CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

76075

CORRESPONDENCE

ANDA 76-075

6

Altana Inc.
Attention: Virginia Carman
60 Baylis Road
Melville, NY 11747

Dear Madam:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act.

NAME OF DRUG: Econazole Nitrate Cream, 1%

DATE OF APPLICATION: December 22, 2000

DATE (RECEIVED) ACCEPTABLE FOR FILING: December 26, 2000

We will correspond with you further after we have had the opportunity to review the application.

Please identify any communications concerning this application with the ANDA number shown above.

Should you have questions concerning this application, contact:

Elaine Hu
Project Manager
(301) 827-5848

Sincerely yours,

/S/ for

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

ALTANA

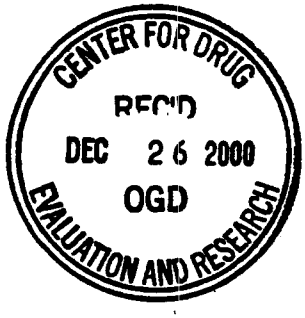
Altana Inc. 60 Baylis Road, Melville, N.Y. 11747 631-454-7677

505(j)(2)(A) OK
26-JAN-2001
Gregory B. Davis

December 22, 2000

Via Federal Express

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855



Original Submission
Abbreviated New Drug Application
Econazole Nitrate Cream , 1%

Dear Sir or Madam:

Pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act and in accordance with the provisions of the Regulations contained in 21 CFR §314.94, Altana Inc., is submitting this Abbreviated New Drug Application to market a new drug, **Econazole Nitrate Cream, 1%.**

The Reference Listed Drug that is the basis for this submission is **Spectazole Cream (econazole nitrate 1%)**, Manufactured by Ortho Pharmaceutical Corporation a Johnson & Johnson Company, NDA 18-751. The proposed drug, Econazole Nitrate Cream , 1%, contains the same active ingredient in the same strength and dosage form, has the same indications and usage, and route of administration as the Reference Listed Drug.
The exhibit batch (#C660) included in this application was fully packaged utilizing the 15 gram, 30 gram and 85 gram presentations for which approval is currently requested. Also included is placebo batch (C673) that was packaged in 85 gram tubes. The number of units filled of each package size and the disposition of any remaining bulk product are reconciled in the exhibit batch record.

Included in this seven (7) volume submission, along with Form FDA 356h, is the required Patent Certification and Exclusivity statements, draft Labeling, Bioequivalence Study, full Components and Composition statements, Raw Materials controls, description of the Manufacturing Facilities, Manufacturing and Processing instructions, In-process Controls, Filling and Packaging procedures, information on the Container/Closure System, controls for the Finished Dosage Form, Analytical Methods, Finished Dosage Form Stability,

Environmental Impact Analysis statement and Certification Requirements of the Generic Drug Enforcement Act of 1992.

All regulatory correspondences related to this Abbreviated New Drug Application should be addressed to:

Virginia Carman
Associate Director
Regulatory Affairs
Altana Inc.
60 Baylis Road
Melville, NY 11747
Tel. No. (631) 454-7677 Ext. 2091
Fax No. (631) 756-5114

A certified copy of this application (consisting of volumes, 1.1, 1.5, 1.6 and 1.7 and a copy of the Methods Validation package) is being sent to the New York District Office under separate cover.

If you require any additional information or clarification please contact me via telephone or facsimile at the above numbers.

Sincerely,
Altana Inc.

Virginia Carman
Associate Director, Regulatory Affairs

Enclosures

VC/ab

C:\ANDAS\Econazole Nitrate Cream , 1%\cover letter.wpd

ALTANA

Altana Inc. 60 Baylis Road, Melville, N.Y. 11747 631-454-7677

August 13, 2001

Office of Generic Drugs
Food and Drug Administration
Center for Drug Evaluation and Research
Metro Park North II
7500 Standish Place
Rockville, Maryland 20855

VIA FEDERAL EXPRESS

N/AM

ORIG AMENDMENT

ANDA 76-075
Econazole Nitrate Cream 1%
MINOR AMENDMENT

Dear Sir or Madam:

Reference is made to the Altana Inc. Abbreviated New Drug Application dated December 22, 2000, submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act for Econazole Nitrate Cream 1% and accepted for filing on December 26, 2000.

Reference is also made to the FDA facsimile correspondence dated June 8, 2001 for Chemistry comments. As requested this correspondence is designated as a **MINOR AMENDMENT** and appears prominently in this cover letter.

Each item has been addressed in **comment/response format.**

Chemistry

A. Deficiencies

1. **The DMF Econazole Nitrate USP, is currently inadequate. The DMF holder, has been notified. Please ensure that there has been a response submitted by the DMF holder.**

   has responded to the deficiencies in the May 22, 2001 FDA correspondence. Included as **Attachment I** is the DMF Amendment cover letter and response package from dated July 10, 2001.

2. **Please give the time period after which raw materials benzoic acid and butylated hydroxyanisole will be re-tested as per your re-test schedule.**

   Altana Inc. performs annual re-testing of the raw materials benzoic acid and butylated hydroxyanisole. Included as **Attachment II** are 12-month re-test specifications AND data for benzoic acid and butylated hydroxyanisole.

