CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

ANDA 76-408

***Name*:** Metronidazole Topical Cream, 0.75%

***Sponsor*:** Altana, Inc.

***Approval Date*:** May 28, 2004

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-408

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-408

APPROVAL LETTER

ANDA 76-408

MAY 28 2004

Altana, Inc.
Attention: Robert J. Anderson, Esq.
60 Baylis Road
Melville, NY 11747

Dear Sir:

This is in reference to your abbreviated new drug application (ANDA) dated May 3, 2002, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act), for Metronidazole Topical Cream, 0.75%.

Reference is also made to your amendments dated February 3, February 14, May 7, and October 15, 2003; and May 3, 2004.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your Metronidazole Topical Cream, 0.75%, to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (MetroCream® Topical Cream, 0.75%, of Galderma Laboratories, LP).

Under Section 506A of the Act, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81 and 314.98. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print.

Submit both copies together with a copy of the final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-40). Please do not use Form FDA 2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-40) with a completed Form FDA 2253 at the time of their initial use.

Sincerely yours,

Gary Buehler 5/28/04
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 76-408
Division File
Field Copy
HFD-610/R. West
HFD-330
HFD-205
HFD-610/Orange Book Staff

Endorsements:
HFD-620/K.Woodland K Woodland 5/18/04
HFD-625/S.Liu
HFD-617/W.Pamphile ~~wf~~ 5/18/04
HFD-613/R.Wu RW~ 5/4/04
HFD-613/J.Grace jm 5/4/04

F/T by wp 5/3/04

V:\FIRMSAM\ALTANA\LTRS&REV\76408.AP.doc

APPROVAL

Robert Lee West
5/28/2004

PS 5/20/04

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-408

LABELING

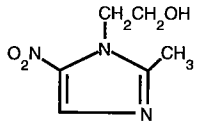
fougera®

METRONIDAZOLE
Topical Cream 0.75%

FOR TOPICAL USE ONLY (NOT FOR OPHTHALMIC USE)

℞ only

DESCRIPTION:
Metronidazole Topical Cream contains metronidazole, USP, at a concentration of 7.5 mg per gram (0.75%) in an emollient cream consisting of emulsifying wax, sorbitol solution, glycerin, isopropyl palmitate, benzyl alcohol, lactic acid, and/or sodium hydroxide to adjust pH, and purified water. Metronidazole is a member of the imidazole class of anti-bacterial agents and is classified therapeutically as an antiprotozoal and anti-bacterial agent. Chemically, metronidazole is 2-Methyl-5-nitroimidazole-1-ethanol. The molecular formula is $C_6H_9N_3O_3$ and molecular weight is 171.16. Metronidazole is represented by the following structural formula:



CLINICAL PHARMACOLOGY:
The mechanisms by which metronidazole acts in the treatment of rosacea are unknown, but appear to include an anti-inflammatory effect.

INDICATIONS AND USAGE:
Metronidazole Topical Cream is indicated for topical application in the treatment of inflammatory papules and pustules of rosacea.

CONTRAINDICATIONS:
Metronidazole Topical Cream is contraindicated in individuals with a history of hypersensitivity to metronidazole, or other ingredients of the formulation.

PRECAUTIONS:
General: Topical metronidazole has been reported to cause tearing of the eyes. Therefore, contact with the eyes should be avoided. If a reaction suggesting local irritation occurs, patients should be directed to use the medication less frequently or discontinue use. Metronidazole is a nitroimidazole and should be used with care in patients with evidence of, or history of blood dyscrasia.
Information for patients: This medication is to be used as directed by the physician. It is for external use only. Avoid contact with the eyes.
Drug interactions: Oral metronidazole has been reported to potentiate the anticoagulant effect of warfarin and coumarin anticoagulants, resulting in a prolongation of prothrombin time. The effect of topical metronidazole on prothrombin time is not known.
Carcinogenesis, mutagenesis, impairment of fertility: Metronidazole has shown evidence of carcinogenic activity in a number of studies involving chronic, oral administration in mice and rats but not in studies involving hamsters.

(over)

Metronidazole has shown evidence of mutagenic activity in several *in vitro* bacterial assay systems. In addition, a dose-response increase in the frequency of micronuclei was observed in mice after intraperitoneal injections and an increase in chromosome aberrations have been reported in patients with Crohn's disease who were treated with 200-1200 mg/day of metronidazole for 1 to 24 months. However, no excess chromosomal aberrations in circulating human lymphocytes have been observed in patients treated for 8 months.

Pregnancy: *Teratogenic effects: Pregnancy category B*

There are no adequate and well-controlled studies with the use of metronidazole topical cream in pregnant women. Metronidazole crosses the placental barrier and enters the fetal circulation rapidly. No fetotoxicity was observed after oral metronidazole in rats or mice. However, because animal reproduction studies are not always predictive of human response and since oral metronidazole has been shown to be a carcinogen in some rodents, this drug should be used during pregnancy only if clearly needed.

Nursing mothers: After oral administration, metronidazole is secreted in breast milk in concentrations similar to those found in the plasma. Even though blood levels are significantly lower with topically applied metronidazole than those achieved after oral administration of metronidazole, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric use: Safety and effectiveness in pediatric patients have not been established.

ADVERSE REACTIONS:

In controlled clinical trials, the total incidence of adverse reactions associated with the use of metronidazole topical cream was approximately 10%. Skin discomfort (burning and stinging) was the most frequently reported event followed by erythema, skin irritation, pruritus and worsening of rosacea. All individual events occurred in less than 3% of patients.

The following additional adverse experiences have been reported with the topical use of metronidazole: dryness, transient redness, metallic taste, tingling or numbness of extremities and nausea.

DOSAGE AND ADMINISTRATION:

Apply and rub in a thin layer of metronidazole topical cream twice daily, morning and evening, to entire affected areas after washing.

Areas to be treated should be washed with a mild cleanser before application. Patients may use cosmetics after application of metronidazole topical cream.

HOW SUPPLIED:

Metronidazole Topical Cream 0.75% is supplied in a
45 gram tube NDC 0168-0323-46

Storage conditions: STORE AT CONTROLLED ROOM TEMPERATURE: 15°-30°C (59°-86°F). (See USP)

E. FOUGERA & CO.
a division of Altana Inc.
MELVILLE, NEW YORK 11747

I2323
R5/03
#29

NDC 0168-0323-46

fougera®

METRONIDAZOLE
Topical Cream 0.75%

℞ only

FOR TOPICAL USE ONLY
NOT FOR OPHTHALMIC USE
STORE AT CONTROLLED ROOM TEMPERATURE 15°-30°C (59°-86°F). (See USP)
WARNING: Keep out of reach of children.

NET WT 45 grams

MAY 28 2004

Usual Dosage: Apply a thin layer to entire affected areas after washing. Use morning and evening or as directed by physician. Avoid application close to the eyes.

Each gram contains: Active: metronidazole 0.75% (7.5 mg).
Inactive: emulsifying wax, sorbitol solution, glycerin, isopropyl palmitate, benzyl alcohol, lactic acid and/or sodium hydroxide to adjust pH, and purified water.

TO OPEN: Use cap to puncture seal.
IMPORTANT: Do not use if seal has been punctured or is not visible.

