/2000	09/18/2014

d. Name of Patent Owner
Romark Laboratories, L.C.

Address *(of Patent Owner)*
6200 Courtney Campbell Causeway, Suite 200

City/State
Tampa, FL

ZIP Code	FAX Number *(if available)*
33607	(813) 282-4910
Telephone Number	**E-Mail Address *(if available)***
(813) 282-8544	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)***

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

PSC Media Arts (301) 443-1090 EF

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?	☐ 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

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
	July 7, 2004

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 6200 Courtney Campbell Causeway, 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

EXCLUSIVITY SUMMARY FOR NDA # ___**21497**

Trade Name _____**Alinia** Generic Name_ **nitazoxanide**

_____

ApplicantName _**Romark Laboratories, L.C.**HFD # _____**590**__

Approval Date If Known __**July 21, 2004**_____

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

_____**505(b)(1)**_____

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 Writen 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# _____ _____

NDA# _____ _____

2. Combination product.

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

YES /___/ NO /_X__/

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

NDA# _____ _____

NDA# _____ _____

NDA# _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 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 /_X__/ 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 /_X__/ 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 /_X__/

(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 RM01-3011: Multicenter, Double-Blind, Placebo-Controlled Study of Nitazoxanide Tablets in the Treatment of Giardiasis 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:

_____ _____

_____ _____

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

Investigation #1 YES /___/ NO /_X__/

Investigation #2 YES /___/ NO /___/

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

_____ _____

_____ _____

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

_____ ***Study RM01-3011: Multicenter, Double-Blind, Placebo-Controlled Study of Nitazoxanide Tablets in the Treatment of Giardiasis in Adults and Adolescents***

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

a) For each investigation identified in response to question

3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # ~~____~~ YES /__X_/ ! NO /___/ Explain: _____

Investigation #2

IND # _____ YES /___/ ! NO /___/ Explain: _____

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

Investigation #1

YES /___/ Explain _____ ! NO /___/ Explain _____

_____ ! _____

_____ ! _____

Investigation #2

YES /___/ Explain _____ ! NO /___/ Explain _____

_____ ! _____

_____ ! _____

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

YES /___/ NO /_X_/

If yes, explain: _____

_____

Signature Date

Title:

Signature of Office/ Division Director

Date

Form OGD-011347 Revised 05/10/2004

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
7/21/04 11:18:49 AM

PEDIATRIC PAGE

(Complete for all APPROVED original applications and efficacy supplements)

NDA/BLA # : 21-497 **Supplement Type (e.g. SE5):** N/A **Supplement Number:** N/A

Stamp Date: January 29, 2004 **Action Goal Date:** July 29, 2004

HFD-590 **Trade and generic names/dosage form:** Alinia (nitazoxanide) Tablets

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

Indication(s) previously approved: Treatment of diarrhea caused by *Cryptosporidium parvum* and *Giardia lamblia* in patients age 1- 11 years of age.

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

Number of indications for this application(s): 1

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

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

- ☐ **Yes: Please proceed to Section A.**

- X **No: Please check all that apply:** ____**Partial Waiver** __X__**Deferred** __X__**Completed**
  NOTE: More than one may apply
  Please proceed to Section B, Section C, and/or Section D and complete as necessary.

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

Reason(s) for full waiver:

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

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

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

Age/weight range being partially waived:

Min_____	**kg**_____	**mo.**_____	**yr.**_____	**Tanner Stage**_____
Max_____	**kg**_____	**mo.**_____	**yr.**_____	**Tanner Stage**_____

Reason(s) for partial waiver:

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

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is

complete and should be entered into DFS.

Section C: Deferred Studies

'First' age/weight range being deferred:

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

'Second' age/weight range being deferred:

Min _____	**kg**_____	**mo.**_____	**yr.**_____	**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: Sponsor has plans to complete studies for this age range

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}

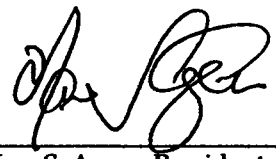
Regulatory Project Manager

cc: NDA 21-498, NDA 21-818
HFD-960/ Grace Carmouze
(revised 9-24-02)

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

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

July 1, 2004

Date

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.