3. **Please provide the DMF information (DMF # and letter of authorization) on the caps for the 85 g tubes prepared from resin by**

   Information on the colorant and resin can be found in the DMF covering the tubes and closures. The DMF letter of authorization and the technical information on the caps for the 85g tubes prepared from resin is included as **Attachment III.**

4. **Please provide liner integrity testing results for all tube sizes. The data provided on page 1870 of your application for the are too old. Please provide recent test results for the tube liner**

All tube sizes have tube liner however, as requested, has been performed on all tube sizes (15, 30 and 85 gram tubes). Included, as **Attachment IV** are the test results.

5. **Please provide dimensional drawings for the 85 g tubes from**

Included, as **Attachment V** is the tube specification and dimensional drawing for 85 gram tubes from

6. **Please tighten your specification for the total aerobic microbial count and include release and stability specifications for the total yeast and mold count.**

We have tightened the specifications for Econazole Nitrate Cream as follows.

Total Aerobic Microbial Count	NMT	:fu/g
Total Combined Molds and Yeast Count	NMT	:fu/g
Free from *P.aeruginosa*		

Included, as **Attachment VI** are revised Finished Product and Stability Specifications.

7. **Please tighten your specification for total and individual impurity/degradant in release and stability protocols based on the observed values from your product and the values from the innovator's product at or near expiry after storage at room temperature.**

Included, as **Attachment VI** are revised Finished Product and Stability Specifications.

8. **Please include a preservative effectiveness test to be performed at time zero and expiration date to justify the proposed specification of % for benzoic acid.**

Altana has included a preservative effectiveness test to be performed at time zero and at the expiration date for the first three production batches to justify the proposed specification. Included, as **Attachment VII** is a revised Post Approval Stability Commitment.

9. **The container system mentioned in the stability results for the 15 g on pages 2328 – 2331 (described as is not consistent with the container system described on page 1798 and other places (described as manufactured by Please explain the inconsistency. Please also confirm that the listed as manufacturer of the 90 g in stability reports and are in fact the same entity.**

The container system for the 15 gram presentation on pages 2328-2331 (described as is a typographical error on the stability sheets. The 15 gram presentation was packaged in as demonstrated throughout the rest of the application. Included as **Attachment VIII** are revised accelerated, controlled room temperature and cycling stability summary sheets. Also included as **Attachment IX** are the specification sheets for and a letter from dated January 5, 1998 explaining the consolidation of all business entities.

10. **(lot # 9803000144) as the supplier of drug substance according to stability summary sheets is inconsistent with as the supplier for the drug substance according to batch records. Please clarify and revise.**

The raw material supplier for Econazole Nitrate USP Lot #9803000144 is and was used in the Exhibit Batch No. C660 for Econazole Nitrate Cream 1%. The Stability Summary Sheets have been corrected to reflect the correct name of the raw material supplier. Please refer to **Attachment VIII** for revised Stability Summary Sheets.

11. **Please tighten your viscosity release and stability specifications based on the observed values of the exhibit batch.**

Please refer to **Attachment VI** for the revised finished product and stability specifications.

12. **Please add quantitative specification for butylated hydroxyanisole in your release and stability protocols.**

A quantitative specification for butylated hydroxyanisole has been added to the release and stability protocols. Please refer to **Attachment VI** for the revised finished product and stability specifications.

13. **Implementation of the post approval reduced testing program for the stability studies requires prior approval supplement supported by appropriate data.**

Altana Inc. acknowledges that a reduced testing program for the stability studies requires Prior Approval Supplement supported by appropriate data. Please refer to **Attachment VII** for the revised Post Approval Stability Commitment.

B. **In addition to responding to the above deficiencies, please note and acknowledge the following comments in your response.**

1. **Your bioequivalence information is pending review. Deficiencies, if any, will be communicated separately.**

Altana Inc. acknowledges the bioequivalence information is pending review and deficiencies, if any, will be communicated separately.

2. **Your labeling information is pending review. Deficiencies, if any, will be communicated separately.**

   Altana Inc. acknowledges the labeling information is pending review and deficiencies, if any, will be communicated separately.

3. **All facilities referenced in the ANDA must have a satisfactory compliance evaluation at the time of approval. We have requested an evaluation from the office of compliance.**

   Altana Inc. acknowledges that all facilities referenced in the ANDA must have a satisfactory compliance evaluation at the time of approval and that FDA has requested an evaluation from the Office of Compliance.

4. **We require an acceptable methods validation on the drug product to support the ANDA and are currently scheduling the study with the District Laboratory. Please provide samples promptly when contacted. Please also provide a commitment to work with us to expeditiously resolve any deficiencies from the methods validation study if the ANDA is approved prior to its completion.**

   Altana Inc. acknowledges that FDA requires an acceptable methods validation on the drug product to support the ANDA and that the study is currently being scheduled with the District Laboratory. Altana will provide samples promptly when contacted. Altana also commits to work with FDA to expeditiously resolve any deficiencies from the method validation study if the ANDA is approved prior to its completion.