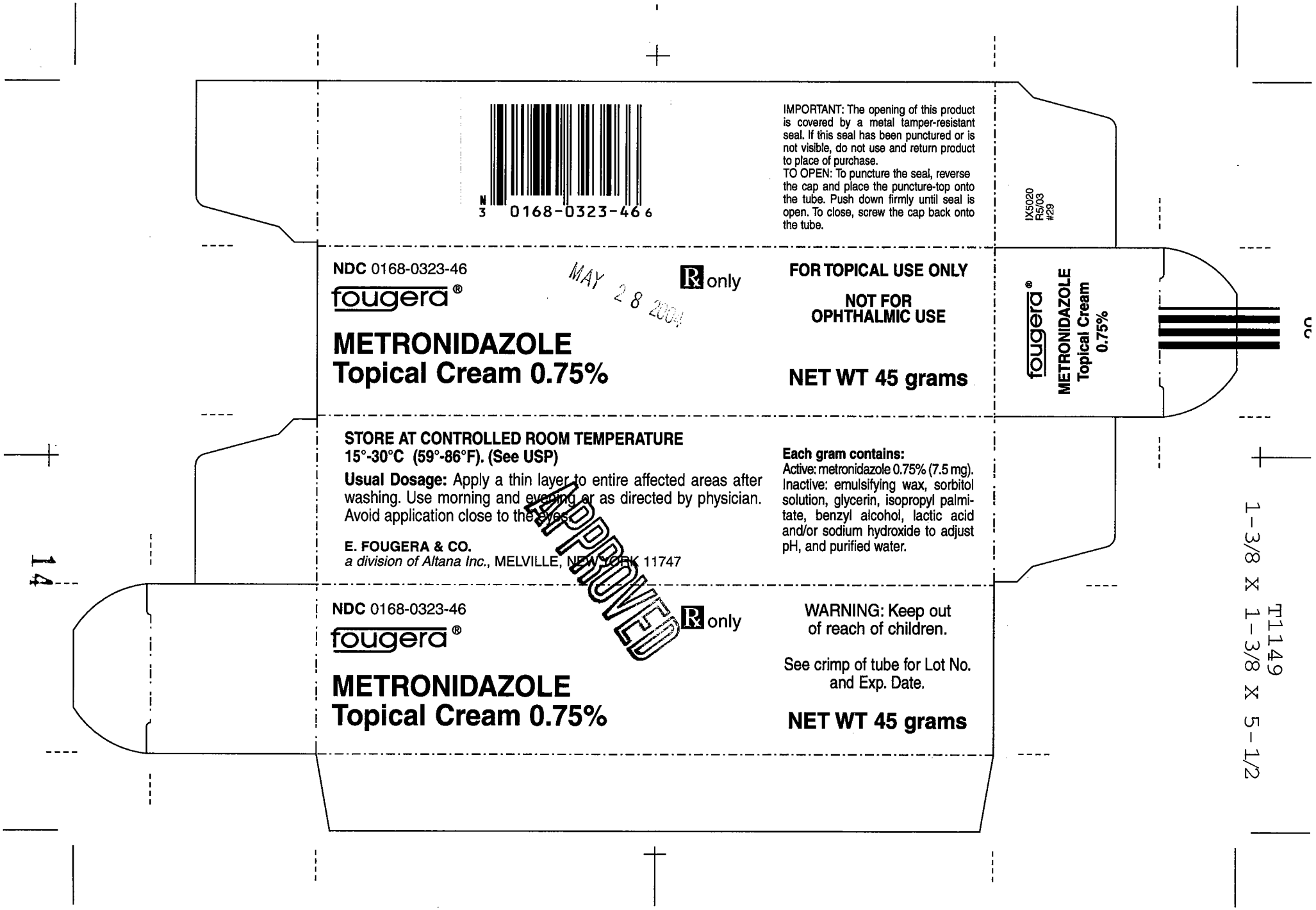
See crimp of tube for Lot Number and Expiration Date.

APPROVED

R5/03

E. FOUGERA & CO.
a division of Altana Inc.
MELVILLE, NEW YORK 11747

3 0168-0323-46 6


0168-0323-46
IMPORTANT: The opening of this product is covered by a metal tamper-resistant seal. If this seal has been punctured or is not visible, do not use and return product to place of purchase.
TO OPEN: To puncture the seal, reverse the cap and place the puncture-top onto the tube. Push down firmly until seal is open. To close, screw the cap back onto the tube.
IX5020
R5/03
#29
NDC 0168-0323-46
fougera®
Rx only
MAY 28 2004
METRONIDAZOLE
Topical Cream 0.75%
FOR TOPICAL USE ONLY
NOT FOR OPHTHALMIC USE
NET WT 45 grams
fougera®
METRONIDAZOLE
Topical Cream
0.75%
STORE AT CONTROLLED ROOM TEMPERATURE
15°-30°C (59°-86°F). (See USP)
Usual Dosage: Apply a thin layer to entire affected areas after washing. Use morning and evening or as directed by physician. Avoid application close to the eyes.
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APPROVED
NDC 0168-0323-46
fougera®
Rx only
WARNING: Keep out of reach of children.
See crimp of tube for Lot No. and Exp. Date.
METRONIDAZOLE
Topical Cream 0.75%
NET WT 45 grams
14
T1149
1-3/8 X 1-3/8 X 5-1/2

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-408

LABELING REVIEWS

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

ANDA Number:	76-408
Date of Submission:	May 3, 2002 (Original Submission)
Applicant's Name:	Altana Inc.
Established Name:	Metronidazole Cream, 0.75%

Labeling Deficiencies:

1. **CONTAINER** – 45 gram tubes
   Storage Recommendation: Add "(See USP)"

2. **CARTON** – (1 x 45 g tube)
   A. TO OPEN statement: "...reverse the cap..." ["the" instead of "he"]
   B. Add "Rx Only" to the main panel
   C. Refer to comment 1.

3. **INSERT** –
   A. DESCRIPTION, chemical name: Revise to read "...2-Methyl-5-nitroimidazole-1-ethanol."
   B. HOW SUPPLIED: See Comment 1

Please revise your labels and labeling, then prepare and submit 12 copies of final print.

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address -

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.

Sincerely Yours,

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

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 23		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	
Because of proposed packaging configuration or for any other reason, does this applicant meet fail to meet all of the unprotected conditions of use of referenced by the RLD?		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.		X	

NOTES/QUESTIONS TO THE CHEMIST: None

FOR THE RECORD: (* FIRST GENERIC *****)**

1. **Model Labeling**: The Reference Listed Drug is MetroCream™, (Metronidazole Topical Cream, 0.75%), Galderma Laboratories Inc, NDA 20-531 (NDA approved 9/20/95; AR 2/13/98).

   The drug substance Metronidazole is USP. The drug product Metronidazole Topical Cream, 0.75% is non-USP.

2. **Manufacturing Facility**: [Vol. B1.2, pg. 2311]
   Altana Inc. (Fougera is a division of Altana Inc.)
   55 Cantiague Rock Road
   Hicksville, NY 11802

3. **Packaging**
   The RLD packages its product in a 45 gram tube
   The applicant's product will be packaged in 45 gram lined aluminum tubes, capped with white, pointed caps. Each filled tube will be individually packaged into a pre-printed carton.

4. **Inactive Ingredients** – There does not appear to be a discrepancy between the listing in inactives in the DESCRIPTION section of the insert labeling and the C&C Statements. (see pg 2147 in vol. B. 1.3)

Component	Function
Metronidazole USP	Active
Emulsifying Wax, NF	Emulsifying agent,
Sorbitol Solution USP	
Glycerin USP	
Isopropyl Palmitate NF	
Benzyl Alcohol NF	
*Lactic Acid USP	For pH adjustment
*Sodium Hydroxide NF	For pH adjustment
Purified Water	[ ]

5. **Finished Product Description**: A white to slightly yellow, smooth and homogeneous cream. [Vol. B2.1, 2/3/2003 amendment, pg. 29]

6. **Storage Recommendation:**
   RLD - stored at controlled room temperature: 15^0-30^0C(59^0-86^0F)
   ANDA – Same as RLD. Will ask firm to add "(See USP)"

7. **Patent and Exclusivity** Search Results from query on 020531 001.

Patent Data

There are no unexpired patents for this product in the Orange Book Database.

Exclusivity Data
There is no unexpired exclusivity for this product.
[Vol. B1.1, pg. 9 & 10]

Date of Review: April 23, 2003 Date of Submission: May 3, 2002

Primary Reviewer: Ruby Wu RW Date: 4/29/03

Team Leader: John Grace John J Grace Date: 4/29/2003

cc: ANDA: 76-408
DUP/DIVISION FILE
HFD-613/RWu/JGrace (no cc)
V:\FIRMSAM\ALTANA\LTRS&REV\76408.na1.L.doc
Review

(First Generic)

APPROVAL SUMMARY

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

ANDA Number:	76-408
Date of Submission:	May 7, 2003 (FPL)
Applicant's Name:	Altana Inc.
Established Name:	Metronidazole Cream, 0.75%

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 – [45 gram tubes]:
Satisfactory in final print as of the May 7, 2003 submission. [Vol. A4.1]

CARTON – [1 x 45 g tube]
Satisfactory in final print as of the May 7, 2003 submission. [Vol. A4.1]

Professional Package INSERT:
Satisfactory in final print as of the May 7, 2003 submission. [Vol. A4.1, R5/03]

Revisions needed post ~~tentative~~ approval: NONE RWL

BASIS OF APPROVAL:

Was this approval based upon a petition? No

What is the RLD on the 356(h) form: MetroCream™

NDA Number: 20-531

NDA Drug Name: MetroCream™, (Metronidazole Topical Cream, 0.75%)

NDA Firm: Galderma Laboratories Inc

Date of Approval of NDA Insert and supplement: NDA approved 9/20/95; AR 2/13/98

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: Side-by-side comparison with innovator labels in jacket.

