CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-502

CORRESPONDENCE

ALTANA

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

June 1, 2001

Lillie Golson
Senior Regulatory Reviewer
Division of Labeling and Program Support
Office of Pharmaceutical Science (HFD-613)
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room, Metro Park North II
7500 Standish Place, Room 200N
Rockville, MD 20855

DRUG AMENDMENT
N/AF
VIA HAND DELIVERY

ANDA 75-502
Clotrimazole and Betamethasone Dipropionate Cream USP, 1%/0.05 (base)
Labeling Amendment

Dear Ms. Golson:

Reference is made to the Altana Inc. abbreviated new drug application submitted on November 11, 1998 pursuant to section 505(j) of the Federal Food, Drug and Cosmetic Act for Clotrimazole and Betamethasone Dipropionate Cream USP, 1%/0.05% (base).

Reference is also made to the telephone conference this morning, June 1, 2001, between you and Ms. Audrey Bialeski of the Altana Inc Regulatory Affairs department. During this communication, Altana Inc was asked to submit twelve double-sided copies of the Final Printed Labeling of the package insert. These data are provided in **Attachment I** and as requested, this response has been appropriately identified as a "LABELING AMENDMENT."

If you have any questions or require additional information, please contact me at (631) 454-7677, extension 2085. FAX communications can be made to (631) 756-5114.

Sincerely,
ALTANA INC.

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

RJA: jfa
Enclosures

ALTANA INC.

ANDA 75-502
Clotrimazole and Betamethasone Dipropionate Cream USP, 1%/0.05 (base)
LABELING AMENDMENT

Table of Contents

ALTANA

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

Telephoned and requested FPL on insert 6/1/01.

May 29, 2001

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

ORIG AMENDMENT
AF

VIA FEDERAL EXPRESS

CENTER FOR DRUG EVALUATION AND RESEARCH
MAY 30 2001
OGD

ANDA 75-502
Clotrimazole and Betamethasone Dipropionate Cream USP, 1%/0.05 (base)
Labeling Amendment

Dear Sir or Madam:

Reference is made to the Altana Inc. abbreviated new drug application submitted on November 11, 1998 pursuant to section 505(j) of the Federal Food, Drug and Cosmetic Act for Clotrimazole and Betamethasone Dipropionate Cream USP, 1%/0.05% (base).

Reference is also made to the FDA fax correspondence from Ms. Lillie Golson dated May 24, 2001 which included comments for Altana's February 21, 2001 Labeling Amendment.

Pursuant to 21 CFR 314.60, this Amendment is being submitted for insert labeling. The container and carton labeling as stated in the May 24, 2001 fax are satisfactory.

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

<u>Labeling</u>

1. **GENERAL COMMENTS: In response to your request to use previously submitted container and carton labeling, please note that to meet the requirements of section 505(j)(2)(A)(v) of the Act and 21 CFR 314.94(a)(8), the container and carton labeling must be the same as the approved labeling for Lotrisone.**

   According to section 505(j)(2)(A)(v) of the Act and 21 CFR 314.94(a)(8), Altana Inc. acknowledges the container and carton labeling must be the same as the approved labeling for Lotrisone.

2. **CONTAINER (15 g and 45 g) – Satisfactory in draft.**

3. **CARTON (15 g and 45 g) – Satisfactory in draft.**

4. **INSERT**
   a. **CLINICAL PHARMACOLOGY (Microbiology – Drug Resistance)**
      Correct the spelling of "resistance" in the second paragraph.

Altana has revised the CLINICAL PHARMACOLOGY (Microbiology – Drug Resistance) section to correct the spelling of the word "resistance" in the second paragraph.

b. PRECAUTIONS (Geriatric Use) – Correct the spelling of "OCCLUSION" in the last sentence.

Altana has revised the PRECAUTIONS (Geriatric Use) section to correct the spelling of the word "OCCLUSION" in the last sentence.

c. OVERDOSAGE – Replace "obtained" with "contained" in the last paragraph.

Altana has revised the OVERDOSAGE section to replace the word "obtained" with the word "contained" in the last paragraph.

5. PATIENT INFORMATION LEAFLET – Satisfactory in draft.

Altana Inc. has made the above revisions and as instructed is submitting in **Attachment I** twelve copies of final printed container, carton and insert labeling. Altana understands that prior to approval, it may be necessary to further revise the labeling subsequent to approved changes for the Reference Listed Drug. Altana will routinely monitor the following website for any approved changes.