5. **Please provide all available long-term stability data to update your studies.**

   Please refer to **Attachment VIII** for updated stability summary sheets, which include 24 month, controlled room temperature data.

If you have any questions or require additional information, please contact me at (631) 454-7677 extension 2091. FAX communications can be made to (631) 756-5114.

Sincerely,

ALTANA INC.

Virginia Carman

Virginia Carman
Associate Director, Regulatory Affairs

VC:jb

ALTANA

Altana Inc. 60 Baylis Road, Melville, N.Y. 11747 631-454-7677

November 21, 2001

Office of Generic Drugs
Food and Drug Administration
Center for Drug Evaluation and Research
Metro Park North II
7500 Standish Place
Rockville, Maryland 20855

VIA FEDERAL EXPRESS

ANDA 76-075
Econazole Nitrate Cream 1%
LABELING AMENDMENT

Dear Sir or Madam:

Reference is made to the Altana Inc. Abbreviated New Drug Application dated December 22, 2000, submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act for Econazole Nitrate Cream 1% and accepted for filing on December 26, 2000.

Reference is also made to the FDA facsimile correspondence dated October 15, 2001 for Labeling comments.

Each item has been addressed in **comment**/response format.

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.**

We have revised the container, carton and insert labeling for the 15, 30 and 85 gram tube sizes to include the degrees centigrade, 30°C with the storage temperature recommendation. Included in **Attachment I** are twelve copies of final printed container, carton and insert labeling.

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/cde/ogd/rld/labeling_review_branch.html.

Altana Inc. has monitored the FDA website, http://www.fda.gov/cder/ogd/rld/labeling and the latest approved labeling supplements for NDA 50-537 (Cleocin T, manufactured by Pharmacia and Upjohn) is March 15, 1989. A copy of the electronic page is included in **Attachment II** Altana Inc. will monitor the site on a routine basis.

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.

To facilitate the review and in accordance with 21 CFR 314.94 (a)(8)(iv), a side-by-side comparison has been provided of the proposed labeling with all differences annotated and explained see **Attachment III.**

If you have any questions or require additional information, please contact me at (631) 454-7677 extension 2091. FAX communications can be made to (631) 756-5114.

Sincerely,

ALTANA INC.

Virginia Carman

Virginia Carman
Associate Director, Regulatory Affairs

VC/jb

ALTANA

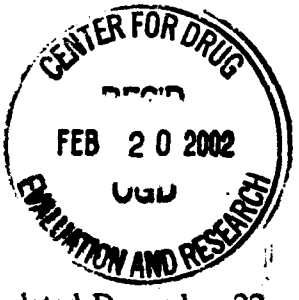
Altana Inc. 60 Baylis Road, Melville, N.Y. 11747 631-454-7677

February 19, 2002

ORIG AMENDMENT
N/AB

Office of Generic Drugs
Food and Drug Administration
Center for Drug Evaluation and Research
Metro Park North II
7500 Standish Place
Rockville, Maryland 20855

VIA FEDERAL EXPRESS



ANDA 76-075
Econazole Nitrate Cream 1%
BIOEQUIVALENCE AMENDMENT

Dear Sir or Madam:

Reference is made to the Altana Inc. Abbreviated New Drug Application dated December 22, 2000, submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act for Econazole Nitrate Cream 1% and accepted for filing on December 26, 2000.

Reference is also made to the FDA facsimile correspondence dated October 24, 2001 for bioequivalence comments. On December 27, 2001 Altana Inc. submitted a request for a Type A meeting to discuss the bioequivalence issues outlined in the October 24, 2001 correspondence and clarify the analysis used for the bioequivalence study. The FDA Office of Generic Drugs, Division of Bioequivalence, subsequently denied this request.

As directed this correspondence is designated as a **BIOEQUIVALENCE AMENDMENT** and appears prominently in this cover letter. Each item has been addressed in **comment**/response format.

Bioequivalence Deficiencies

Your clinical endpoint study fails to demonstrate bioequivalence between your product, Econazole Nitrate Cream, 1% and the Reference Listed Drug (RLD), Spectrazole® (Ortho McNeil Pharmaceuticals) in the treatment of tinea pedis due to the following reasons:

1. **The study report gave two definitions of Total Cure, each analyzed separately. Definition 1 is given in the protocol and is the standard definition for a primary outcome in tinea pedis studies. Total cure is defined as those who had complete resolution on the Physicians Global Assessment plus mycological cure (negative KOH and fungal cure). The second definition expands the clinical cure to complete and excellent response on the Physicians Global Assessment. There was no explanation given to justify this change and it is not listed in the changes in the planned analyses.**

This definition is not accepted as a definition of cure for tinea pedis. You did summarize the results stating that when using the original definition, the study fails to show bioequivalence between test and reference, and when using the second definition, the study meets the bioequivalence criteria. This represents a post hoc change in clinical endpoints based on a failure of the data to meet the original endpoint criteria for success.

Altana Inc. had an expert Biostatistician perform an evaluation of the Bioequivalence study and data for Econazole Nitrate Cream 1% in response to the above deficiency.

