CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-497

21-498/S-001

CHEMISTRY REVIEW(S)

NDA 21-497

Alinia™ (nitazoxanide) Tablets

Romark Laboratories, L.C.

Gene W. Holbert, Ph.D.

Division of Special Pathogen and Immunologic Drug Products

Table of Contents

Chemistry Review Data Sheet

1. NDA 21-497

2. REVIEW #2

3. REVIEW DATE: 24-JUN-2004

4. REVIEWER: Gene W. Holbert, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
NDA 20-871	26-DEC-1997
Amendment	25-FEB-1998
Amendment	03-MAR-1998
Amendment	27-APR-1998
CMC Review	18-MAY-1998
NA Letter	30-JUN-1998
NDA 21-497	28-MAY-2002
Amendment (BC)	23-OCT-2002
CMC Review	09-OCT-2003

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
NDA 21-497 (Resubmitted)	28-JAN-2004
Amendment (BZ)	18-JUN-2004
Amendment (BZ)	25-JUN-2004
Amendment (BC)	07-JUL-2004

7. NAME & ADDRESS OF APPLICANT:

Name:	Romark Laboratories, L.C.
Address:	6200 Courtney Campbell Causeway, Suite 200 Tampa, FL 33607
Representative:	Marc S. Ayers, President
Telephone:	(813) 282-8544

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Alinia™
b) Non-Proprietary Name (USAN): Nitazoxanide
c) Code Name/# (ONDC only): NTZ
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 1
- Submission Priority: P

9. LEGAL BASIS FOR SUBMISSION: 505(b)(1)

10. PHARMACOL. CATEGORY: Antiprotozoal

11. DOSAGE FORM: Tablets

12. STRENGTH/POTENCY: 500 mg

13. ROUTE OF ADMINISTRATION: Oral

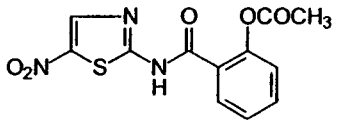
14. Rx/OTC DISPENSED: __X__Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product – Form Completed

__X___Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical Name: 2-(Acetyloxy)-*N*-(5-nitro-2-thiazolyl)benzamide
Structural Formula:



Molecular Formula: $C_{12}H_9N_3O_5S$
Molecular Weight: 307.29
CAS: 55981-090-4

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
	II		Nitazoxanide	1	Adequate	15-SEP-2002	LOA 28-JAN-2002
	III			1	Adequate	15-SEP-2000 (D.N.Klein)	LOA 26-FEB-2002
	III			1	Adequate	27-SEP-2000 (D.N.Klein)	LOA 27-FEB-2002 Bottles found adequate
	III			1	Adequate	05-JUL-1994 (J.Fan)	LOA 26-FEB-2002 Bottles found adequate
	III			1	Adequate	06-AUG-2002 13-AUG-1993	LOA 03-APR-2002
	IV			4	N/A		LOA 30-JAN-2002
	III			1	Adequate	27-MAR-2002 (E.Chikhale)	LOA 211-JAN-2004
	III			1	Adequate	29-OCT-1997 (S.K. Kim)	LOA 26-JAN-2004
	III			1	Adequate	15-OCT-2001 (D.N. Klein)	LOA 27-JAN-2004
	III			1	Adequate	29-OCT-2003 (S.C. Pope)	LOA 09-JUN-2004

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA	20-871	Nitazoxanide Tablets
NDA	21-498	Nitazoxanide Suspension
IND		
IND		
IND		
IND		

18. STATUS:

CONSULTS / CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics			
EES	Adequate	03-MAR-2004	
Pharm/Tox			
Biopharm	Approval	12-JUL-2004	Dakshina M. Chilukuri, Ph.D
LNC			
Methods Validation	Not required		
ODS	Minor labeling changes	28-JUN-2004	Alina R. Mahmud,R.Ph
EA	N/A		
Microbiology			

APPEARS THIS WAY
ON ORIGINAL

The Chemistry Review for NDA 21-497

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From the chemistry, manufacturing and controls standpoint, this application may be Approved.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Alinia™ (nitazoxanide) Tablets are proposed for treatment of diarrhea caused by — *Giardia lamblia* — This product has been designated as an Orphan Drug for each of these indications since there is no alternative therapy. Alinia™ was therefore granted a priority review.

Each yellow, film-coated tablet contains 500 mg of the active ingredient, nitazoxanide, and the following excipients: maize starch, pregelatinized corn starch, hydroxypropyl methylcellulose, sucrose, sodium starch glycolate, talc, magnesium stearate, soy lecithin, polyvinyl alcohol, xanthan gum, titanium dioxide, talc, FD&C Yellow No. 10 Aluminum Lake, FD&C Yellow No. 6 Aluminum Lake, and FD&C Blue No. 2 Aluminum Lake.

The active ingredient, nitazoxanide (NTZ) is a synthetic antiprotozoal agent for oral administration. The chemical name for NTZ is 2-acetyloxy-*N*-(5-nitro-2-thiazolyl)-benzamide. NTZ is a light yellow crystalline powder and is practically insoluble in water.

