CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-498

Chemistry Review(s)

NDA 21-498

Nitazoxanide for Oral Suspension

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 21-498

2. REVIEW #: 1

3. REVIEW DATE: 15-NOV-2002

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

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
None	

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original	28-MAY-2002
Amendment (BC)	23-OCT-2002
Amendment (BC)	12-NOV-2002

7. NAME & ADDRESS OF APPLICANT:

Name:	Romark Laboratories, L.C.
Address:	6200 Courtney Campbell Causeway Suite 880 Tampa, FL 33607
Representative:	Marc S. Ayers, President
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): 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: Powder for Oral Suspension

12. STRENGTH/POTENCY: 100 mg/5 mL

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: __X__Rx ___OTC

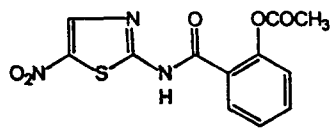
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

____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: 55981-09-4

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	16-JUL-1999	LOA 14-NOV-2002
IV			1	Adequate (based on review of a desk copy of the DMF, which the document room has not yet processed)		LOA 30-OCT-2002 Could not obtain DMF from document room.

[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	
NDA		
IND		
IND		
IND		
IND		

18. STATUS:

CONSULTS/CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics			
EES	Pending		
Pharm/Tox			
Biopharm	NLT [redacted]% (Q) of the labeled amount dissolved as nitazoxanide and desacetylnitazoxanide combined in 30 minutes.		Dakshima Chilukuri
LNC			
Methods Validation			
DMETS	Does not recommend use of the name "Cryptaz". Sponsor has countered with the name "Alinia". DMETS has found Alinia to be acceptable.	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	J. Rogers

The Chemistry Review for NDA 21-498

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From a CMC perspective, this application may be Approved.

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

II. Summary of Chemistry Assessments

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

Nitazoxanide for Oral Suspension is proposed for the treatment of diarrhea caused by *Cryptosporidium parvum* and *Giardia lamblia* . This product has been designated as an Orphan Drug for each of these indications since there is no alternative therapy. Nitazoxanide was therefore granted a priority review.

After reconstitution, the product contains 100 mg nitazoxanide in 5 mL of suspension and the following inactive ingredients: sodium benzoate, sucrose, xanthan gum, microcrystalline cellulose and carboxymethylcellulose sodium, anhydrous citric acid, sodium citrate dihydrate, acacia gum, sugar syrup, FD&C Red #40 and natural strawberry flavoring.

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.

For the majority of chemistry, manufacturing and controls information regarding the drug substance, reference is made to DMF which was reviewed and found acceptable on 15-SEP-2002.

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

Nitazoxanide for Oral Suspension is proposed for the treatment of diarrhea caused by *Cryptosporidium parvum* and *Giardia lamblia* in pediatric patients ages 1-11 years

without AIDS. Effectiveness of nitazoxanide in adolescents (12 years of age and above) and in adults without AIDS had not yet been determined. There is little clinical experience with nitazoxanide for treatment of cryptosporidial diarrhea in AIDS patients, and Nitazoxanide for Oral Suspension is not indicated in that patient population.

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

Nitazoxanide for Oral Suspension should be taken with food, and diabetics should note that the oral suspension contains 1.48 g sucrose per 5 mL.

No interactions with other drug products have been reported, but no studies have been performed to exclude the possibility of drug-drug interactions. No long-term carcinogenicity studies have been conducted.

The suspension is prepared when dispensed by addition of 48 mL water. The bottle is tapped until the powder flows freely, and about half of the required amount of water is added. The bottle is then shaken vigorously to suspend the powder. The remaining water is added and the bottle is then well shaken. The recommended dosage is as follows:

Age 12-47 months:	5 mL (200 mg nitazoxanide) every 12 hours for 3 days.
Age 4-11 years:	10 mL (200 mg nitazoxanide) every 12 hours for 3 days.

The container should be kept tightly closed and the bottle should be shaken thoroughly before each dose is removed. The suspension may be stored for seven days, after which any remaining suspension must be discarded.

Nitazoxanide for Oral Suspension is a pink-colored powder formulation that, when reconstituted as directed, contains 100 mg nitazoxanide in 5 mL of suspension. The reconstituted suspension has a pink color and strawberry flavor. The product is supplied in a 60 mL ——— bottle with a child resistant cap.

C. Basis for Approvability or Not-Approval Recommendation

The NDA submission and the Drug Mater File ultimately provided adequate information on the chemistry and manufacturing controls for the production of Nitazoxanide for Oral Solution. During the review, a number of issues, including the following were resolved:

- No DMF reference with letter of authorization or list of components and composition was submitted for the flavoring agent.
- Acceptance criteria for the drug substance were modified to reflect the capabilities of the manufacturer. The proposed limits for desacetylnitazoxanide were reduced from —% at release/ —% at expiry to —% at release/ —% at expiry.
- The sponsor was reminded that all compendial articles, if tested using USP methods, must meet USP requirements.

- No limits were proposed for unspecified and total degradation products for either release or stability. The sponsor was asked to propose those specifications.
- No commitments were made in the original submission to add one batch annually to the stability program, to submit the results of stability studies in the annual reports, or to withdraw from the market any batches of drug product found to fall outside of the approved specifications.

As amended, all tests, analytical methods and acceptance criteria 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 —— 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 does not object to the alternate name —— Most recently, the sponsor has proposed the name "Alinia", which is still under review by DMETS.

III. Administrative

A. Reviewer's Signature

/S/

B. Endorsement Block

Chemist Name/Date: Gene W. Holbert, Ph.D./01-NOV-2002
Chemistry Team Leader Name/Date: Norman R. Schmuff, Ph.D.
Project Manager Name/Date: Kristen Miller. Pharm.D.

C. CC Block

Redacted 32

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/s/

Gene Holbert
11/22/02 04:25:25 PM
CHEMIST

Norman Schmuff
11/26/02 06:40:48 AM
CHEMIST