After review of the bioequivalence report for Study ALT 01/99F, the Biostatistician determined there were errors in the report which need to be corrected to properly determine the bioequivalency of Altana's Econazole Nitrate Cream 1% to Spectrazole Cream 1%.

Attachment I contains the Biostatistician's report and statistical data. This evaluation addresses the observations and corrects the analyses of the efficacy results. The corrected analyses demonstrate that Altana's Econazole Nitrate Cream, 1% is bioequivalent to Spectrazole Cream, 1% and that both products have superior efficacy over that of the placebo (Altana vehicle).

2. **You outlined several changes in the planned analyses in the study report and the method for carrying forward missing values for the MITT was further clarified. You introduced the concept of invalid visits for this population, including visits outside the prescribed time window and visits after a prohibited medication was taken. In these instances, the last valid observation was carried forward. Since the MITT population was not defined by adherence to the protocol, this method is not appropriate. Only missing visit data should be substituted by carrying the last observation forward.**

   Last Observation Carried Forward (LOCF) was only used for missing visits. Page 12, section 5.7.2 of the Case Study Report states "Day 43 visit measurements that were outside the 43-49 Day window were used as the Visit 4 measurement. Baseline data were carried forward for Day 5, provided the subject had a valid visit for either Day 29 or 43." If necessary, the wording for this section of the report can be changed to clarify that LOCF was not used for out-of-window data at the Test of Cure visit (Visit 4).

3. **Patient number 06-002 was listed as a withdrawal because of an insufficient therapeutic response and should therefore be included in all analysis populations as a treatment failure.**

   Altana acknowledges that subject #06-002 was discontinued as a treatment failure. However, the protocol, as approved by FDA, states that treatment failure dropouts are to be included in the PP analysis population only if they received at least 14 days of treatment. #06-002 only received 7 doses before stopping the medication on her own.

If you have any questions or require additional information, please contact me at (631) 454-7677 extension 2091. FAX communications can be made to (631) 756-5114.

Sincerely,

ALTANA INC.

for Audrey Scaloski

Virginia Carman
Associate Director, Regulatory Affairs

VC/jb

ALTANA

Altana Inc. 60 Baylis Road, Melville, N.Y. 11747 631-454-7677

June 6, 2002

Gary Buehler, Director
Office of Generic Drugs
FDA, CDER
MPN II, HFD-600, Room 286
7500 Standish Place
Rockville, MD 20855

ORIG AMENDMENT
N/NC/810
VIA FEDERAL EXPRESS

ANDA 76-075
Econazole Nitrate Cream 1%

Dear Mr. Buehler:

Reference is made to the Altana Inc. Abbreviated New Drug Application dated December 22, 2000, submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act for Econazole Nitrate Cream 1% and accepted for filing on December 26, 2000.

Reference is also made to the FDA facsimile correspondence dated April 19, 2002 for Bioequivalence deficiencies. Altana has submitted two separate requests for meetings with the OGD Division of Bioequivalence to discuss the bioequivalence issues and both requests have been denied. The two requests, dated December 27, 2001 and April 25, 2002, have been enclosed for your review.

According to the CDER, Manual of Policies and Procedures, *Formal Meetings Between CDER and CDER's External Constituents*, "formal meetings serve a beneficial purpose for both the center and its external constituents to provide clarity and resolve issues related to the drug development and review processes, compliance actions, and policy development". Altana Inc. has not been afforded this opportunity.

Altana Inc. is seeking approval of its Econazole Nitrate Cream 1% with the correct bioequivalence rating or an opportunity for a meeting to discuss possible alternatives.

FDA's Non-Conformance to Good Guidance Practices

The Division of Bioequivalence has based their determination on a 1990 Draft Guidance. The guidance entitled, "Draft Guidance for the Performance of a Bioequivalence Study for Topical Antifungal Products" has remained in draft for 12 years. It has never been published in the Federal Register Notice whereby an appropriate review and comment period could be conducted. This guidance is being applied to Altana's study as though it has been finalized in accordance with the principles of Good Guidance Practices.

Inappropriate Standard

The 1990 Draft Guidance uses an inappropriate standard to establish bioequivalence of two topical antifungal products. Primary weight is given to the evaluation performed at the two-week follow-up visit rather than the end of treatment visit. In addition, this evaluation includes the subjective analysis of the Physicians Global Assessment of clinical cure. The standard for establishing the bioequivalence of topical antifungals should be "not less effective than" the Reference Listed Drug. Primary weight should be given to the end of treatment visit and/or the objective measurement of mycological cure.

Altana's Bioequivalence Study is Acceptable

The results of the bioequivalence study demonstrated the Altana product was not less effective than the Reference Listed Drug, Spectazole® and there were no differences in the safety profiles between the two products. Furthermore, the Altana product was equivalent to the Reference Listed Drug for mycological and clinical cure for all time points up to and including the End of Treatment visit. This was the standard used to approve the Reference Listed Drug, Spectazole. In addition, the two products were equivalent for mycological cure at the 2-week follow up visit. The Altana product was only slightly better for the subjective Physicians Global Assessment, not statistically better, at the two-week follow up visit.