PATENTS/EXCLUSIVITIES
Patent and Exclusivity Search Results from query on 020531 001.

Patent Data

There are no unexpired patents for this product in the Orange Book Database.

Exclusivity Data
There is no unexpired exclusivity for this product.

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 23		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	
Because of proposed packaging configuration or for any other reason, does this applicant meet fail to meet all of the unprotected conditions of use of referenced by the RLD?		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.		X	

NOTES/QUESTIONS TO THE CHEMIST: None

FOR THE RECORD: (* FIRST GENERIC *****)**

1. **Model Labeling:** The Reference Listed Drug is MetroCream™, (Metronidazole Topical Cream, 0.75%), Galderma Laboratories Inc, NDA 20-531 (NDA approved 9/20/95; AR 2/13/98).

   The drug substance Metronidazole is USP. The drug product Metronidazole Topical Cream, 0.75% is non-USP.

2. **Manufacturing Facility**: [Vol. B1.2, pg. 2311]
   Altana Inc. (Fougera is a division of Altana Inc.)
   55 Cantiague Rock Road
   Hicksville, NY 11802

3. **Packaging**
   The RLD packages its product in a 45 gram tube
   The applicant's product will be packaged in 45 gram lined aluminum tubes, capped with white, [redacted] pointed caps. Each filled tube will be individually packaged into a pre-printed carton.

4. **Inactive Ingredients** – There does not appear to be a discrepancy between the listing in inactives in the DESCRIPTION section of the insert labeling and the C&C Statements. (see pg 2147 in vol. B. 1.3)

Component	Function
Metronidazole USP	Active
Emulsifying Wax, NF	Emulsifying agent
Sorbitol Solution USP	[redacted]
Glycerin USP	
Isopropyl Palmitate NF	
Benzyl Alcohol NF	
*Lactic Acid USP	For pH adjustment
*Sodium Hydroxide NF	For pH adjustment
Purified Water	[redacted]

5. **Finished Product Description**: A white to slightly yellow, smooth and homogeneous cream. [Vol. B2.1, 2/3/2003 amendment, pg. 29]

6. **Storage Recommendation:**
   RLD - stored at controlled room temperature: 15^0-30^0C(59^0-86^0F)
   ANDA – Same as RLD. Will ask firm to add "(See USP)"

7. **Patent and Exclusivity** Search Results from query on 020531 001.

   Patent Data

   There are no unexpired patents for this product in the Orange Book Database.

   Exclusivity Data
   There is no unexpired exclusivity for this product.
   [Vol. B1.1, pg. 9 & 10]

Date of Review: May 15, 2003 Date of Submission: May 7, 2003

Primary Reviewer: Ruby Wu RWu Date: 5/15/03

Team Leader: John Grace John J Grace Date: 5/16/2003

cc: ANDA: 76-408
DUP/DIVISION FILE
HFD-613/RWu/JGrace (no cc)
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Review

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-408

CHEMISTRY REVIEWS

#1

CHEMISTRY REVIEW

ANDA 76-408

Metronidazole Topical Cream, 0.75%

Altana Inc.

Kathy P. Woodland
Division of Chemistry I

Table of Contents

Chemistry Review Data Sheet

1. ANDA 76-408

2. REVIEW #: 1

3. REVIEW DATE: August 23, 2002

4. REVIEWER: Kathy P. Woodland

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original submission	May 3, 2002
FDA Acknowledgment letter (acceptable for filing on May 7, 2002)	July 8, 2002

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original submission	May 3, 2002
Amendment (Re: CGMP issue)	June 26, 2002

7. NAME & ADDRESS OF APPLICANT:

Name:	Altana Inc.
Address:	60 Baylis Road Melville, NY 11747
Representative:	Robert J. Anderson, Esq.
Telephone:	631-454-7677 x2085

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: None
b) Non-Proprietary Name (USAN): Metronidazole Topical Cream

9. LEGAL BASIS FOR SUBMISSION:

The applicant has certified that to the best of their knowledge, all listed patents claimed for the drug product have expired. The Reference Listed Drug is MetroCream™, (Metronidazole Topical Cream, 0.75%), Galderma Laboratories Inc, NDA 20-531. There is no unexpired exclusivity for RLD.

10. PHARMACOL. CATEGORY:
Indicated for topical application in the treatment of inflammatory papules and pustules of rosacea.

11. DOSAGE FORM: Cream

12. STRENGTH/POTENCY: 0.75%

13. ROUTE OF ADMINISTRATION: Topical

14. Rx/OTC DISPENSED: _x__Rx ___OTC

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

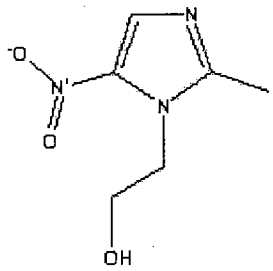
_____SPOTS product – Form Completed

____x_Not a SPOTS product

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

2-Methyl-5-nitro-1Himidazole-1-ethanol

$C_6H_9N_3O_3$, 171.1554



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
	II			1	Adequate	10/8/02	
	III			4			
	III			4			
	III			4			
	III			4			

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

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

B. Other Documents:

Chemistry Review Data Sheet

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
None		

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
EES	Pending		
Methods Validation	Pending		
Labeling	Pending		
Bioequivalence	Pending		
EA	N/A		
Radiopharmaceutical	N/A		

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt. __x__ Yes
____ No If no, explain reason(s) below:

APPEARS THIS WAY
ON ORIGINAL

The Chemistry Review for ANDA 76-408

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability: The ANDA is not approvable pending clarification of MINOR Chemistry issues. Labeling, Bio, and Method Validation are pending.

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

N/A

II. Summary of Chemistry Assessments

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

- Altana's Metronidazole Topical Cream, 0.75% is a FIRST GENERIC.
- The drug substance Metronidazole is USP. The drug product Metronidazole Topical Cream, 0.75% is non-USP. The product will be packaged in 45 gram lined aluminum tubes, capped with white, —— pointed caps. Each filled tube will be individually packaged into a pre-printed carton.
- The DMF associated with this application (DMF ——) was found to be adequate on 10/8/02.
- Altana has developed their own in-house methods for the drug product identification, Metronidazole assay, benzyl alcohol assay, and degradation products and related substances methods. The method validations were submitted.

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

A thin layer of Metronidazole Topical Cream, 0.75% should be applied and rubbed into the entire affected areas {after washing, twice daily (morning and evening)}. Areas to be treated should be washed with a mild cleanser before application.

Metronidazole Topical Cream is indicated for topical application in the treatment of inflammatory papules and pustules of rosacea.

Tubes are to be stored at controlled room temperature: 15^0-30^0C(59^0-86^0F). The expiration for the product is 24 months.

C. Basis for Approvability or Not-Approval Recommendation

The ANDA is not approvable at this time for the following reasons:

MINOR Chemistry issues (manufacturing and processing, laboratory controls, stability)

Pending Labeling
Pending Method Validation
Pending Bio

III. Administrative

A. Reviewer's Signature

Kathy P. Woodland

Kathy P. Woodland

B. Endorsement Block

HFD-627/K.Woodland/
HFD-627/S.Liu,PhD/
HFD-617/W.Pamphile, PM/
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F/T by:

C. CC Block

APPEARS THIS WAY
ON ORIGINAL

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confidential commercial

information from

CHEMISTRY REVIEW #1

c. [redacted]

d. [redacted]

e. [redacted]

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

1. We require an acceptable Methods Validation to support the ANDA and will schedule the study after all testing issues are resolved. Please 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.

2. Please submit accrued stability data.

3. All facilities referenced in the ANDA should have a satisfactory compliance evaluation at the time of approval. We have requested an evaluation from the Office of Compliance.

