CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

76075

ADMINISTRATIVE DOCUMENTS

MEMORANDUM

To: ANDA 76-075
Drug Product: Econazole Nitrate Cream, 1%
Sponsor: Altana, Inc.
Reference Listed Drug: Spectazole® Cream, 1%, Ortho-McNeil Pharmaceuticals

From: Dena R. Hixon, M.D.
Associate Director for Medical Affairs
Office of Generic Drugs

Date: September 12, 2002

Background

Altana Inc. submitted ANDA 76-075 on December 22, 2000. The proposed product is indicated for the treatment of tinea pedis, tinea cruris, tinea corporis, cutaneous candidiasis, and tinea versicolor.

Because the product is a topical, locally acting drug product, a 6-week comparative clinical endpoint study was conducted with 447 subjects having signs and symptoms of tinea pedis. Subjects were randomized to three treatment arms, Altana's test product, the reference product, and the vehicle as placebo. Altana's protocol included 4 weeks of treatment and a follow-up evaluation 2 weeks after discontinuation of treatment. The primary efficacy endpoint was total cure, defined as complete cure on the Investigator's Global Evaluation of all treated areas AND mycological cure (negative 10% KOH prep and negative fungal culture) at Day 43 (2 weeks after end of treatment). The protocol was submitted for review under IND and was accepted by OGD.

When the ANDA was submitted, the sponsor included a new definition of Total Cure, expanding the clinical cure to include both Complete and Excellent response on the Physician's Global Assessment. Using the original definition of clinical cure, the study failed to show bioequivalence between test and reference, but using the new definition, it met bioequivalence criteria.

The definition of clinical cure had been previously discussed with Dr. Jonathan Wilkin, Director, Division of Dermatologic and Dental Drug Products (DDDDP). In the original NDA for the reference product, the term "excellent response" was used to describe complete resolution of the infection, and the next category was called "partial response". The Physician's Global Assessment used in this ANDA describes the best possible therapeutic response as a "complete cure", which allows for some mild residual erythema and scaling. The next possible category is "excellent" and is defined as "approximately 75% or more improvement in signs and symptoms present at entry, but less than complete improvement." This category was deemed by DDDDP to be a partial response and was considered to be a failure in the original NDA. The 1990 *Draft Guidance for Industry: Bioequivalence Studies with Clinical Endpoints for Topical Antifungal*

Products defines clinical cure as "the signs and symptoms of the disease have cleared." Other sponsors have defined clinical cure as a total score of no more than 2, and no individual score of more than 1 on any of 6 clinical parameters. This is consistent with the protocol-defined definition of complete cure, which allows for some residual erythema and scaling.

The sponsor's efficacy analysis of the per protocol population using the complete response for clinical cure gave the following 90% confidence intervals of the difference between the test and reference products at 4 and 6 weeks:

	Clinical cure	**Mycological cure**	**Therapeutic cure**
4 weeks (end of treatment)	-12.56%, 9.98%	-11.17%, 6.00%	-11.52%, 10.85%
6 weeks (2 wk follow up)	0.46%, 23.73%	-12.13%, 2.77%	-1.17%, 22.14%

Discussion

The sponsor has conducted bioequivalence trials in 447 subjects to evaluate a clinical endpoint that is considerably more variable than the standard PK endpoints that are commonly studied in far fewer subjects for products that act through systemic exposure. Treatment with the proposed product resulted in a slightly better cure rate at the follow up visit than that achieved by the reference product. There is no known or theoretical safety concern and no increase in adverse reactions with the proposed product.

Given the variability in clinical endpoint study results, the 1990 draft guidance deserves further re-evaluation. Meanwhile, it would be inconsistent and inappropriate to change the bioequivalence criteria for an individual product.

An endpoint of therapeutic cure at both 4 and 6 weeks is consistent with the draft guidance. Evaluating therapeutic cure at the end of treatment and at the two week follow up visit should minimize false negative culture results and confirm clinical cures. It is actually a more stringent definition than that previously evaluated.

The FDA statistician calculated the following 90% confidence intervals of the difference between products in the proportion of subjects that had a complete cure at both 4 weeks (end of treatment) and at 6 weeks (2 week follow up): clinical cure (-8.0%, 13.6%), mycological cure (-11.9%, 6.9%), and therapeutic cure (-8.6%, 12.6%). These confidence intervals are all within the acceptable limits for bioequivalence. In addition, both the test and reference products showed results at 4 weeks, at 6 weeks, and at both 4 and 6 weeks that were significantly different than placebo.