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

To facilitate review of the submission and in accordance with 21 CFR 314.94(a)(8)(iv), Altana has provided in **Attachment II** a side by side comparison of the proposed labeling with the last submission. All differences have been annotated and explained.

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.

Audrey Bialeski for

Virginia Carman
Associate Director, Regulatory Affairs

VC/jb

C:\Jackie\FDA\ClotrimazoleBDCream.labelingamend.052901.doc

ALTANA

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

ORIG AMENDMENT
N/FA

May 24, 2001

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 20855-2773

VIA TELEFAX AND FEDERAL EXPRESS

ANDA 75-502
Clotrimazole and Betamethasone Dipropionate Cream USP, 1%/0.05 (base)
FAX AMENDMENT

Dear Sir or Madam:

Reference is made to the Altana Inc. original Abbreviated New Drug Application for Clotrimazole and Betamethasone Dipropionate Cream USP, 1%/0.05 (base) submitted November 11, 1998, pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act.

Reference is also made to Altana's Amendments dated November 11, 2000 and April 11, 2001 as well as to the FDA facsimile correspondence dated May 17, 2001 which included Chemistry and Bioequivalence comments. On May 23, 2001 Altana responded to FDA's comments with a Fax Amendment.

On May 24, 2001 a teleconference call was held between Altana representatives (Virginia Carman and Audrey Bialeski, Regulatory Affairs and Karin Keane, Methods Development) and FDA (Dr. Paul Schwarz and Dr. Nashed). The purpose of this teleconference was to discuss the proposed stability specifications for the drug product.

Based on the commitments made during the teleconference, Altana Inc. is providing the following information for review. This submission has been organized to include the FDA comment in **BOLD** followed by the Altana response in regular type.

1. **Please tighten the stability specifications regarding the betamethasone degradation products for the peak at RRT 0.50, others and Total Degradation.**

   Altana Inc. has tightened the stability specifications for the degradation products related to betamethasone dipropionate as follows:

	Proposed	Previously Submitted
Peak at RRT 0.50		
Others		
Total		

   It should be noted that the specification for other degradation products is based on the 1.0% limit allowed in the USP monograph for the Betamethasone Dipropionate raw material. See Attachment I for the revised specifications.

2. **Please be informed that the reduced testing stability protocol requires prior approval.**

   Altana Inc. has revised the Post-Approval Stability Commitment to state that once at least Three Production Batches have successfully completed their 24-month stability period and sufficient data has been acquired, a Prior-Approval Supplement will be submitted to the application for a Reduced Testing Program. See Attachment II.

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/ab

ALTANA INC.
60 Baylis Road
Melville, NY 11747

ANDA 75-502
Clotrimazole and Betamethasone Dipropionate Cream USP, 1%/0.05 (base)
FAX AMENDMENT

Table of Contents

ALTANA

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

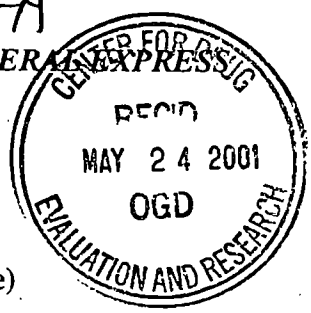
May 23, 2001

ORIG AMENDMENT

FA

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

VIA FACSIMILE and FEDERAL EXPRESS



ANDA 75-502
Clotrimazole and Betamethasone Dipropionate Cream USP, 1%/0.05 (base)
FAX AMENDMENT

Dear Sir or Madam:

Reference is made to the Altana Inc. abbreviated new drug application submitted on November 11, 1998 pursuant to section 505(j) of the Federal Food, Drug and Cosmetic Act for Clotrimazole and Betamethasone Dipropionate Cream USP, 1%/0.05% (base).

Reference is also made to Altana's Amendments dated November 11, 2000 and April 11, 2001 as well as to the FDA facsimile correspondence dated May 17, 2001, which includes Chemistry and Bioequivalance comments.

As requested, this response to the May 17, 2001 correspondence has been appropriately identified as a "FAX AMENDMENT" and is being submitted within 30 calendar days.