4. The bioequivalence portion of the submission is pending review. Deficiencies, if any will be communicated separately.

5. The labeling portion of the submission is pending review. Deficiencies, if any will be communicated separately.

Sincerely yours,

Paul Schwerd for 10/29/02

Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

cc: ANDA 76-408
ANDA DUP 76-408
DIV FILE
Field Copy

Endorsements (Draft and Final with Dates):

HFD-627/K.Woodland/ 10/22/02 K Woodland 10/23/02
HFD-627/S.Liu,PhD/ 10/22/02 S.H. Liu 10/23/02
HFD-617/W.Pamphile, PM W. Pamphile 10/23/02

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F/T by:

TYPE OF LETTER: NOT APPROVABLE - MINOR

APPEARS THIS WAY ON ORIGINAL

#12

CHEMISTRY REVIEW

ANDA 76-408

Metronidazole Topical Cream, 0.75%

Altana Inc.

Kathy P. Woodland
Division of Chemistry I

Table of Contents

Chemistry Review Data Sheet

1. ANDA 76-408

2. REVIEW #: 2

3. REVIEW DATE: March 11, 2003
   May 18, 2004 (revised)

4. REVIEWER: Kathy P. Woodland

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original submission	May 3, 2002
Amendment (Re: CGMP issue)	June 26, 2002
FDA Acknowledgment letter (acceptable for filing on May 7, 2002)	July 8, 2002
Bio	February 14, 2003
New Correspondence	March 19, 2003
Labeling Amendment	May 7, 2003
Telephone Amendment	October 15, 2003
New Correspondence	November 12, 2003
New Correspondence	March 11, 2003

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment	February 3, 2003
Amendment	May 3, 2004

Chemistry Review Data Sheet

7. NAME & ADDRESS OF APPLICANT:

Name:	Altana Inc.
Address:	60 Baylis Road Melville, NY 11747
Representative:	Robert J. Anderson, Esq.
Telephone:	631-454-7677 x2085

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: None
b) Non-Proprietary Name (USAN): Metronidazole Topical Cream

9. LEGAL BASIS FOR SUBMISSION:

The applicant has certified that to the best of their knowledge, all listed patents claimed for the drug product have expired. The Reference Listed Drug is MetroCream™, (Metronidazole Topical Cream, 0.75%), Galderma Laboratories Inc, NDA 20-531. There is no unexpired exclusivity for RLD.

10. PHARMACOL. CATEGORY:

Indicated for topical application in the treatment of inflammatory papules and pustules of rosacea.

11. DOSAGE FORM: Cream

12. STRENGTH/POTENCY: 0.75%

13. ROUTE OF ADMINISTRATION: Topical

14. Rx/OTC DISPENSED: _x__Rx ___OTC

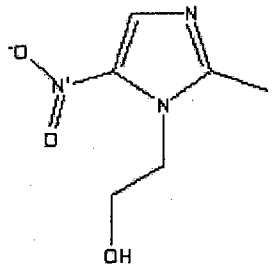
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

____x_Not a SPOTS product

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

2-Methyl-5-nitro-1Himidazole-1-ethanol
$C_6H_9N_3O_3$, 171.1554



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
	II			3	Adequate	6/26/2003	Reviewed by B. Lim
	III			4			
	III			4			
	III			4			
	III			4			

[1] Action codes for DMF Table:

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

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

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	15-326	Metronidazole Topical Cream, 0.75%, submitted by Altana

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
EES	Acceptable	6/25/2003	D'Ambrogio
Methods Validation	Not required		
Labeling	Acceptable	5/16/2003	R.Wu
Bioequivalence	Acceptable	5/18/2004	S. Ho
EA	N/A		
Radiopharmaceutical	N/A		

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt. __x__ Yes
____ No If no, explain reason(s) below:

APPEARS THIS WAY
ON ORIGINAL

The Chemistry Review for ANDA 76-408

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability: The ANDA is approvable.

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

II. Summary of Chemistry Assessments

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

- Altana's Metronidazole Topical Cream, 0.75% is a FIRST GENERIC.
- The drug substance Metronidazole is USP. The drug product Metronidazole Topical Cream, 0.75% is non-USP. The product will be packaged in 45 gram lined aluminum tubes, capped with white, ——— pointed caps. Each filled tube will be individually packaged into a pre-printed carton.
- The DMF associated with this application (DMF———) was found to be adequate on 6/26/2003 and there have been no updates since.
- Altana has developed their own in-house methods for the drug product identification, Metronidazole assay, benzyl alcohol assay, and degradation products and related substances methods. The method validations were submitted and found acceptable.

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

A thin layer of Metronidazole Topical Cream, 0.75% should be applied and rubbed into the entire affected areas {after washing, twice daily (morning and evening)}. Areas to be treated should be washed with a mild cleanser before application.

Metronidazole Topical Cream is indicated for topical application in the treatment of inflammatory papules and pustules of rosacea.

Tubes are to be stored at controlled room temperature: 15^0-30^0C(59^0-86^0F). The expiration for the product is 24 months.

C. Basis for Approvability or Not-Approval Recommendation

CMC, bio, labeling, and EER are all acceptable.

III. Administrative

A. Reviewer's Signature

Kathy P. Woodland

Kathy P. Woodland

B. Endorsement Block

HFD-627/K.Woodland/ KWoodland 5/18/04
HFD-627/S.Liu,PhD/ S Liu 5/18/04
HFD-617/W.Pamphile, PM/ WP 5/19/04
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F/T by:

C. CC Block

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ON ORIGINAL

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information from

CHEMISTRY REVIEW #2

30. MICROBIOLOGY N/A

31. SAMPLES AND RESULTS/METHODS VALIDATION STATUS

A method validation is not necessary.

32. LABELING Acceptable, R. Wu, 5/16/2003

33. ESTABLISHMENT INSPECTION Acceptable, 6/25/2003, D'Ambrogio

34. BIOEQUIVALENCE Acceptable 5/18/2004

35. ENVIRONMENTAL IMPACT CONSIDERATIONS/CATEGORICAL EXCLUSION:

Altana stated that they are claiming a categorical exclusion. To the best of their knowledge they are in compliance with all applicable federal, state, and local environmental laws.

cc: ANDA 76-408
ANDA DUP 76-408
DIV FILE
Field Copy

Endorsements (Draft and Final with Dates):

HFD-627/K.Woodland/ KWoodland 5/18/04 VJL & Shylaz 5/18/04
HFD-627/S.Liu,PhD/
HFD-617/W.Pamphile,PharmD/ WP 5/19/04

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F/T by:

TYPE OF LETTER: APPROVABLE

APPEARS THIS WAY ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-408

BIOEQUIVALENCE REVIEW

Review of a Bioequivalence study with Clinical Endpoint

ANDA: 76-408
Drug Product: Metronidazole Topical Cream, 0.75%
Sponsor: Altana Inc.
Reference Listed Drug: Metrocream® Galderma Laboratories, Inc., NDA 20-531
Reviewer: Sarah Ho, Pharm.D.
Submission dates: 5/3/02, 2/14/03, 11/12/03
Date of Review: 5/10/04
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I. Introduction

Metrocream®

Metrocream® is indicated for the treatment of inflammatory papules and pustules of rosacea. This topical cream contains 0.75% metronidazole. Metronidazole is a member of the imidazole class of antibacterials and is classified as an antiprotozoal and antibacterial agent.

Rosacea

Rosacea is a chronic dermatologic disorder of uncertain etiology characterized by papules, pustules, erythema, and telangiectasia. An initial sign of Rosacea is transient blushing and redness on the cheeks. Facial papules result from a granulomatous inflammatory infiltrate in the skin. These lesions are usually round and firm in consistency. Pustules, when present, are often small and on the apex of the papule. The dermatologic findings of rosacea are characteristically in a symmetrical distribution on the face involving the cheeks, chin, forehead, and nose. They are rarely found on the neck, chest, back, and scalp. Common triggers include alcohol, hot drinks, spicy foods, stress, sunlight, and extreme heat or cold. As the condition progresses, patients experience inflammatory lesions (papules and pustules), vivid erythema, and telangiectasia. Comedones are notably absent. Possible complications include keratoconjunctivitis and sebaceous hyperplasia or rhinophyma.