Conclusion

Using definitions of clinical, mycological, and therapeutic cure that incorporate results at both 4 weeks (end of treatment) and 6 weeks (2 weeks post-treatment follow up), the

study submitted to ANDA 76-075 on December 22, 2000 is adequate to demonstrate bioequivalence of Altana Inc's Econazole Nitrate Cream, 1% with the reference listed drug, Ortho McNeil Pharmaceuticals' Spectazole Cream, 1%.

/S/ 9/12/02

Dena R. Hixon, M.D.
Associate Director for Medical Affairs
Office of Generic Drugs

/S/ 9/12/02

APPROVAL SUMMARY
REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 76-075

Dates of Submission: November 21, 2001 (Amendment -FPL)

Applicant's Name: Altana Inc.

Established Name: Econazole Nitrate Cream, 1%

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):

Do you have 12 Final Printed Labels and Labeling? Yes

CONTAINER Labels (15 g, 30 g, 85 g):
Satisfactory in FPL as of the November 21, 2001 submission. [Vol. A1.1]

CARTON Labeling (15 g, 30 g, 85 g):
Satisfactory in FPL as of the November 21, 2001 submission. [Vol. A1.1]

PROFESSIONAL PACKAGE Insert Labeling:
Satisfactory in FPL as of the November 21, 2001 submission. [Vol. A1.1, Rev. 10/01, Code: 12312]

Revisions needed post-approval: None.

Patent Data – NDA 18-751

Patent No.	Patent Expiration	Use Code	Description	How Filed	Labeling Impact
None	None	None	There are no unexpired patents for this product in the Orange Book Database.	N/A	None

Exclusivity Data– NDA 18-751

Code	Reference	Expiration	Labeling Impact
None	There is no unexpired exclusivity for this product in the Orange Book Database.	N/A	None

BASIS OF APPROVAL:

Was this approval based upon a petition? No

What is the RLD on the 356(h) form: SPECTAZOLE®

NDA Number: 18-751

NDA Drug Name: SPECTAZOLE® (econazole nitrate) Cream

NDA Firm: Ortho Pharmaceutical Corp., a Johnson & Johnson Co.

Date of Approval of NDA Insert and Supplement: Approved February 24, 1995/S-011

Has this been verified by the MIS system for the NDA? Yes

Was this approval based upon an OGD labeling guidance? No

Basis of Approval for the Container Labels: Most recently approved labeling of the reference listed drug.

Basis of Approval for the Carton Labeling: Most recently approved labeling of the reference listed drug.

NOTES/QUESTIONS TO THE CHEMIST: None

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		X	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 24		X	
Is this name different than that used in the Orange Book?		X	
If not USP, has the product name been proposed in the PF?		X	
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.		X	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?			X
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			X
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.		X	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			X
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?			X
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		X	
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?			X
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Labeling(continued)	**Yes**	**No**	**N.A.**
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels		X	

and labeling? Is "Jointly Manufactured by...", statement needed?			
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?			X
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.			
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?			X
Has the firm failed to describe the scoring in the HOW SUPPLIED section?			X
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	
Do any of the inactives differ in concentration for this route of administration?		X	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?			X
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?			X
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)			X
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		X	
Does USP have labeling recommendations? If any, does ANDA meet them?		X	
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?		X	
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.		X	
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?			X
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.			

FOR THE RECORD:

1. MODEL LABELING: Review based on the labeling of the reference listed drug (Spectazole Cream (NDA 18-751/S-011); revised March 1994; approved February 24, 1995).

2. FINISHED DOSAGE MANUFACTURING FACILITY (Vol. A1.5; Section 9; Page 1432)

   Altana Inc.
   60 Baylis Road
   Melville, NY 11747

3. STORAGE RECOMMENDATIONS

   USP – N/A
   RLD –Store below 86°F.
   ANDA – Store below 86°F.