Physicians would use Altana product

Altana is prepared to obtain and submit to FDA several affidavits from prominent investigators and clinicians in the field of dermatology to document their disbelief that the Office of Generic Drugs would prevent the introduction of a generic product which has been demonstrated to be at least as effective as the Reference Listed Drug for the approved duration of treatment.

FDA's Congressional Mandate

Altana is also prepared to advise and enlist the assistance of its congressmen and senators to address the review and acceptance of this important generic topical product. This product has been found to be at least as effective as the Reference Listed Drug and represents a suitable substitute for Spectazole® in the treatment of fungal infections. In light of Congressional efforts to control prescription drugs costs, it is unconscionable that OGD would deny the public access to an affordable generic that clinicians find an appropriate therapeutic remedy.

Altana strongly believes it deserves the right to meet, discuss and resolve the issues related to the approval of the proposed drug, Econazole Nitrate Cream 0.1% as a generic equivalent to Spectazole®.

I am looking forward to discussing these issues with you in the near future. Please contact me at (631) 454-7677 extension 2085 or by fax at (631) 756-5114.

Sincerely,

ALTANA INC.

Robert J. Anderson, Esq.
Sr. Director, Scientific Affairs

RJA/jb

ALTANA

Altana Inc. 60 Baylis Road, Melville, N.Y. 11747 631-454-7677

June 25, 2002

ORIG AMENDMENT
N/AM

Office of Generic Drugs
Food and Drug Administration
Center for Drug Evaluation and Research
Metro Park North II
7500 Standish Place
Rockville, Maryland 20855

VIA FEDERAL EXPRESS

ANDA 76-075
Econazole Nitrate Cream 1%
MINOR AMENDMENT

Dear Sir or Madam:

Reference is made to the Altana Inc. Abbreviated New Drug Application dated December 22, 2000, submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act for Econazole Nitrate Cream 1% and accepted for filing on December 26, 2000.

Reference is also made to the FDA facsimile correspondence dated September 5, 2001 for Chemistry comments. As requested this correspondence is designated as a **MINOR AMENDMENT** and appears prominently in this cover letter.

Each item has been addressed in **comment**/response format.

Chemistry

A. **Deficiencies**

1. **The DMF Econazole Nitrate USP, is currently inadequate. The DMF holder, has been notified. Please do not submit a MINOR amendment until the DMF holder has informed you that a complete response to the DMF deficiency letter has been submitted to the Agency.**

   Attachment I contains the correspondence from the DMF holder, that indicates they have responded to the DMF deficiency letter.

2. **You failed to demonstrate the liner integrity of packaging tubes in your amendment dated August 13, 2001. Please provide the liner integrity test results for all tube sizes to demonstrate that there is no voids/bare metal exposure areas in the containers.**

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JUN 2 7 2002
OGD / CDER

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Attachment II contains the Altana results on all tube sizes (15, 30 and 85 gram). These results were also included in the Minor Amendment submitted August 13, 2001 (pp 25-27) and in the original Abbreviated New Drug Application on page 1882, 1888 and 1894 respectively and show passing results.

3. **Your proposed release and stability specifications for total impurities and stability specification for the individual impurity are still not acceptable. Since the full-term stability data of your product show that the product is stable, please tighten your release specifications for total impurities and stability specifications for individual impurities.**

The Altana In-Process and Finished Product Specifications for Total Impurities have been set to the limit of the Raw Material Specification supplied by the manufacturer and have remained unchanged. The Stability Specifications have been tightened based on the stability data we have obtained to date.

Attachment III contains revised Stability Specifications.

4. **Please provide data to support the effectiveness of benzoic acid as effective microbial preservative at the proposed lower limit of %.**

The antimicrobial effectiveness test was conducted using a formulation of Econazole Nitrate Cream with only % of the labeled amount of Benzoic Acid. The results indicated this formulation met the USP requirements for Antimicrobial Agent Effectiveness. This data confirms the effectiveness of the Benzoic Acid at the proposed lower limit of %. **Attachment IV** contains the Antimicrobial Effectiveness Test Report.

5. **The method currently used for butylated hydroxyanisole (BHA) is a qualitative method. Please submit the modified test method and the validation data to show that the method is adequate for determining the amount of BHA at release and expiry. The proposed lower limit for BHA contents should be supported by the data showing the effectiveness of BHA at the proposed level.**

Attachment V contains the modified test method and the validation report VD 0312.00 to show that the method is adequate for determining the amount of BHA at release and expiry.

Regarding the effectiveness of BHA at the proposed lower limit, the Econazole Nitrate Cream is packaged in a blind-end tube that is filled to capacity, thereby greatly reducing the possibility of oxidation. In addition, the product is formulated with an extremely low level of BHA (0.001%) indicating its role, as an antioxidant may be minimal at best.

Review of the stability data gathered to date demonstrates the product has remained well within the established specifications for the proposed shelf-life of 24 months. Total degradation was found to be %. The product is also within specifications for its physical characteristics. The stability data acquired to date confirms the effectiveness of the BHA. Altana's finished product release specification of % for BHA will ensure the stability of the product throughout its shelf-life.