II. Background

The Sponsor previously submitted a protocol (#ALT 00-0323-5) for review by the Office of Generic Drugs (OGD). On July 3, 2001, the OGD Associate Director for Medical Affairs, Dr. Fanning, completed the protocol review and issued the following comments to the Sponsor on July 5, 2001:

1. Your protocol lists "a clinically meaningful laboratory abnormality" as a reason for discontinuation from the study. However, the protocol does not indicate that any laboratory testing, except for pre-enrollment urine pregnancy tests, will be done. Please clarify or correct your protocol.
2. Your protocol does not describe how compliance will be monitored. Please provide details on the criteria to be assessed.
3. The eligibility criteria are acceptable, except that the washout period for systemic retinoids should be 6 months.
4. The endpoints are appropriate but the investigator's Global Evaluation should be revised.

It should be similar to the one used in the innovator study using a static descriptive definition of each category instead of the current response categories that are defined as certain percentages of improvement. In addition, the Global Evaluation should **not** include an effect on the erythema of rosacea as part of the evaluation.

On August 21, 2001, the Agency issued the corrected comments to the Sponsor:

"In addition, the Global Evaluation **should include** an effect on the erythema of rosacea as part of the evaluation."

Reviewer's Comments: *Consult from Division of Dermatologic and Dental Drug Products (DDDDP) dated June 21, 2001 indicates that the investigator's Global Evaluation "should **not** include an effect on the erythema of rosacea as part of the evaluation."*

III. Study Information

Protocal Number: ALT 00-0323-05

Title: A Multi-center, Double-Blind, Randomized, Vehicle-Controlled, Parallel-Group Study to Determine the Therapeutic Equivalence of Two Metronidazole 0.75% Cream Formulations in the treatment of Rosacea.

Study Objective:
To evaluate the safety and therapeutic equivalence of Altana, Inc.'s Metronidazole Cream, 0.75% to Galderma Laboratories, Inc.'s Metrocream® (metronidazole cream 0.75%) and its efficacy over its vehicle (placebo) in the treatment of rosacea.

Study Design:
A randomized, double-blind, vehicle-controlled, parallel-group multi-center study in which patients were randomized in a 2:2:1 ratio to one of the following 3 groups:

1. Metronidazole Cream 0.75% (Altana, Inc.) twice daily for 12 weeks, *Lot #E906*
2. Metrocream® (Galderma Laboratories, Inc.) twice daily for 12 weeks, *Lot #PHP-1*
3. Vehicle Control (placebo) (Altana, Inc.), twice daily for 12 weeks, *Lot # E931*

Study Population:
Patients, at least 18 years of age, with rosacea of moderate severity. For inclusion into the study, the patients had a minimum of 6, but no more than 25, facial papules and pustules combined and moderate or greater erythema. Telangiectasis did not have to be present.

Inclusion Criteria
1. Patients gave written informed consent.
2. Male or female patients of any race, at least 18 years of age or older.
3. Sexually active females of childbearing potential had to be using an acceptable

method of birth control and have a negative pregnancy test prior to enrollment. Females who were of non-childbearing potential, i.e., pre-menses, post-menopausal, or hysterectomized, were not required to have a urine pregnancy test.
4. Outpatients with a definite clinical diagnosis of rosacea of moderate severity
5. Baseline erythema score of >/= 2 (moderate or greater).
6. A minimum of 6, but no more than 25, combined papules/pustules on the face. These were to be limited to the facial treatment area. Inflammatory lesions involving the eyes, nasal folds, and scalp were excluded from the count.
7. Patients who were willing to minimize external factors that might produce exacerbation of their rosacea [e.g., hot (temperature) and/or spicy foods, very hot beverages, hot environments, prolonged sun exposure, and alcoholic beverages].
8. Patients who were able to understand the requirement of the study, abide by the restrictions, and return for the required treatment period visits.
9. Patients who were in good health and free from any clinically significant disease, other than rosacea, that might interfere with the study evaluations.
10. Patients who had no facial makeup or had used the same brand of make-up for a minimum period of two months prior to baseline and did not change make-up brands or types during the study.

Exclusion Criteria

1. Patients who were pregnant or nursing.
2. Patients who had more than 2 nodules (defined as a papule/pustule >/= 5 mm diameter), presence of moderate or severe rhinophyma, dense telangiectases, plaque-like facial edema.
3. Patients who had ocular involvement, such as conjunctivitis, episcleritis, iritis, and keratitis.
4. Patients who had shown hypersensitivity to metronidazole (in any dose form) or to any of the ingredients of the study medications.
5. Patients treated with systemic antibiotics or systemic anti-rosacea drugs (e.g., metronidazole) within a period of 4 weeks prior to the study start.
6. Patients treated with prescription and/or over-the-counter topical antibiotics, topical corticosteroids, or topical anti-inflammatories on facial areas within a period of 2 weeks prior to study start.
7. Patients who were taking or who had been treated with oral/systemic steroids within 4 weeks prior to the study start (intranasal or inhaled corticosteroids are acceptable if kept constant throughout the study).
8. Patients who started hormonal therapy within 6 months of study start. Such therapy started >/= 6 months previously must remain constant throughout the study. These treatments included, but were not limited to, estrogenic and progestational agents such as birth control pills, as well as estrogen given to women for hot flashes.
9. Patients who had received oral retinoids (e.g., Accutane) within the past 3 months or topical retinoids (e.g., tretinoin, tazarotene, adapalene) to the face within the past 4 weeks.
10. Patients who had laser therapy or electrodesiccation to the facial area for telangiectasia or any other condition within 6 weeks prior to study start.
11. Patients who had received radiation therapy and/or anti-neoplastic agents within 3

months prior to study start.

12. Patients who were taking vasodilators, vasoconstrictors, beta-blockers, or anticoagulant therapy who started or changed their dose level or regimen within the past 3 months.
13. Patients who had systemic or dermatologic diseases that had the potential to interfere with the evaluation of facial rosacea (e.g., seborrheic dermatitis, perioral dermatitis, acne vulgaris, corticosteroid-induced rosacea, carcinoid syndrome, mastycytosis, acneiform eruptions caused by medication, facial psoriasis, etc.).
14. Patients with bacterial folliculitis.
15. Patients with beards and/or long side-burns (a modest mustache is acceptable).
16. Patients whose activities involved excessive or prolonged exposure to sunlight.
17. Patients with a history of alcohol or drug abuse.
18. Patients who had been treated with an investigational drug within a period of 30 days prior to study start.
19. Patients previously enrolled in this study.

Reviewer's Comments:

- *For #9 - Washout period for systemic retinoids should be 6 month per NDA exclusion criteria and previous recommendation to sponsor. The inclusion and exclusion questions were stated as yes/no questions; therefore, this reviewer could not exclude patients that received systemic retinoids within 3 to 6 months.*
- *Patients with evidence of or history of blood dyscrasia should have been excluded. (Metronidazole is a nitroimidazole.) However, there was no laboratory test done except for the urine pregnancy test.*

Concomitant/Prohibited Medications

The following medications were not to be taken at any time during this study:

1. Any treatment for rosacea other than the test treatment. No new cosmetics, new cleansers or new medicated make-up were permitted to be started during the treatment period.
2. Systemic anti-acne drugs, retinoids, or corticosteroids.
3. Systemic antibiotics known to impact on the severity of facial rosacea (e.g., tetracycline and its derivatives, erythromycin and its derivatives, bactrim, trimethoprim).
4. Topical antibiotics, anti-acne drugs, retinoids, or corticosteroids to the face.
5. Alcoholic toners, astringents, medicated topical preparations (prescriptions and over-the-counter), or medicated make-up on the facial treatment area.
6. Abrasive cleaners or washes.

Reviewer's Comments:

- *For #3 - Patients on any antibiotic were excluded from the PP population.*

Precautions taken during the study

1. Tanning booths, sunbathing, or excessive exposure to the sun were to be avoided. When excessive exposure was unavoidable, patients were to wear appropriate

protective clothing and use a sunscreen.
2. Patients were instructed to avoid common triggers for rosacea (e.g., hot weather, hot beverages, spicy foods, alcohol).
3. Patients did not wear makeup at study visits so as not to interfere with the evaluations.
4. Patients were not permitted to use a sauna within 48 hours of each visit.