4. INACTIVE INGREDIENTS

There is no discrepancy between the listing in the DESCRIPTION section of the insert labeling and the Components and Composition Statements. (Vol. A1.5; Section 7; Page 1329)

5. PRODUCT LINE

The innovator packages its product as follows:
15 g, 30 g, and 85 g

The applicant is proposing to package its products as follows:
15 g, 30 g, and 85 g aluminum tubes with HDPE puncture tip caps (Vol. A1.6; Section 13; Pages 1798, 1799, and 1800)

6. BIOEQUIVALENCE ISSUES - Pending

Date of Review:
June 12, 2002

Date of Submission:
November 21, 2002

Primary Reviewer M Dillahunt /S/ **Date** June 19, 2002

Team Leader **Date** 6/20/2002

---

cc: ANDA 76-075
DUP/DIVISION FILE
HFD-613/MDillahunt/LGolson (no cc)
V:\FIRMSAM\ALTANA\LTRS&REV\76075ap.labeling.doc
Review

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 76-075

Date of Submission: December 22, 2000 (Original Submission)

Applicant's Name: Altana, Inc.

Established Name: Econazole Nitrate Cream, 1%

Labeling Deficiencies:

1. CONTAINER: 15 g, 30 g, and 85 g - Include the degrees centigrade, 30°C, with your storage temperature recommendation (i.e., 86°F (30°C).

2. CARTON: 15 g, 30 g, and 85 g - See CONTAINER comment.

3. PACKAGE INSERT LABELING (HOW SUPPLIED) - See CONTAINER comment.

Please revise your labels and labeling, as instructed above, and then submit in final print.

Prior to approval, it may be necessary to further revise your labeling subsequent to approved changes for the reference listed drug. We suggest that you routinely monitor the following website for any approved changes -

http://www.fda.gov/cder/ogd/rld/labeling_review_branch.html

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

/S/

Wm Peter Rickman
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

NOTES/QUESTIONS TO THE CHEMIST: None

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		X	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 24		X	
Is this name different than that used in the Orange Book?		X	
If not USP, has the product name been proposed in the PF?		X	
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.		X	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?			X
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			X
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.		X	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			X
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?			X
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		X	
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?			X
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Labeling(continued)	**Yes**	**No**	**N.A.**
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?			X
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.			

Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?			X
Has the firm failed to describe the scoring in the HOW SUPPLIED section?			X
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	
Do any of the inactives differ in concentration for this route of administration?		X	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?			X
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?			X
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)			X
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		X	
Does USP have labeling recommendations? If any, does ANDA meet them?		X	
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?		X	
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.			
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?			X
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.			

FOR THE RECORD:

1. MODEL LABELING: Review based on the labeling of the reference listed drug (Spectazole Cream (NDA 18-751/S-011); revised March 1994; approved February 24, 1995).

2. PATENTS/EXCLUSIVITIES:

Patent Data – NDA 18-751

No	Expiration	Use Code	Use	File
		There are no unexpired patents for this product in the Orange Book database		

Exclusivity Data For NDA 18-751

Code/sup	Expiration	Use Code	Description		Labeling Impact
			There is no unexpired exclusivity for this product		

3. FINISHED DOSAGE MANUFACTURING FACILITY (Vol. 1.5; Section 9; Page 1432)

Altana Inc.
60 Baylis Road
Melville, NY 11747

4. STORAGE RECOMMENDATIONS

USP – N/A
RLD –Store below 86°F.
ANDA – Store below 86°F.

5. INACTIVE INGREDIENTS

There is no discrepancy between the listing in the DESCRIPTION section of the insert labeling and the Components and Composition Statements. (Vol. 1.5; Section 7; Page 1329)

6. PRODUCT LINE

The innovator packages its product as follows:
15 g, 30 g, and 85 g

The applicant is proposing to package its products as follows:
15 g, 30 g, and 85 g aluminum tubes with HDPE puncture tip caps (Vol. A1.6; Section 13; Pages 1798, 1799, and 1800)

7. BIOEQUIVALENCE ISSUES - Pending

Date of Review:
October 12, 2001

Date of Submission:
December 22, 2000 (Original submission)

Primary Reviewer:
LGolson

Date:
10/12/01

Team Leader:
/S/

Date:
10/15/2001

cc: ANDA 76-075
DUP/DIVISION FILE
HFD-613/LGolson/JGrace (no cc)
V:\FIRMSAM\ALTANA\LTRS&REV\76075na1.l
Review