Alinia™ Tablets are packaged in — olister packs of 6 tablets and in HDPE bottles of 60 tablets.

For the majority of chemistry, manufacturing and controls information regarding the drug substance, reference is made to DMF — A majority of the information on the drug product is incorporated by cross-reference to NDA 20-871 for Alinia™ (nitazoxanide) Tablets. NDA 20-871 was submitted in December 1997 for treatment of cryptosporidial diarrhea in AIDS patients. That application was not approved for reasons of efficacy. This review — current application, NDA 21-497.

B. Description of How the Drug Product is Intended to be Used

Alinia™ (nitazoxanide) Tablets are proposed for treatment of diarrhea caused by — 1 *Giardia lamblia* —

This product is contraindicated in patients with known hypersensitivity to nitazoxanide.

For each of the therapeutic indications, the recommended dose in adults and adolescents 12 years of age and older is 500 mg every 12 hours for 3 days. Tablets should be taken with food.

The safety and effectiveness of this product in children younger than 12 years of age have not been studied. An application for Alinia™ Oral Suspension (NDA 21-498) for use in the pediatric population was submitted and approved on 22-NOV-2002.

Alinia™ Tablets are supplied as round, yellow film-coated tablets debossed with ALINIA on one side and 500 on the other. Each tablet contains 500 mg nitazoxanide. The tablets are packaged in white HDPE bottles, 60 tablets per bottle or in PVC blister packs of 6 tablets.

The tablets are to be stored at controlled room temperature (15-25°C, 59-77°F).

C. Basis for Approvability or Not-Approval Recommendation

The NDA submissions and the Drug Master File ultimately provided adequate information on the chemistry and manufacturing controls for the production of Alinia® Tablets. During the review, a number of issues, including the following were resolved:

- Containers used for storage of the bulk tablets prior to final packaging were not described.

- Acceptance criteria for the drug product were modified to reflect the capabilities of the manufacturer. The proposed limits for desacetyl nitazoxanide were reduced from [redacted] at release/ [redacted] at expiry to [redacted] at release/ [redacted] at expiry. The limit for Total Degradation Products was reduced from not more than [redacted] to not more than [redacted] at expiry.
- No [redacted] data using the current film coating had been provided.
- The original NDA 20-871 contained only [redacted] of stability data for the proposed commercial formulation.

As amended, all acceptance criteria and analytical method were found adequate to ensure the identity, strength, quality, purity and potency of the drug product.

The firm had originally proposed the proprietary name "NTZ" for nitazoxanide tablets in NDA 20-871. NTZ was found to be unacceptable to the CDER Labeling and Nomenclature Committee at the time. The LNC found the name "Cryptaz" to be acceptable. Most recently, DDMAC has found the name "Cryptaz" to be objectionable since it suggests indications for the product such as cryptosporidium and cryptococcus. DDMAC did not object to the alternate name [redacted]. Ultimately the sponsor chose the name "Alinia", to which the agency agreed.

III. Administrative

A. Reviewer's Signature

{Signed electronically in DFS}

B. Endorsement Block

Chemist Name/Date: Gene W. Holbert/
Chemistry Team Leader Name/Date: Mark R. Seggel (acting)
Project Manager Name/Date: Kristen E. Miller

C. CC Block

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/s/

Gene Holbert
7/9/04 10:42:24 AM
CHEMIST

Mark Seggel
7/9/04 12:53:03 PM
CHEMIST

CHEMISTRY REVIEW

NDA 21-497

Cryptaz (nitazoxanide) Tablets

Romark Laboratories, L.C.

Gene W. Holbert, Ph.D.

Division of Special Pathogen
and Immunologic Drug Products

Table of Contents

Chemistry Review Data Sheet

1. NDA 21-497

2. REVIEW #: 1

3. REVIEW DATE: 09-OCT-2002

4. REVIEWER: Gene W. Holbert

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
NDA 20-871	26-DEC-1997
Amendment	25-FEB-1998
Amendment	03-MAR-1998
Amendment	27-APR-1998
CMC Review	18-MAY-1998
NA Letter	30-JUN-1998

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original	28-MAY-2002
Amendment (BC)	23-OCT-2002

7. NAME & ADDRESS OF APPLICANT:

Name:	Romark Laboratories, L.C.
Address:	6200 Courtney Campbell Causeway Suite 800 Tampa, FL 33607
Representative:	Marc S. Ayers
Telephone:	(813) 282-8544

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Cryptaz®
b) Non-Proprietary Name (USAN): nitazoxanide
c) Code Name/# (ONDC only): PH 5776, NTZ
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type : 1
- Submission Priority : P

9. LEGAL BASIS FOR SUBMISSION: 505(b)(1)

10. PHARMACOL. CATEGORY: Antiprotozoal

11. DOSAGE FORM: Tablets

12. STRENGTH/POTENCY: 500 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: __X__Rx ___OTC

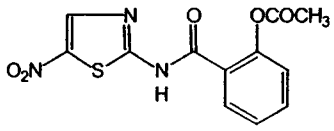
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

__X___Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical Name: 2-(Acetyloxy)-*N*-(5-nitro-2-thiazolyl)benzamide
Structural Formula:



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	III			1	Adequate	15-SEP-2000	LOA 26-FEB-2002
	III			7	N/A		LOA 27-FEB-2002 Bottles found adequate
	III			7	N/A		LOA 26-FEB-2002 Bottles found adequate
	III			1	Adequate	06-AUG-2002 13-AUG-1993	LOA 03-APR-2002
	IV			4	N/A		LOA 30-JAN-2002

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B. Other Documents:

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NDA	20-871	NTZ Tablets
NDA	21-498	NTZ Suspension
IND		
IND		
IND		
IND		

18. STATUS:

CONSULTS/CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics			
EES	Pending		
Pharm/Tox			
Biopharm	NLT —(Q) of the labeled amount dissolved as nitazoxanide and tizoxanide (desacetylnitazoxanide) combined at 60 minutes.		Dakshina Chilukuri
LNC			
Methods Validation			
DMETS	Does not recommend use of the name "Cryptaz"	01-NOV-2002	Tia M. Harper-Velazquez
EA	N/A		
Microbiology	N/A		
DDMAC	"Cryptaz" acceptable if approved for a Cryptosporidium indication.	11-OCT-2002	Jim Rogers

Executive Summary Section

The Chemistry Review for NDA 21-497

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From the chemistry, manufacturing and controls standpoint, this application may be Approved.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Cryptaz® (nitazoxanide) Tablets are proposed for treatment of diarrhea caused by *Giardia lamblia* [redacted] This product has been designated as an Orphan Drug for each of these indications since there is no alternative therapy. Cryptaz® was therefore granted a priority review.

Each yellow, film-coated tablet contains 500 mg of the active ingredient, nitazoxanide, and the following excipients: maize starch, pregelatinized corn starch, hydroxypropyl methylcellulose, sucrose, sodium starch glycolate, talc, magnesium stearate, soy lecithin, polyvinyl alcohol, xanthan gum, titanium dioxide, talc, FD&C Yellow No. 10 Aluminum Lake, FD&C Yellow No. 6 Aluminum Lake, and FD&C Blue No. 2 Aluminum Lake.

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B. Description of How the Drug Product is Intended to be Used

Cryptaz® (nitazoxanide) Tablets are proposed for treatment of diarrhea caused by *Giardia lamblia*

This product is contraindicated in patients with known hypersensitivity to nitazoxanide.

For each of the therapeutic indications, the recommended dose in adults and adolescents 12 years of age and older is 500 mg every 12 hours for 3 days. Tablets should be taken with food.

The safety and effectiveness of this product in children younger than 12 years of age have not been studied. An application for Cryptaz® Oral Suspension (NDA 21-498) for use in the pediatric population has been submitted and is under active review at this time.

Cryptaz® Tablets are supplied as round, yellow film-coated tablets debossed with CRYPTAZ on one side and 500 on the other. Each tablet contains 500 mg nitazoxanide. The tablets are packaged in white HDPE bottles, 60 tablets per bottle.

The tablets are to be stored at controlled room temperature (15-25°C, 59-77°F).

C. Basis for Approvability or Not-Approval Recommendation

The NDA submissions and the Drug Mater File ultimately provided adequate information on the chemistry and manufacturing controls for the production of Cryptaz® Tablets. During the review, a number of issues, including the following were resolved:

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DDMAC does not object to the alternate name '

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

Chemist Name/Date:	Gene W. Holbert/09-OCT-2002
Chemistry Team Leader/Date:	Norman R. Schmuff//
Project Manager Name/Date:	Kristen Miller/

C. CC Block

20 Page(s) Withheld

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

/s/

Gene Holbert
11/22/02 04:21:31 PM
CHEMIST

Norman Schmuff
11/26/02 06:37:14 AM
CHEMIST

ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application : NDA 21497/000
Org Code : 590
Priority : 1P

Stamp Date : 29-MAY-2002
PDUFA Date : 29-NOV-2002
Action Goal :
District Goal: 28-JAN-2003

Sponsor: ROMARK
6200 COURTNEY CAMPBELL CAUSEWAY STE
880
TAMPA, FL 33607

Brand Name : CRYPTAZ (NITAZOXANIDE) 500MG
TABLETS
Estab. Name:
Generic Name: NITAZOXANIDE
Dosage Form: (TABLET)
Strength : 500 MG

FDA Contacts:			
L. CHAN	Project Manager (HFD-104)	301-827-2513
G. HOLBERT	Review Chemist (HFD-590)	301-827-2399
N. SCHMUFF	Team Leader (HFD-590)	301-827-2425

Overall Recommendation: ACCEPTABLE on 18-NOV-2002by S. ADAMS (HFD-324) 301-594-0095

Establishment : CFN : FEI :

DMF No: AADA:

Responsibilities:

Profile : CSN OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 18-NOV-02
Decision : ACCEPTABLE
Reason : DISTRICT RECOMMENDATION

Establishment : CFN : FEI :
SA

DMF No: AADA:

Responsibilities:

Profile : TCM OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 18-NOV-02
Decision : ACCEPTABLE
Reason : DISTRICT RECOMMENDATION