Criteria for Discontinuation of Patients

1. If the patient withdrew his/her consent for any reason.
2. If the patient's condition had worsened to the degree that the investigator felt it was unsafe for the patient to continue in the study.
3. If there was a clinically meaningful laboratory abnormality that in the opinion of the investigator prevented continuation.
4. If an adverse event occurred for which the patient desired to discontinue treatment or the investigator determined that it was in the patient's best interest to be discontinued.
5. If there was a significant protocol violation.
6. If a concomitant therapy was reported or required which was liable to interfere with the results of the study.
7. If the patient was lost to follow-up. The investigator tried twice to reach the patient by telephone and sent a certified follow-up letter before considering that patient lost to follow-up.
8. If a patient became pregnant.
9. Administrative reasons.

Reviewer's comments:

- *For #2: Patient were counted as study "failure" and LOCF used in the PP population irregardless of the length of treatment received.*
- *For #3: There was no laboratory test performed as part of this study other than the urine pregnancy test.*
- *For #7: If the patient was lost to follow-up then LOCF was used in the MITT population as long as the patient returned for at least one post-baseline visit. However, the patient was excluded in the PP population.*
- *Compliance was not noted as a reason for discontinuation in the protocol. However, the CRF instructed to discontinue the patient if the patient missed more than 5 consecutive days of medication.*

Randomization/Blinding:

Randomization

A patient number was assigned to each patient by an independent third-party dispenser. The patient number corresponded to a computer-generated randomized treatment group. The randomization scheme was generated so that Test Product, Reference Product, and Vehicle were assigned in a 2:2:1 ratio. The patient numbers for study medication were assigned sequentially in the order in which patients came to the center for initial dispensing of study medication.

Blinding

All study medications were supplied in similar 45 gm tubes, three tubes per patient. Opaque black shrink-wrap plastic concealed the identity of the sample tubes. A two-piece, double blind label consisting of a fixed portion and a tear-off portion was attached to each patient kit. The fixed portion displayed the following information: protocol number, patient number, an investigational use statement, warning statements, and the sponsoring company's name. After dispensing, the tear off section was attached to the label page of the CRF. The tear off portion consisted of a two-part label. One section repeated the information on the fixed portion, and the other contained the blinded portion identifying the product. In order to nullify any remaining differences in product packaging, study medication was dispensed by an independent third-party dispenser who was not performing the clinical evaluations. The investigator performing the clinical evaluations did not dispense or retrieve study medication.

> ***Reviewer's comments***: *DSI evaluation has been requested to pay particular attention to the blinding of this study.*

Study Procedures:

Baseline

The baseline visit consisted of obtaining written informed consent, review of inclusion/exclusion criteria, medical history, physical exam, review of concomitant medications, urine pregnancy test for all sexually active females of childbearing potential, lesion counts, erythema assessment of intensity, note of telangiectasia, study medication dispensation and accountability, patient instruction (including application of first dose), scheduling next visit, and completion of CRF. The following scale was used for erythema evaluation:

0	=	None
1	=	Mild (barely perceptible)
2	=	Moderate (distinct)
3	=	Severe (intense)

Weeks 3, 6, 9 and 12 (Days 22, 43, and 64 +/- 7, and 85 +/- 10) Evaluations

Changes in concurrent medications, adverse events, study medication dispensing/accountability were recorded during the post baseline visits. Lesion counts and Investigator Global Evaluations (IGE) were performed. For the Global Evaluation of treatment response compared to baseline, the assessment incorporated reduction in lesions, skin parameters such as pigmentation change, and a general clinical assessment. In addition, the following scale was used:

Investigator's Global Evaluation

0	=	Condition unchanged or worsened
1	=	Poor response, 1% - 24% improvement
2	=	Fair response, 25% - 49% improvement
3	=	Good response, 50% - 74% improvement
4	=	Excellent response, 75% - 99% improvement
5	=	Completely cleared, 100% improvement

"Cured" was defined as an IGE score of 4 or 5.

Reviewer's comments:

- *Patients were given a visit window of +/- 7 days for Visits 2, 3, and 4 (Days 22, 43, and 64), and +/- 10 days for Visit 5 (Day 85). Previous recommendations did not comment on visit windows. Thus, all analyses included patients with a visit window of +/-7 days or +/-10 days. OGD has customarily recommended a visit window of +/- 4 days. A statistical consultation is requested to perform a subset analysis to exclude patients who were +/- 4 days from their visit for all post baseline visits.*
- *An objective morphologic description of each category should have been used to enable consistent and reproducible use among centers. Global assessments should have been dichotomized to success/failure for efficacy and bioequivalence evaluations. The scales used and what will constitute "success/cure" should have been clearly defined prior to conducting the study. The sponsor indicated that "a static IGE, such as that used by the innovator, had not been included in the current study because when erythema was eliminated as a factor what remained was essentially a repetition of the lesion counts." As per July 5, 2001 recommendations to sponsor, a static score describing the condition was recommended. Whereas a static score consistent with a condition of clear or almost clear was needed for success/cure, only a score of 5 on the above scale is acceptable for success/cure.*
- *Compliance was measured in Visits 2, 3, 4, and 5 simply via a visual inspection of each patient's returned tubes of study medication and with this question: "Did the subject miss more than 5 consecutive days of medication up to this point in time?" If the answer was "yes" then the patient was discontinued from the study. A dosing diary was not kept by the patients.*

Safety:

The safety parameter was the incidence of all adverse events reported during the study. Tolerability assessments of localized skin reactions were also performed at all visits.

Statistical Plan:

Primary Endpoint

1. Mean percent change from baseline to Visit 5 (Day 85) in the number of total lesions (papules and pustules).
2. Proportion of "cured" patients at Visit 5 (Day 85). "Cure" was defined as an IGE score of 5 (completely cleared) or 4 (excellent response).

Reviewer's Notes:

- *As per July 5, 2001 recommendations to sponsor, a static score describing the condition was recommended. Whereas a static score consistent with a condition of clear or almost clear was needed for cure, only a score of 5 (completely cleared) is acceptable for cure.*

Secondary Endpoint

1. Mean percent change in the number of papules from Baseline to Visit 5 (Day 85).
2. Mean percent change in the number of pustules from Baseline to Visit 5 (Day 85).

Sample Size

Approximately 470 patients were to be enrolled into the study to obtain 405 evaluable patients, 162 in each active arm and 82 in the vehicle group. This sample size was expected to provide approximately 80% probability of establishing a therapeutic equivalence of the two active products and show their superiority over the vehicle. This was based on the assumption that the active products have an equivalent percent reduction in combined papules and pustules of approximately 50% and the vehicle percent of no greater than 25%.

Analysis

Three patient populations were defined as follows:

1. intent-to-treat (ITT)
   - enrolled into the study
   - received at least one dose of study medication
2. modified intent-to-treat (MITT)
   - enrolled into study
   - met inclusion/exclusion criteria
   - received at least one dose of study medication
   - had at least one post-Baseline efficacy evaluation
3. per-protocol (PP)
   - enrolled into study
   - met inclusion/exclusion criteria
   - complied with minimum treatment course of 63 days
   - did not have any major protocol violations (e.g., treatment with conflicting antibiotics)
   - did not miss more than 5 consecutive days of dosing
   - did not miss more than 2 consecutive visits
   - had evaluable data on the primary efficacy variables of lesion counts and investigator global evaluation at Visit 5 within the specified window (Day 85 +/- 10 days) or was discontinued due to treatment failure or adverse event after having received at least 6 weeks of treatment.

Reviewer's Comments:

- *In the PP population, if the patient terminated the study prematurely due to intolerable adverse events after having received at least 6 weeks (42 days) of treatment then the patient should be excluded from analysis.*
- *Patients who discontinued at any time due to lack of treatment effect should be analyzed as study "failure" and LOCF should be used in the PP population irregardless of the length of treatment received.*
- *If the patient came for the final visit (Visit 5) then the patient was included in the PP population for the proportion of "cured" patients. Missing any visits prior to Visit 5 would not alter the final result.*

For the mean percent change from Baseline to Visit 5 (Day 85) in the number of total lesions (papules and pustules), a two-sided 90% confidence interval about the difference between the test and reference products was constructed by a two-way analysis of variance (ANOVA) by the

sponsor. The test product was judged clinically equivalent to the reference product in the reduction of inflammatory lesions if the confidence bounds of the 90% confidence interval were within +/-20% of the reference product mean percent reduction.