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information		
NDA: **21-497**	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: **(X)** 505(b)(1) ( ) 505(b)(2)	Reference Listed Drug (NDA #, Drug name): **N/A**	

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

❖ Exclusivity (approvals only)	
• Exclusivity summary	**X- July 21, 2004**
• 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	
• Proposed action	**(X)** AP ( ) TA ( ) AE ( ) NA
• Previous actions (specify type and date for each action taken)	**AE- November 22, 2002**
• Status of advertising (approvals only)	**(X)** Materials requested in AP letter ( ) Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	**(X)** Yes ( ) Not applicable
• Indicate what types (if any) of information dissemination are anticipated	( ) None [redacted] ( ) Talk Paper ( ) Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable)	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	**X**
• Most recent applicant-proposed labeling	**Same as Division's proposed labeling**
• Original applicant-proposed labeling	**X**
• Labeling reviews (including DDMAC, Office of Drug Safety trade name review, nomenclature reviews) and minutes of labeling meetings *(indicate dates of reviews and meetings)*	**DDMAC review- 5/13/04** **Trade name review- 11/22/02** **LabelingTcon minutes- 7/21/04**
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	**N/A**
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	**N/A**
• Applicant proposed	**X**
• Reviews	**Under Label/Labeling Consults:** **DMETS review: 7/2/04**
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	**N/A**
• Documentation of discussions and/or agreements relating to post-marketing commitments	**Telecons: 7/16/04** **7/19/04**
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	**N/A – No issues arose that required letters/ faxes/ etc.**
❖ Memoranda and Telecons	**Parasitologic response- 7/9/04**
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	**N/A- no meeting occurred as all of the information was gathered under Unimed for NDA 20-871 (NA in 1998).**
• Pre-NDA meeting (indicate date)	**No minutes available (9/19/01)**

• Pre-Approval Safety Conference (indicate date; approvals only)	**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- (7/21/04)**
❖ 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: July 19, 2004

Application Numbers: NDA 21-497

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 — . *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

After discussing with several pediatricians in CDER about the occurrence of diarrhea caused by *Giardia lamblia* in infants, the Review Team is deferring pediatric studies in patients age zero to 12 months for five years, rather than waiving any part of that age group. —

— . The details of a pediatric study of diarrhea caused by *Giardia lamblia* can be further discussed at a later time; however, the study should be designed to assess a 14 day endpoint following the end of treatment, and address the relationship between the clinical and parasitological response.

Post-Marketing Commitments

No post-marketing commitments will be required with this action. Interesting academic issues surrounding nitazoxanide still exist and the [redacted]. 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. [redacted]

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

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 — . *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, —
— 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:

Pediatric Requirements and Post-Marketing Commitments

The Review Team stated that pediatric patients,

The details of this study can be further discussed at a later time, although the study will be designed primarily to collect safety data.

Administrative Items

-

  . 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.

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

Teleconference Minutes

Teleconference Date: July 8, 2004

Application Numbers: NDA 21-497
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

Renata Albrecht, M.D.	Director
Steve Gitterman, M.D., Ph.D.	Deputy Director
Joette Meyer, Pharm.D.	Clinical Reviewer
Philip Colangelo, Pharm.D., Ph.D.	Clinical Pharmacology & Biopharmaceutics Team Leader
Gene Holbert, Ph.D.	Chemistry 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 — *Giardia lamblia* in patients 12 years of age and older.

The Division combined the label for Alinia for oral suspension with the tablet labeling, and sent the proposal to Romark on July 8, 2004. This teleconference was requested by the Division to discuss the proposed Alinia labeling.

Discussion

Indication and Usage

- *Romark would like to remove the sentence* "A single Alinia tablet contains a greater amount of nitazoxanide than is recommended for pediatric dosing and should therefore not be used in pediatric patients 11 years or younger" — *from the* — *section as this is already listed in the DOSAGE AND*

ADMINISTRATION section.

The Review Team's goal was to avoid confusion regarding use in pediatric patients. This will be discussed.

Addendum: The Review Team agreed to remove this sentence from the section.

- *In the indication '* *Romark would like to remove the phrase '* . The Review Team agrees.

- *Romark would prefer the phrase "have not been shown to be superior to placebo" in the sentence "Alinia Tablets and Alinia for Oral Suspension have not been shown to be superior to placebo for the treatment of diarrhea caused by Cryptosporidium parvum in HIV-infected or immunodeficient patients (see **CLINICAL STUDIES**)." be replaced with '*

Romark has conducted studies of nitazoxanide in HIV-infected patients and the drug was not shown to be effective. The Agency has been criticized for implying in labeling that negative studies equal the absence of studies. Therefore, the Division feels strongly that the study results must remain for now, but Romark can propose slightly modified wording.

Romark understands, and is willing to keep this wording.

- *Romark would like the word to be removed from the sentence "The safety and effectiveness of Alinia for Oral Suspension or Alinia Tablets for the treatment of diarrhea caused by Cryptosporidium parvum in patients 12 years of age and older have not been established".* The Review Team will discuss this.

  Addendum: The Review Team informed Romark that the word must remain in the statement.