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

Chemistry

1. **Please tighten the stability specifications regarding betamethasone degradation product and identify the peak at RRT 0.50 and provide limits for it.**

Page(s) 1

Contain Trade Secret, Commercial/Confidential Information and are not releasable.

5/23/01

ANDA 75-502
Clotrimazole and Betamethasone Dipropionate Cream USP, 1%/0.05 (base)
FAX Amendment
May 23, 2001

Bioequivalance

Altana, Inc. acknowledges that there are no further questions at this time.

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,

Virginia Carman

ALTANA INC.
Virginia Carman
Associate Director, Regulatory Affairs

ALTANA

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

February 16, 2001

BIOAVAILABILITY

Dr. Dale Conner
Director
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place
Rockville, Maryland 20855

NEW CORRESP
NC/Bio

ANDA 75-502 Facsimile Bioequivalence Telephone Amendment

Clotrimazole and Betamethasone Dipropionate Cream USP, 1%/0.05% (base)

Dear Dr. Conner:

Reference is made to Altana Inc's Abbreviated New Drug Application for Clotrimazole and Betamethasone Dipropriate Cream USP, 1%/0.05% (base) submitted November 11, 1998 pursuant to section 505(j) of the Federal Food Drug and Cosmetic Act.

Reference is also made to Altana Inc.'s correspondence of November 29, 2000, which contained the results of a vasoconstrictor study to determine the bioequivalence of two clotrimazole/betamethasone dipropionate creams.

We also refer to a telephone request of February 13, 2001 at which time the Office asked Altana Inc. to supply the expiration date for the Reference Listed Drug (RLD) used in the study.

Please be advised that the same lot of RLD was used to perform both the pilot and pivotal vasoconstrictor study as well as the clinical bioequivalence study. The lot number was 6NBN106, with an expiration date of 5/98.

The test product Altana Inc.'s Clotrimazole and Betamethasone Dipropionate Cream USP, 1%/0.05% (base) was lot #8077, manufactured 11/9[illegible]

If any additional information is required, please contact me at (631) 454-7677, extension 2091. Facsimile communications can be forwarded to (631) 756-5114.

Sincerely,

ALTANA INC.

Virginia Carman

Virginia Carman
Associate Director, Regulatory Affairs

VC/et

ALTANA

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

April 11, 2001

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

VIA FEDERAL EXPRESS

ORIG AMENDMENT
N/A

ANDA 75-502
Clotrimazole and Betamethasone Dipropionate Cream USP, 1%/0.05 (base)
GRATUITOUS AMENDMENT

Dear Sir or Madam:

Reference is made to the Altana Inc. Abbreviated New Drug Application submitted on November 11, 1998 pursuant to section 505(j) of the Federal Food, Drug and Cosmetic Act for Clotrimazole and Betamethasone Dipropionate Cream USP, 1%/0.05% (base).

Reference is also made to Altana's Major Amendment dated November 10, 2000 and Labeling Amendment dated February 21, 2001. As discussed on April 10, 2001 with Ms. Elaine Hu this Amendment is titled **GRATUITOUS AMENDMENT** in order to submit current information. Ms. Hu instructed Altana to phone to confirm this Gratuitous Amendment was sent and therefore will be reviewed simultaneously with the November 10, 2000 and February 21, 2001 Amendments.

This Amendment is being submitted to provide current information to facilitate the review of the November 10, 2000 Major Amendment. The specifications for degradation products (relative to betamethasone dipropionate) in Betamethasone Diproionate Raw Material have been revised in accordance with USP 24 to each not more than 1.0% and total not more than 2.0%. Accordingly, the In-Process and Finished Product Specifications have been revised to match the raw material. **Attachment I** contains the Betamethasone Dipropionate Raw Material Specifications and the In-Process and Finished Product Specifications for the drug product. The Stability Specifications remain unchanged, a copy has been provided as **Attachment II** for ease in review.

Altana Inc. has also provided as **Attachment III** updated stability reports for the two exhibit batches (8077 and 8078) submitted in the original ANDA. Both lots demonstrate acceptable stability results through the proposed expiration period of 24 months.

A revised stability commitment to remove the reference to , which is not part of the product formulation, is provided as **Attachment IV**. Further explanation of the proposed reduced testing program is included for ease in review.