For the proportion of "cured" patients at Visit 5 (Day 85), a two-sided 90% confidence interval about the difference in cured proportions between the test and reference products was constructed by Wald's method with Yates' continuity correction based on the data pooled from all clinical sites by the sponsor. The clinical equivalence of the test product to the reference product in the proportion of "cured" patients based on the Investigator's Global Evaluation score was established if the confidence bounds of the 90% confidence interval were contained within the limits -0.20 to 0.20. The analysis in the PP population was considered primary and that in the MITT population as supportive.

The primary evaluations of efficacy also included a comparison of each active treatment to the vehicle control with respect to the mean percent reduction in total lesion counts from Baseline to Visit 5 (Day 85) and the proportion of "cured" patients at Visit 5 (Day 85). For the mean percent reduction in lesion counts, the differences were evaluated by the sponsor using a two-way analysis of variance (ANOVA) with a two-sided significance level of 5%. For the proportion of "cured" patients, the treatment difference was compared by the sponsor using two-sided Z-test at the 5% level of significance and included Yates' continuity correction. The analysis in the MITT population was considered primary and that in the PP population as supportive.

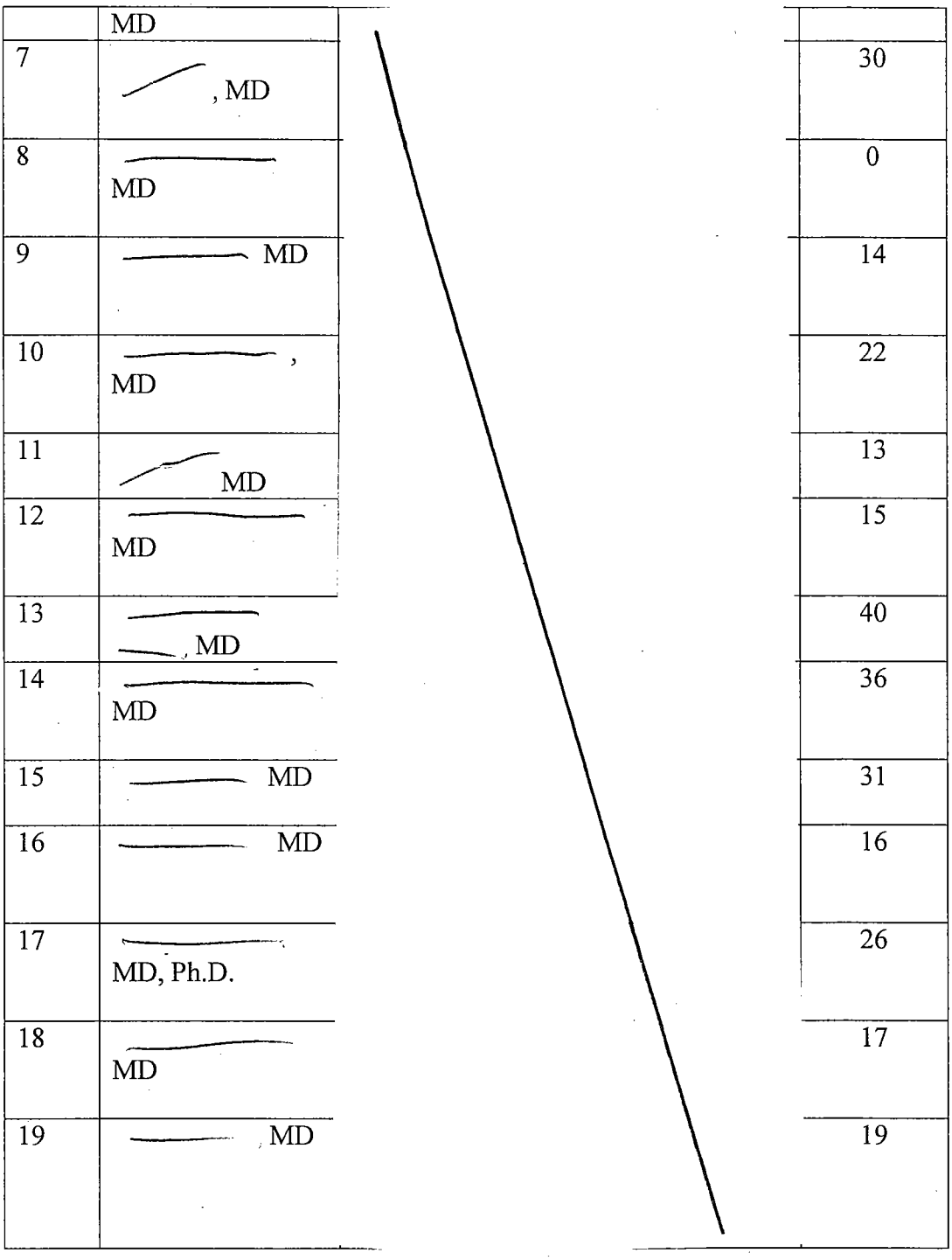
IV. Results

CRO: [redacted]

Study period: March 14, 2001 to October 31, 2001.

Study Centers: 19 sites

Site #	Investigator	Address	# patients enrolled
1	[redacted], Ph.D.	[redacted]	60
2	[redacted], MD		50
3	[redacted], MD		22
4	[redacted], MD		20
5	[redacted], MD		17
6	[redacted]		47



Study Enrollment:

A total of 495 patients were enrolled into the study with 200 randomized to Altana's Metronidazole Cream, 0.75%, 197 to Metrocream®, and 98 to the vehicle arm. Of these, 1 patient did not meet the inclusion criteria, 2 patients did not meet exclusion criteria, and 21 patients did not return for at least one post-baseline visit and were excluded from the MITT population analyses. In addition, 1 patient requested to be removed from the study prior to any

post-baseline visit and was also excluded from the MITT population analyses. The distribution of patients in the three analysis population is summarized in Table I.

Table I - Distribution of Patients in the Three Analysis Population (per reviewer)

Population	Test	Reference	Vehicle
Intent-to-Treat (ITT)	200	197	98
No post-baseline visit	-6	-10	-5
Did not meet inclusion criteria	0	-1	0
Did not meet exclusion criteria	-1	-1	0
*Other	0	-1	0
Modified Intent-to-Treat (MITT)	**193**	**184**	**93**
** Lost to follow up	-4	-4	-5
Outside visit window for Visit 5 (+/- 10 days)	-4	-7	-1
Adverse event	-4	-4	-3
Missed > 5 consecutive days of doses	-8	-2	-2
Used prohibited medication	-20	-13	-5
Noncompliance	-1	-2	0
^^Combination	-3	-2	-2
*Other	-3	-1	0
Per Protocol (PP)	**146**	**149**	**75**

*Other: 2 patients requested to be removed from the study, 2 patients were out of town for follow up visits, and 1 patient discontinued from the study due to other illness.
^^Combination: any combination of out of visit window, missed doses, and use of prohibited medication.
**Lost to follow up: Patients that had at least one post-baseline visit.

The efficacy analyses were conducted on the PP and MITT populations. Safety analyses were conducted on the ITT population.

Table II - Patients excluded from MITT population (per reviewer)

Reason	Total	Test	Reference	Vehicle
No post-baseline visit	21	6 (4-70, 5-94, 7-122, 13-530, 14-450, 18-360)	10 (2-30, 5-89, 6-467, 13-242, 13-249, 13-254, 13-528, 13-535, 13-537, 19-380)	5 (3-52, 4-79, 5-88, 13-522, 13-538)
Did not meet inclusion criteria	1	0	1 (5-84)	0
Did not meet exclusion criteria	2	1 (7-138)	1 (17-610)	0
Other*	1	0	1 (9-169)	0
Overall	**25**	**7**	**13**	**5**

Patients are identified in parenthesis by site number followed by patient number. (e.g. 13-242)
*Patient requested to be removed from study prior to any post-baseline visit.