6. **The release specification of NLT % of label claim for BHA is not acceptable. Please set a range for BHA in line with the initial formulation.**

The Finished Product Specifications have been revised to include a range for BHA of %. **Attachment VI** contains the revised Finished Product Specifications.

B. In addition to responding to the above deficiencies, please note and acknowledge the following comments in your response.

1. **Your bioequivalence information is pending review. Deficiencies, if any, will be communicated separately.**

Altana Inc. acknowledges the bioequivalence information is pending review and deficiencies, if any, will be communicated separately.

2. **Your labeling information is pending review. Deficiencies, if any, will be communicated separately.**

Altana Inc. acknowledges the labeling information is pending review and deficiencies, if any, will be communicated separately.

If you have any questions or require additional information, please contact Ms. Audrey Bialeski, *Manager*, Regulatory Affairs at (631) 454-7677 extension 3007. FAX communications can be made to (631) 756-5114.

Sincerely,

ALTANA INC.

Virginia Carman

Virginia Carman
Associate Director, Regulatory Affairs

VC/jb

ALTANA

ana Inc. 60 Baylis Road, Melville, N.Y. 11747 631-454-7677

August 2, 2002

Gary Buehler, Director
Office of generic Drugs
Food and Drug Administration
Center for Drug Evaluation and Research
Metro Park North II, Room 286 (HFD-600)
7500 Standish Place
Rockville, Maryland 20855

VIA FEDERAL EXPRESS

NEW CORRESP

ANDA 76-075
Econazole Nitrate Cream 1%

Dear Mr. Buehler:

Reference is made to the Altana Inc. Abbreviated New Drug Application dated December 22, 2000 submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act for Econazole Nitrate Cream 1% and accepted for filing on December 26, 2000.

Reference is also made to the June 6, 2002 Altana correspondence requesting a meeting with the Office of Generic Drugs to discuss the bioequivalence issues for Econazole Nitrate Cream 1%. Altana also acknowledges the July 31, 2002 teleconference call held between Mr. Gary Buehler and Altana representatives to discuss a meeting date.

Altana Inc. is submitting this correspondence to confirm the meeting date of Monday, September 16, 2002 at 10:00 am. Altana is prepared to submit the clinical data analysis package on August 12, 2002 as requested by the Division of Bioequivalence.

Altana appreciates the opportunity to meet with FDA to discuss this product. If you have any questions or require any additional information please contact me at (631) 454-7677 extension 2085. FAX communications may be made to (631) 756-5114.

Sincerely,

ALTANA INC.

Audrey Bialeski for

Robert J. Anderson, Esq.
Senior Director, Scientific Affairs

RJA/ab

RECEIVED
AUG 0 5 2002
OGD / CDER

ALTANA

Altana Inc. 60 Baylis Road, Melville, N.Y. 11747 631-454-7677

EH
8/14/02
N/APD

August 12, 2002

ORIG AMENDMENT

Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

VIA FEDERAL EXPRESS

ANDA 76-075
ECONAZOLE NITRATE CREAM 1%
BIOEQUIVALENCE AMENDMENT

Dear Mr. Conner:

Reference is made to the Altana Inc. Abbreviated New Drug Application dated December 22, 2000 submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act for Econazole Nitrate Cream 1% and accepted for filing on December 26, 2000.

Reference is also made to the FDA facsimile correspondence dated April 19, 2002 for Bioequivalence deficiencies. As directed, this correspondence is designated as **BIOEQUIVALENCE AMENDMENT** and appears prominently in this cover letter. Each item has been addressed in **Comment**/response format.

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BIOEQUIVALENCE DEFICIENCIES

1. **Your original analysis using the correct clinical cure definition fails to demonstrate bioequivalence between your product, Econazole Nitrate Cream 1%, and the reference listed drug (RLD), Spectazole® (Ortho McNeil Pharmaceuticals) in the treatment of tinea pedis.**

2. **The primary endpoints for bioequivalence studies with clinical endpoints have been carefully selected in consultation with the appropriate new drug division. These are not always the same endpoints as those that are used to evaluate efficacy of a new drug product. Please refer to the "1990 Draft Guidance for the Performance of a Bioequivalence Study for Topical Antifungal Products." This guidance was prepared by the Office of Generic Drugs with consultation from the CDER division responsible for topical antifungal drug products. In discussing the primary endpoints, the guidance states: "While these comparisons should be evaluated at the end of treatment and at the two week follow-up visits, primary weight will be given to the two week follow-up evaluation in determining if bioequivalence has been established." The primary endpoint in your reanalysis is the end of treatment visit clinical and mycological cure. This endpoint is not acceptable for this study and the analysis should be done using the data from these evaluations at the follow-up visit two weeks after the end of treatment.**

   Altana has prepared a clinical study report for Protocol ALT 01/99F. This report was prepared in response to the teleconferences held on July 11 and 31, 2002, between the FDA Division of Bioequivalence and Altana representatives. The report has been organized in accordance with the ICH Guideline "Structure and Content of Clinical Study Reports" November 30, 1995. Also included is a compact disk containing all requested electronic data. All electronic data is virus free. Data was scanned using Norton Antivirus Software (Corporate Edition Version 7.5, Symantec Corporation).