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

C:\Jackie\FDA\ClotrimazoleBDCream.gratuitousamend.041001.doc

ALTANA

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

February 21, 2001

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

VIA FEDERAL EXPRESS

ORIG AMENDMENT
AF

ANDA 75-502
Clotrimazole and Betamethasone Dipropionate Cream USP, 1%/0.05 (base)
Labeling Amendment

Dear Sir or Madam:

Reference is made to the Altana Inc. abbreviated new drug application submitted on November 11, 1998 pursuant to section 505(j) of the Federal Food, Drug and Cosmetic Act for Clotrimazole and Betamethasone Dipropionate Cream USP, 1%/0.05% (base).

Reference is also made to the FDA facsimile correspondence from Ms. Lillie Golson dated January 9, 2001 which included copies of the revised innovator container, carton, package insert and Patient Information Leaflet labeling for Lotrisone Lotion, manufactured by Schering Corporation.

Pursuant to 21 CFR 314.60, this Amendment is being submitted for revised container, carton and insert labeling and to also include a Patient Information Leaflet. Included in **Attachment I** are four copies of draft container, carton and combined insert labeling (including a Patient Information Leaflet).

In anticipation of approval, final printed componentry was ordered prior to the implementation of the additional warning statement on the Reference Listed Drug. Altana Inc. requests to use the previously submitted container (pre-printed tube) and carton labeling with the revised package insert containing the Patient Information Leaflet for initial distribution.

In addition Altana would like to update the submission to include correspondence regarding the DMF for Betamethasone Dipropionate USP. Altana Inc. has received correspondence from the DMF holder, that they have responded to a FDA deficiency letter for ated December 11, 2000. Please refer to **Attachment II** for a copy of their correspondence.

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

C:\Jackie\FDA\ClotrimazoleBDCream.labelingamend.021601.doc

CENTER FOR DRUG
RECD
FEB 26 2001
OGD
EVALUATION AND RESEARCH

ALTANA

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

November 29, 2000

Via Federal Express

ORIG AMENDMENT
N/AB

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

ANDA 75-502
Clotrimazole and Betamethasone Dipropionate Cream USP, 1% / 0.05%(base)
Bioequivalence Amendment

Dear Dr. Patel:

Reference is made to the Altana Inc. Abbreviated New Drug Application for Clotrimazole and Betamethasone Dipropionate Cream USP, 1% / 0.05%(base) submitted November 11, 1998, pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act.

Altana Inc. acknowledges receipt of the following FDA correspondence dated December 27, 1999. As requested this response has been appropriately identified as a Bioequivalence Amendment.

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

1. **You have not conducted a clinical study including a pharmacodynamic/clinical endpoint to the activity of the betamethasone dipropionate component. You only submitted the results of a potency ranking study based on the outdated single-point (16 hr) skin blanching assay. This data does not support bioequivalence. The use of this single-point vasoconstrictor assay for documentation of bioequivalence was discontinued in 1992 due to lack of sensitivity.**

   Our Original application did contain a single point potency ranking study as requested in the Agency's original letter dated July 17, 1996.

   Single point skin blanching studies are still used to determine potency of cortocosteroid products.

   Our clinical endpoint study submitted in the original application contains the efficacy of the product "Clotrimazole and Betamethasone Dipropionate Cream" and not just the clotrimazole portion of the product.

CENTER FOR DRUG EVALUATION AND RESEARCH
RECD
NOV 30 2000
OGD

However, as noted in the response to comment 2, a bioequivalence study was performed, and the results enclosed.

2. **You should conduct an *in-vivo* study to document bioequivalence of the betamethasone dipropionate component of your formulation. This study should be based on the June 2, 1995 Guidance, Topical Dermatologic Corticosteroids: *in-vivo* Bioequivalence. The dose duration to be used for comparison of the test and reference products should be based on the results of a pilot study on the reference listed drug.**

Altana Inc. has conducted a Vasoconstrictor Study to Determine the Bioequivalence of Two Clotrimazole/Betamethasone Dipropionate Topical Creams". This study was based on the June 2, 1995 Guidance, Topical Dermatologic Corticosteroids *in-vivo* Bioeqiuvalence.

Analytical results for the test product and reference product used to conduct the study have also been provided.

This concludes Altana's response to this Bioequivalence Amendment. If you have any questions or require additional clarification please contact me at (631) 454-7677 extension 2091. Fax communications may be made to (631) 756-5114.