- *Romark would like to remove*

The Review Team stated that since package inserts are not read straight through, the information must be presented in a clear manner for ease of use. *Romark agreed.*

<u>*Drug Interactions*</u>

- In the Drug Interactions subsection under the Clinical Pharmacology and the Precaution sections, the word "inhibitory" was added to the sentence "*In vitro* metabolism studies have demonstrated that tizoxanide has no significant inhibitory effect on cytochrome P450 enzymes". *Romark agrees.*

Adverse Reactions

- The sentence " — 1% of the 1,628 patients age 12 years and older discontinued therapy because of an adverse event." —

Romark feels that it is more informative to use a large data set. They will look into the numbers and respond.

Addendum: Romark responded that the 1% is calculated as 1 discontinuation divided by the sum of 54 patients in the 3011 study and 47 patients in the 98-001 study (1/101 = 0.99%). *The Review Team agreed to use "approximately 1%".*

Minor/ Editorial Changes

- In Table 2 under Clinical Pharmacology and table under the Dosage and Administration section, the age — will be changed to 1-3 years. *Romark agreed.*

Action Items

1. The Review Team will discuss removing the sentence "A single Alinia tablet contains a greater amount of nitazoxanide than is recommended for pediatric dosing and should therefore not be used in pediatric patients 11 years or younger." —
2. The Review Team will discuss removing the word — from the sentence "The safety and effectiveness of Alinia for Oral Suspension or Alinia Tablets for the treatment of diarrhea caused by *Cryptosporidium parvum* in patients 12 years of age and older have not been established".
3. Romark will verify the number of patients that discontinued Alinia because of adverse events, and will provide the Review Team with rationale for 1%.

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

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

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/s/

Kristen Miller
7/21/04 03:51:14 PM
CSO

Renata Albrecht
7/21/04 04:43:27 PM
MEDICAL OFFICER

DIVISION DIRECTOR REVIEW of RESUBMISSION

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

Drugs: NDA 21-497 —
Alinia ™ (nitazoxanide oral tablets) 500 mg
NDA 21-498/S-001
Alinia ™ (nitazoxanide for oral suspension) 100 mg/5 mL

Date of Submissions:

Original NDAs:	May 29, 2002
	(initial User Fee due date November 29, 2002)
Resubmission:	January 28, 2004
User Fee Date:	July 28, 2004

Proposed Indications:

- NDA 21-497 and NDA 21-498/S-S001, Treatment of diarrhea caused by *Giardia lamblia* in patients 12 years and older (adolescent and adult patients)

Proposed Age Groups and Dosage Regimens:

- Age 12 years and above: 500 mg Tablets or Oral Suspension PO BID for 3 days

Purpose of Review:

The purpose of this review is to provide a brief summary of the Division's recommendations on these applications, including the scientific and regulatory issues surrounding the approval of nitazoxanide tablets.

Recommended Regulatory Actions/ Outstanding Issues:

- NDA 21-497 and NDA 21-498/S-001 should be issued an APPROVAL letter for the treatment of diarrhea caused by *Giardia lamblia* in patients 12 years of age and older, at a dose of 500 mg BID (either tablet or suspension) PO for 3 days

-

- Note: The applicant currently holds NDA 20-871 the indication of *Cryptosporidium parvum* in adult patients infected with HIV; and than NDA was issued a NONAPPOVAL letter June 30, 1998.

- The proposed Alinia Tablet labeling was combined with the already-approved Alinia for oral suspension labeling to form one package insert. After labeling negotiation with the company, text for this combined labeling was agreed-upon. The joint suspension/tablet labeling should be APPROVED. In addition, per DMETS recommendation, a revised "Alinia" logo was agreed upon, modifying the "sweep" in the letter "A".

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

Background:

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

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

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

On November 22, 2002, NDA 21-498, Alinia, (nitazoxanide) for Oral Suspension was approved for the treatment of diarrhea due to *C. parvum* and *G. lamblia* in patients 1

through 11 years of age. Two adequate and well-controlled studies demonstrated that nitazoxanide oral suspension was superior to placebo for *C. parvum*. One adequate and well-controlled study was submitted demonstrating efficacy in *G. lamblia*; the results of this study were corroborated by evidence of superiority of nitazoxanide tablets compared to placebo in a limited number of adults treated with diarrhea where *G. lambia* was the sole pathogen. However, neither rigorous microbiological data nor substantial evidence of the correlation between clinical and microbiological endpoints was shown at this time to [redacted]

The efficacy results are presented below:

Results of Clinical Studies of *GIARDIA LAMBLIA*
that supported approval and labeling of original NDA for Alinia for oral suspension
for pediatric patients 1 through 11 years of age

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

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

Results of Clinical Studies of *CRYPTOSPORIDIUM PARVUM*
that supported approval and labeling of original NDA for Alinia for oral suspension
for patients 1 to 11 years of age

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