   The Clinical Study Report was saved in two software formats:

   Word 2000 (version 10.0)
   Microsoft Corporation

   Adobe Acrobat (Version 5.0.0)
   Adobe Systems Incorporated

   The report was viewed using Adobe Acrobat Reader (Version 5.0.5, Adobe Systems Incorporated).

A document containing the contents of the compact disc (CD) has been enclosed with the CD as well as included as page 1a of this submission.

If you have any questions, or require additional information please contact Ms. Audrey Bialeski, Manager, Regulatory Affairs, at (631) 454-7677 extension 3007. FAX communications may be made to (631) 756-5114.

Sincerely,
ALTANA INC.

Audrey Bialeski for

Virginia Carman
Associate Director, Regulatory Affairs

VC:tw

Encl.

Pharma

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ALTANA

September 11, 2002

N CORRESP
N C

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Gary Buehler, Director
Office of Generic Drugs
FDA, CDER
MPN II, HFD-600, Room 286
7500 Standish Place
Rockville, MD 20855

VIA TELEFAX (301) 594-0183 and FEDERAL EXPRESS

ANDA 76-075
Econazole Nitrate Cream 1%

Dear Mr. Buehler:

Reference is made to the Altana Inc. Abbreviated New Drug Application dated December 22, 2000, submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act for Econazole Nitrate Cream 1% and accepted for filing on December 26, 2000 and the meeting scheduled for Monday, September 16, 2002 at 10:00AM.

This correspondence is to confirm the discussion held this morning regarding the cancellation of the September 16, 2002 meeting.

It is our understanding the Econazole Nitrate Cream 1% bioequivalence issues have been resolved and the September 16, 2002 meeting is no longer necessary.

As discussed, our response to the August 28, 2002 FDA correspondence is currently being prepared.

I would like to take this opportunity to thank you for all of your assistance with this submission. Altana Inc. is anxiously waiting approval of Econazole Nitrate Cream 1%.

If you have any questions or require additional information please contact Ms. Audrey Bialeski, *Manager*, Regulatory Affairs at (631) 454-7677 extension 3007 or by fax at (631) 756-5114.

Sincerely,

ALTANA INC.

for Audrey Bialeski

Robert J. Anderson, Esq.
Sr. Director, Scientific Affairs

RJA/jb

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ALTANA

November 6, 2002

ORIG AMENDMENT

Rashmikant M. Patel, Ph.D.
Director
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Office of Generic Drugs
Center for Drug Evaluation and Research
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N/Am

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VIA TELEFAX and FEDERAL EXPRESS

ANDA 76-075
Econazole Nitrate Cream 1%
TELEPHONE AMENDMENT

Dear Dr. Patel:

Reference is made to the Altana Inc. Abbreviated New Drug Application dated December 22, 2000, submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act for Econazole Nitrate Cream 1% and accepted for filing on December 26, 2000.

Reference is also made to the Telephone Amendment dated October 21, 2002 and the November 6, 2002 teleconference between FDA and Altana representatives regarding the Finished Product and Stability specifications for Microbial Limits. As requested this correspondence is designated as a **TELEPHONE AMENDMENT**.

Altana Inc. has revised the Total aerobic microbial count from (as discussed in the teleconference. Altana has also provided the following rationale for deleting this test.

Econazole Nitrate Cream 1% has enough intrinsic antifungal activity to warrant exclusion of the yeast/mold requirement for the Microbial Limit Test. According to Martindale 28th Edition, "Econazole is an imidazole antifungal agent with similar antimicrobial action and activity to Ketoconazole." Ketoconazole has a wide spectrum of antimicrobial activity against organisms including *Candida* spp, *Asperigillus* spp, and some gram positive bacteria as per Martindale 28th edition. The appropriate pages from the Martindale are included in **Attachment I** for review.

In addition, Altana performed a microbial limit test validation of Econazole Nitrate Cream 1% at a 1:25 dilution in TAT broth. At this dilution, *P. aeruginosa* and *B. subtillis* were recovered with inoculum levels of ~10 cfu, *C. albicans* and *A. niger* were not recovered at this inoculum level. The product was then re-validated at 1:25 dilution level with a higher inoculum level of <100 of *C. albicans* and *A.niger*. Scant growth of both fungal organisms were detected in the incubated product broth. The resultant scant fungal growth is attributed to the active ingredient, econazole nitrate. Econazole Nitrate Cream 1% is inimical to low level challenge and that low number, if present, would be injured/killed and would not be recovered using the standard microbial limit test methodologies.

Attachment II contains the revised Finished Product and Stability Specifications. **Attachment III** contains the updated Controlled Room Temperature Stability Reports for Lot C660 and J179 with the reflected change.

If you have any questions or require additional information, please contact Ms. Audrey Zaweski, *Manager*, Regulatory Affairs at (631) 454-7677 extension 3007. FAX communications can be made to (631) 756-5114.

Sincerely,

ALTANA INC.