Sincerely
Altana Inc.

Virginia Carman
Associate Director, Regulatory Affairs

VC:ab

Enclosures

C:\Amendments\Clotrimazole & B.D. Crem. 1% 0.05% (base)\Deficiency letter of 12-27-99.

ALTANA

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

November 10, 2000

Rashmikant M. Patel, Ph. D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place
Rockville, MD 20855

Via Federal Express

ANDA ORIG AMENDMENT
AC

ANDA 75-502
Clotrimazole and Betamethasone Dipropionate Cream USP, 1% / 0.05%(base)
MAJOR AMENDMENT

Dear Dr. Patel:

Reference is made to the Altana Inc. Abbreviated New Drug Application for Clotrimazole and Betamethasone Dipropionate Cream USP, 1% / 0.05%(base) submitted November 11, 1998, pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act.

Altana Inc. acknowledges receipt of the following FDA correspondence dated July 3, 2000. As requested this response has been appropriately identified as a MAJOR AMENDMENT.

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

1

2.

RECD
NOV 13 2000
OGD
EVALUATION AND RESEARCH

Page(s) 2

Contain Trade Secret, Commercial/Confidential Information and are not releasable.

11/10/00

In addition, Altana Inc. is hereby submitting a revised Post-Approval Stability Commitment and Protocol that can be found as Attachment XI.

This concludes Altana's response to this Minor Amendment. If you have any questions or require additional clarification please contact me at (631) 454-7677 extension 2091. Fax communications may be made to (631) 756-5114.

Sincerely
Altana Inc.

Virginia Carman
Associate Director
Regulatory Affairs

VC:ab

Enclosures
C:\Amendments\Clotrimazole & B.D. Crem. 1% 0.05% (base)\Deficiency letter of 7-3-00.wpd

ALTANA

Altana Inc. 60 Baylis Road, Melville, N.Y. 11747 516-454-7677 Fax: 516-756-5114 BYK GULDEN PHARMA GROUP

January 7, 2000

Rashmikant M. Patel, Ph.D.
Director, Division of Chemistry 1
Office of Generic Drugs (HFD-600)
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II, Room 286
7500 Standish Place
Rockville, Maryland 20855-2773

NDA ORIG AMENDMENT
N/AC

VIA FEDERAL EXPRESS

ANDA 75-502
Clotrimazole and Betamethasone Dipropionate Cream USP, 1%/0.05% (base)
Major Amendment

Dear Dr. Patel:

Reference is made to the Altana Inc. original Abbreviated New Drug Application for Clotrimazole and Betamethasone Dipropionate Cream USP, 1%/0.05% (base) submitted November 11, 1998, pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act.

Reference is also made to FDA correspondence dated May 3, 1999. The following information is being presented in **comment**/response format to address the outstanding issues.

A. Deficiencies

1. P
   p
   s

   A
   Forms (Certificate of Analysis) f
   r
   I

2.

OGD
EVALUATION AND RESEARCH

Page(s) 2

Contain Trade Secret, Commercial/Confidential Information and are not releasable.

1/7/00

Labeling Deficiencies:

1. **CONTAINER (15 g and 45 g)**

   a. **Include the product strength with the established name of your product. For example:**

      Clotrimazole and
      Betamethasone Dipropionate
      Cream USP, 1%/0.05% (base)

   b. **Relocate "FOR DERMATOLOGIC USE ONLY. NOT FOR OPHTHALMIC USE." To the main display panel.**

   c. **In the "Each gram contains" statement:**

      i. **Delete use of the terminal zero (i.e., 10-mg rather than 10.0 mg).**

      ii. **Delete "USP".**

      iii. **Revise the ultimate sentence to read, Benzyl alcohol added as a preservative.**

      Revised container labeling, which incorporates all of the FDA comments is included in Attachment IX.

2. **CARTON (15 g and 45 g)**

   See CONTAINER comments (a) and (c).

   The carton labeling has been revised to incorporate the FDA comments. See Attachment X.

3. **INSERT**

   a. **DESCRIPTION**

      i. **See CONTAINER comments under (c).**

      ii. **Replace "empirical" with "molecular" in the second and fourth paragraphs.**

      iii. **Subscript the "7" in the molecular formula for clotrimazole.**

3. **INSERT (continued)**

   b. **CLINICAL PHARMACOLOGY**

      Revise the ultimate sentence of paragraph 7 to read, ...dressing of 0.5 ml...

   c. **PRECAUTIONS**

      i. **Information for Patients**

         Replace "of" with "or" in the ultimate sentence of #2.

      ii. **Pediatric Use**

         Replace "children" with "pediatric patients".

      iii. **ADVERSE REACTIONS**

         Delete the colon following "cream" in the first paragraph.

         Revised insert labeling, which incorporates the FDA comments is included in Attachment XI.

To facilitate the review of this submission and in accordance with 21 CFR 314.94(a)(8)(iv), a side-by-side comparison of the proposed labeling with the last submission is provided as follows:

Container	Attachment XII
Carton	Attachment XIII
Package Insert	Attachment XIV

Please contact me at (631) 454-7677 extension 2091, if you require any additional information or clarification. FAX communications may be made to (631) 756-5114.

Sincerely,

ALTANA INC.

Virginia Carman
Associate Director, Regulatory Affairs

VC/et

Statistical Report: Altana Inc., Clotrimazole, 1% and Betamethasone Dipropionate, 0.05% Cream USP; Office of Generic Drugs; ANDA 75-502

OGD reviewer: Mary M. Fanning, MD, Ph.D.

This was a double-blind, randomized, three treatment, parallel-group, vehicle-controlled study in 402 subjects (age 18 to 87) with interdigital tinea pedis (positive KOH preps) but otherwise reasonably healthy. The purpose of the study was to show the therapeutic equivalence between the test product, Altana Inc., Clotrimazole, 1% and Betamethasone Dipropionate, 0.05% cream USP (Altana combination) and the reference product, Schering Corporation, Lotrisone cream, and show effectiveness between the active treatments and placebo, cream vehicle.

Study Design

This was a 3 arm parallel double-blind study in subjects with clinical diagnoses of interdigital tinea pedis. The three creams were the test product, Altana Inc., Clotrimazole, 1% and Betamethasone Dipropionate, 0.05% cream USP, the reference product, Schering Corporation, Lotrisone cream, and the placebo, a cream vehicle. Subjects whose KOH preps were positive were enrolled. Inclusion in the efficacy analysis populations required confirmation of dermatophtosis by positive mycological culture. A total of 402 males and females with ages ranging from 18 to 87 were enrolled into the study. The subjects were randomized to one of the three treatment groups in a 2:2:1 ratio (test:reference:placebo). One hundred and sixty (160) subjects were randomized to treatment with Altana's combination cream, 162 to Schering's Lotrisone cream, and 80 to placebo. All treatments were applied twice daily for 28 days with a two-week untreated follow-up period. The subjects were examined at visit 1 (Day 0, baseline), visits 2, 3, 4 (Days 3, 7, 14), visit 5 (Day 28, end of treatment), and visit 6 (Day 42, follow-up). Mycological evaluation (both KOH and culture test) was performed at each visit except visit 2 (Day 3). At visit 1, the most severely affected interdigital site was identified as the primary test site for all future evaluations. Sign and symptom scores of tinea pedis including pruritus, burning, maceration, fissuring, erythema, scaling, vesicles, papules, and pustules were assigned with score (0-3: absent, mild, moderate, and severe) at each visit. From visit 2, the physician's global assessment was performed using scale (1-7: complete, excellent, good, fair, poor, no change, and worse) at each visit.

Outcome Variables

The primary variable used to assess efficacy and equivalence was the rate of overall cure, defined as both a clinical cure (physician's global assessment of complete/100% improvement) and a mycological cure (both KOH and culture negative) at the Day 7, 14, 28, and 42 visits. The secondary variables were individual sign and symptom scores, physician's global assessment scores, mycological cure rate, and clinical cure rate.

The primary time point for comparison of the 3 groups was the Day 42 visit, with the Day 28 visit (end of treatment) as secondary.

All analyses were performed for both the MITT (Modified Intent-To-Treat) and PP (Per Protocol) populations. The MITT population included all eligible culture positive individuals who received study drug and completed at least one follow-up visit. The subjects in the MITT population actually completed all the visits. This is the primary population for analysis and comparison of the three treatments. The PP population included those subjects in the MITT population who completed all visits and procedures required by the study protocol.