Audrey Zaweski for
Virginia Carman
Associate Director, Scientific Affairs

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Pharma

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ORIG AMENDMENT

N/AM

October 21, 2002

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VIA TELEFAX (301) 594-0180
AND FEDERAL EXPRESS

ANDA 76-075
Econazole Nitrate Cream, 1%
TELEPHONE AMENDMENT

Dear Dr. Patel:

Reference is made to the Altana Inc. Abbreviated New Drug Application dated December 22, 2000 submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act for Econazole Nitrate Cream, 1%, and accepted for filing on December 26, 2000, as well as the minor amendment submitted September 17, 2002.

Reference is also made to a teleconference of October 18, 2002 between representatives of Altana Inc. and the Office. Altana has prepared this correspondence to address the items discussed during the conference call.

As requested, Altana Inc. has revised the release specifications and stability specifications for "other" degradation products/related substances. Therefore, all individual degradation products/related substances have been limited to % for in-process, finished product and stability specifications. This information may be found in Attachment 1.

Altana was also requested to provide the actual data on which Altana based the revision of the BHA limit from %.

Attachment 2 contains the data to support the lowering of the stability specification for the BHA to %. 36-month data is included for lot C660. Please note that the quantitative specification is recorded for the first time at the 36-month stability interval for lot C660. The "presence" test was performed prior to this time.

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Additionally, stability data is included for recently manufactured lot # J179. Data from this lot indicates that the level of BHA drops off quickly. At 3 months accelerated the level is approximately %.

At the time the presence test was developed, testing indicated that a positive presence test equated to a % level of BHA. It has since been determined that at levels of approximately % the product still exhibits a positive result for the presence test.

As noted previously the product is formulated with an extremely low level of BHA %) indicating its role, as an antioxidant is minimal at best.

Antimicrobial effectiveness testing has proven, that at the lower specification limit for the preservative benzoic acid, the stability of the product is adequately maintained. Stability data at 36 months indicate that the product remains within the set specifications for all physical and chemical characteristics.

If you have any questions or require additional information, please contact Ms. Audrey Zaweski, *Manager,* Regulatory Affairs at (631) 454-7677, ext. 3007. Fax communications can be made to (631) 756-5114.

Sincerely,

ALTANA INC.

Virginia Carman for

Robert J. Anderson, Esq.
Sr. Director, Scientific Affairs

RJA:vc

Pharma

ALTANA

September 17, 2002

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VIA FEDERAL EXPRESS

ORIG AMENDMENT
N/AM

ANDA 76-075
Econazole Nitrate Cream 1%
MINOR AMENDMENT

Dear Sir or Madam:

Reference is made to the Altana Inc. Abbreviated New Drug Application dated December 22, 2000, submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act for Econazole Nitrate Cream 1% and accepted for filing on December 26, 2000.

Reference is also made to the FDA correspondence dated August 28, 2002 for Chemistry comments. As requested this correspondence is designated as a **MINOR AMENDMENT** and appears prominently in this cover letter.

Each item has been addressed in **comment**/response format.

Chemistry

A. **Deficiencies**

1. **The DMF Econazole Nitrate USP, is currently inadequate. The DMF holder, has been notified. Please do not submit a MINOR amendment until the DMF holder has informed you that a complete response to the DMF deficiency letter has been submitted to the Agency.**

   Altana Inc. has been informed that the DMF holder, has responded to the DMF deficiency letter. The date of the response was September 17, 2002. A copy of the cover letter from the US Agent is included in **Attachment I.**

2. **Please identify and establish specifications for the individual (known and unknown) for the finished product release and stability.**

   Altana has revised the In-Process, Finished Product and Stability Specifications to include the identification and establishment of the individual (known and unknown) degradation products. The revised specifications have been included with this submission in **Attachment II.**

In addition, the lower limit for BHA on the proposed Stability Specifications has been revised to %. Altana Inc. has reviewed stability data acquired for the exhibit batch and found the level of BHA after more than 36 months storage at controlled room temperature is approximately %. Data for an additional batch puts the level at approximately % after 3 months at 40°C. The original limit for BHA was established upon completion of the methods validation with minimal stability data. At this time Altana has tested two separate lots of Econazole Nitrate Cream (one lot stored at controlled room temperature for over 36 months and one stored at accelerated conditions for 3 months) using the validated method and found the results to be consistent. Data for the assay, degradation products and preservative are all well within established limits for both batches of Econazole Nitrate Cream. The stability profile of the product does not appear to be impacted by the level of BHA in the formulation. Included in **Attachment III** is the revised report *Validation of the Assay for Butylated Hydroxyanisole in Econazole Nitrate Cream, 1%.*

B. In addition to responding to the above deficiencies, please note and acknowledge the following comments in your response.

1. Your bioequivalence information is pending review. Deficiencies, if any, will be communicated separately.

Altana Inc. acknowledges the bioequivalence information is pending review and deficiencies, if any, will be communicated separately.

If you have any questions or require additional information, please contact Ms. Audrey Bialeski, *Manager*, Regulatory Affairs at (631) 454-7677 extension 3007. FAX communications can be made to (631) 756-5114.

Sincerely,

ALTANA INC.

Virginia Carman

Virginia Carman
Associate Director, Scientific Affairs

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