Statistical Analysis Methods

Efficacy Analysis

Tests of comparisons for overall cure rate, mycological cure rate, clinical cure rate, physician's global assessment, and sign/symptom scores were made between treatment arms at the (two-sided) 5% level significance. The efficacy analysis for each active treatment was tested separately by comparing it with the placebo. All treatment arms should be similar for sign/symptom scores at the Day 0 visit. The active treatments should be more distinguishable from placebo as the study progressed. The primary time point for comparison was the Day 42 visit, with the Day 28 visit as secondary.

The efficacy analyses for all variables were carried out by using Fisher's exact test for each active treatment versus placebo.

Equivalence Analysis

Based on the usual method used in OGD for binary outcomes, the 90% confidence interval for the difference in proportions between test and reference treatment should be contained within -.20 to .20 in order to establish equivalence.

The compound hypothesis to be tested is:

H_0: $p_T - p_R \leq -.20$

or $p_T - p_R \geq .20$

versus

H_A: $-.20 < p_T - p_R < .20$

where p_T = cure rate of test treatment p_R = cure rate of reference treatment

Let n_T = sample size of test treatment n_R = sample size of reference treatment

and $se = (\hat{p}_T(1 - \hat{p}_T)/n_T + \hat{p}_T(1 - \hat{p}_T)/n_R)^{1/2}$

The 90% confidence interval for the difference in proportions between test and reference was calculated as follows, using Yates' correction:

$$L = (\hat{p}_T - \hat{p}_R) - 1.645\ se - (1/n_T + 1/n_R)$$

$$U = (\hat{p}_T - \hat{p}_R) + 1.645\ se + (1/n_T + 1/n_R)$$

and reject H_0 if $L > -.20$ and $U < .20$

Rejection of the null hypothesis H_0 supports the conclusion of equivalence of the two products.

The physician's global assessment grades were dichotomized to two levels: Good (complete, excellent, or good) versus Poor (fair, poor, no change, or worse), then the proportion of subjects with a Good score out of the total number of subjects was obtained. The sign/symptom scores were also dichotomized to two levels: absent versus others (mild, moderate, or severe), then the proportion of subjects with a score of absent out of the total number of subjects was obtained.

We analyzed the data for efficacy and equivalence for overall cure rate and mycological cure rate at the Day 7, 14, 28, and 42 visits; clinical cure rate and dichotomized global assessment at the Day 3, 7, 14, 28, and 42 visits; and dichotomized sign/symptom scores at each visit. The analysis was performed for both MITT and PP populations.

Statistical Analysis Results

Efficacy Analysis

The MITT population included 305 subjects (121, Altana combination; 126, Lotrisone; 58, placebo). Eighty-four subjects (34, Altana; 31, Lotrisone; 19, placebo) out of a total of 97 excluded subjects were excluded due to negative baseline culture, and others were due to lost to follow-up, protocol violation, and administrative reason. The PP population was reduced to 286 subjects (119, 113, and 54 in each group), mostly because of protocol violations.

A summary of the results for overall cure rate, mycological cure rate, clinical cure rate, and dichotomized global assessment for the MITT and PP populations at the Day 28 and 42 visits is given in Table 1. The test and reference treatments were significantly better than placebo for all variables for both populations at the Day 28 and 42 visits except overall cure rate and clinical cure rate for the test treatment versus the placebo treatment at the Day 28 visit for the PP population.

A summary of the results for dichotomized sign/symptom scores for the MITT population at the Day 0, 28, and 42 visits is given in Table 2. There was no significant difference between treatment arms for all the variables at the Day 0 visit. The test and reference treatments were significantly better than the placebo treatment for pruritus, burning, maceration, fissures, erythema, and scaling at the Day 28 and 42 visits except burning

and fissures for the reference treatment versus the placebo treatment at the Day 28 visit. The percentages of the absent score for vesicles, papules, and pustules were above 87.5% at the Day 0 visit and 94.8% at the Day 28 and 42 visits. The changes for three scores were too small to make sense of the statistical test. The test for the PP population obtained similar results.

Equivalence Analysis

The results of the equivalence analyses are summarized in Table 3 and 4. All of the tests showed the equivalence test except dichotomized global assessment at the Day 7 visit for both populations (test was better than reference). The results of the dichotomized sign/symptom scores for the PP population were similar to the MITT population.

Figure 1 shows the mycological, clinical, and overall cure rates for both MITT and PP populations. Figure 2 shows the dichotomized global assessment, i.e., good versus poor, for both MITT and PP populations. Figure 3 shows the dichotomized sign/symptom scores, i.e., absent versus others, for MITT population.

Adverse Event Analysis

Adverse events were experienced by subjects in all three groups: Altana, 30 subjects (19%) and 37 events; Lotrisone, 30 subjects (19%) and 43 events; vehicle, 13 subjects (16%) and 19 events. There were 15 subjects who had headache and 12 subjects had skin allergy. The three rates are quite similar.

Sponsor's Analysis

The sponsor assessed the paired (test vs. reference, test vs. placebo, and reference vs. placebo) difference of mycological cure rate, clinical cure rate, and overall cure rate for both populations at each visit by using Fisher's exact test. The test and reference treatments were significantly better than placebo for three cure rates for both populations at the Day 28 and 42 visits. There was no significant difference between test and reference treatments for both populations at the Day 28 and 42 visits.

The sign/symptom scores and the physician's global assessment results were analyzed with a one-way ANOVA and its paired (test vs. reference, test vs. placebo, and reference vs. placebo) contrasts. The results from analyses showed: no significant difference for sign/symptom scores at baseline for three treatment groups; significant differences for most variables except vesicles, papules, and pustules between each active treatment versus placebo at the Day 28 and 42 visits; and no significant differences between the two active treatments. Results for the MITT and PP populations were quite similar.

The sponsor concluded that the test treatment was equally as safe and effective as the reference treatment and both active treatments were significantly more effective than the placebo.

Conclusion

Efficacy: Our analysis showed that the test and reference products were both statistically significantly better than placebo for overall cure rate (primary variable), mycological cure rate, clinical cure rate, dichotomized global assessment and sign/symptom scores at the Day 28 and 42 visits for both MITT and PP populations except several separately cases as below. The differences between the test treatment and the placebo treatment for clinical cure rate and overall cure rate at the Day 28 visit for the PP population were not significant. There was no significant difference between the reference treatment versus the placebo treatment for the burning and fissures scores at the Day 28 visit for both populations. So few subjects had no-absent scores for vesicles, papules, and pustules scores at the Day 28 and 42 visits for both populations that little statistical inference can be made about treatment group differences..

Equivalence: The test and reference treatments were found equivalent for all variables at all visits for both MITT and PP populations except for the dichotomized global assessment at the Day 7 visit for both populations (where the test product was better than the reference product).

10/13/99

Huaixiang Li, Ph.D.
Mathematical Statistician, QMR

Stella C. Machado 10/12/99

Stella Machado, Ph.D.
Director, QMR

cc:

ALTANA

Altana Inc. 60 Baylis Road, Melville, N.Y. 11747 516-454-7677 Fax: 516-454-6389 BYK GULDEN PHARMA GROUP

Federal Express

November 11, 1998

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

Re: Original Submission
Abbreviated New Drug Application
Clotrimazole and Betamethasone Dipropionate Cream, USP

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, Clotrimazole and Betamethasone Dipropionate Cream, USP.

The reference listed drug that is the basis for this submission is Lotrisone ® (brand of clotrimazole and betamethasone dipropionate) Cream, USP (NDA 18-827), manufactured by Schering Corporation. The proposed drug, Clotrimazole and Betamethasone Dipropionate Cream, USP 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 three exhibit batches (#8077-Bioequivalence and Stability, #8078-Stability) and (#8076-Placebo) included in this application were fully packaged utilizing the 15 gram and 45 gram presentations for which approval is currently requested. The number of units filled of each package size and the disposition of any remaining bulk product are reconciled in the exhibit batch records.

Included in this twelve (12) 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. (516) 454-7677 Ext. 2091
Fax No. (516) 777-3916

A certified copy of this application (consisting of volumes 1.1, 1.8, 1.9, 1.10, 1.11, and 1.12 and a copy of the Methods Validation package) is being sent to the New York District Office under separate cover.

We trust that this submission will meet with your approval. Please advise us if you require any additional information.

Sincerely,
Altana Inc.

Virginia Carman
Associate Director, Regulatory Affairs

Enclosures

VC/ps

A:\draft COVER.LTR.wpd