Table III - Patients excluded from Per-Protocol population (per reviewer)

Reason	Total	Test	Reference	Vehicle
No post-baseline visit	21	6 (4-70, 5-94, 7-122, 13-530, 14-450, 18-360)	10 (2-30, 5-89, 6-467, 13-242, 13-249, 13-254, 13-528, 13-535, 13-537, 19-380)	5 (3-52, 4-79, 5-88, 13-522, 13-538)
Lost to follow up	13	4 (1-16, 6-476, 13-248, 13-540)	4 (2-421, 11-204, 13-523, 13-528)	5 (11-205, 12-234, 13-529, 13-534, 17-339)
Outside visit window for Visit 5 (+/- 10 days)	12	4 (1-2, 12-229, 13-245, 15-281)	7 (1-487, 2-48, 6-120, 12-224, 15-545, 15-550, 17-608)	1 (12-226)
Adverse event	11	4 (3-47, 3-55, 15-551, 17-337)	4 (6-102, 13-521, 15-283, 18-350)	3 (6-112, 6-470, 17-606)
Missed > 5 consecutive days of doses	12	8 (1-481, 1-485, 3-51, 4-78, 10-182, 12-235, 13-524, 17-331)	2 (13-246, 13-256)	2 (1-6, 1-516)
Used prohibited medication	38	20 (1-490, 3-46, 3-59, 4-73, 5-82, 5-83, 6-111, 6-114, 6-474, 6-478, 12-223, 12-231 14-265, 14-270, 15-294, 15-297, 17-323, 17-609, 19-364, 19-374)	13 (1-520, 2-428, 3-60, 5-93, 6-110, 7-139, 10-185, 15-296, 15-543, 16-312, 17-326, 17-333, 17-611)	5 (1-1, 6-106, 6-116, 13-244, 15-293)
^Noncompliance	3	1 (2-430)	2 (11-207, 17-335)	0
Did not meet inclusion criteria	1	0	1 (5-84)	0
Did not meet exclusion criteria	2	1 (7-138)	1 (17-610)	0
^^Combination	7	3 (4-74, 7-136, 10-190)	2 (12-228)	2 (3-49, 13-255)
*Other	4	3 (2-149, 4-68, 18-353)	1 (9-169)	0
Overall	**124**	**54**	**47**	**23**

Patients are identified in parenthesis by site number followed by patient number. (e.g. 13-242)

^Noncompliance: 1 patient applied medication only once daily, 1 patient used the entire study medication by Visit 4, and 1 patient refused to shave his beard.

^^Combination: any combination of out of visit window, missed doses, and use of prohibited medication.

*Other: 2 patients requested to be removed from the study, 2 patients were out of town for follow up visits, and 1 patient discontinued from the study due to other illness.

Reviewer's comments:

- *Tables II and III, on the previous pages, identify those patients that were excluded in the MITT and PP populations. Of these patients, this reviewer excluded the following patients that the sponsor included:*
    1. *Patient 01-490 was on a prohibited concomitant medication (i.e. Penicillin).*
    2. *Patient 17-610 did not meet exclusion criteria (i.e. mild seborrheic dermatitis on face).*
    3. *Patients 6-112 and 18-350 did not have 12 weeks data or earlier failure. However, the sponsor included in the PP population because these patients received at least 9 weeks of treatment. This is not consistent with the intended 12 week treatment duration*
- *This reviewer was not able to properly evaluate the exclusion criteria for the washout period for systemic retinoids. The washout period for systemic retinoids should have been 6 months per NDA exclusion criteria and previous recommendation to the sponsor. This particular criteria was stated in a yes/no format as "has received oral retinoid (e.g., Accutane) within the past 3 months..." on the CRF. Therefore, this reviewer was not able to distinguish if the patients had oral retinoid within 6 months prior to enrollment.*

Table IV - Patients incorrectly excluded from the PP population (per reviewer)
(These patients need to be included in analysis.)

Reason	Total	Test	Reference	Vehicle
#Not outside visit window	3	1 (11-202)	1 (2-431)	1 (11-208)
*LOCF as treatment failure	2	2 (13-251, 13-253)	0	0
Overall	**5**	**3**	**1**	**1**

Patients are identified in parenthesis by site number followed by patient number. (e.g. 13-242)
#The sponsor considered as out of visit window for Visit 5. However, these patients were +10 days for Visit 5.
*The sponsor excluded these patients because they discontinued from the study due to treatment failure and they did not comply with a minimum treatment course of 4 weeks. However, these patients should be included in the analysis using LOCF.

Reviewer's comments:

- *Table IV identifies those patients that the sponsor excluded from the PP population, but which this reviewer included for the following reasons:*
    1. *The sponsor incorrectly identified 3 patients as out of visit window for Visit 5. These patients were at +10 days for Visit 5, and the designated visit window is +/- 10 days according to the protocol.*
    2. *The sponsor excluded in the PP population any patient without at least 6 weeks of treatment if the patient discontinued due to insufficient treatment response. However, these patients should have been analyzed as treatment failure in the IGE analysis and included in the analysis for mean percent reduction of lesion counts. Two patients (test: 13-251 and 13-253) in the PP population discontinued prior to 6 weeks of treatment due to" worsening rosacea."*

Demographics

Of the four hundred ninety-five (495) patients in the ITT population, 336 were females and 159 were males. Most of the patients were Caucasian (91%); 2 patients were Black (0.4%), 4 patients were Asian (0.8%), and 38 patients were of other races (8%). Patients ranged in age from 20 to 83 years. The ITT treatment groups were comparable for all demographic characteristics (all $p>0.05$). Per sponsor's data, the demographic characteristics for the ITT population were similar to the MITT and PP populations. See Table V for the reported demographic characteristics for the ITT population.

Table V - Demographic Characteristics for Intent-to-Treat patients (per sponsor)

Characteristic		Metronidazole Cream, 0.75% (N=200)	Metrocream® (Metronidazole 0.75%) (N=197)	Vehicle (N=98)	p-value
Gender	Male	63 (32%)	65 (33%)	31 (32%)	0.956[1]
	Female	137 (69%)	132 (67%)	67 (68%)	
Race	CAUCASIAN	183 (92%)	178 (90%)	90 (92%)	0.523[1]
	BLACK	0 (0%)	1 (1%)	1 (1%)	
	ASIAN	1 (1%)	1 (1%)	2 (2%)	
	NATIVE AMERICAN	0 (0%)	0 (0%)	0 (0%)	
	OTHER	16 (8%)	17 (9%)	5 (5%)	
Age (years)	Mean ± Std	49.6 ± 13.0	48.7 ± 12.6	50.3 ± 13.6	0.587[2]
	Min - Max	20 - 79	23 - 80	25 - 83	

[1] P-values for treatment comparisons from Cochran-Mantel-Haenszel test, adjusted for site.

[2] P-value for treatment comparisons from two-way analysis of variance with factors of treatment and site.

Baseline Disease Severity

The sponsor tabulated the baseline clinical diagnosis, including lesion counts and clinical signs and symptoms for the MITT population in Table VI. Lesion counts and ratings for erythema, dryness, pruritus, stinging/burning, and facial edema were comparable at Baseline for the three treatment groups in the MITT population. A greater proportion of patients in the test group had telangiectasia at Baseline ($p=0.025$). Across treatment groups, ratings were higher for erythema and dryness than other symptoms. There were no statistically significant differences between treatments in the MITT population with regard to the number of papules ($p=0.463$), the number of pustules ($p=0.658$), pruritus ($p=0.917$), stinging/burning ($p=0.282$), or facial edema ($p=0.177$). Similarly, there were no statistically significant differences for PP patients except for telangiectasia.

Table VI - Baseline Dermatological Examination for MITT Patients (per sponsor)

Parameter	Category	Metronidazole Cream, 0.75% (N=193)	Metrocream® (Metronidazole 0.75%) (N=185)	Vehicle (N=93)	p-value
Number of Papules	Mean ± Std	11.8 ± 5.6	11.6 ± 5.7	11.7 ± 5.8	0.463[1]
	Min - Max	1 - 25	0 - 25	1 - 25	
Number of Pustules	Mean ± Std	1.8 ± 2.8	2.1 ± 3.4	1.8 ± 3.2	0.399[1]
	Min - Max	0 - 19	0 - 23	0 - 17	
Total Lesion Count	Mean ± Std	13.6 ± 5.9	13.7 ± 6.1	13.5 ± 6.1	0.625[1]
	Min - Max	6 - 25	6 - 25	6 - 25	
Erythema	MODERATE	160 (83%)	142 (77%)	77 (83%)	0.132[2]
	SEVERE	33 (17%)	43 (23%)	16 (17%)	
Telangiectasia	PRESENT	171 (89%)	147 (79%)	74 (80%)	0.025[2]
	ABSENT	22 (11%)	38 (21%)	19 (20%)	
Dryness	NONE	79 (41%)	79 (43%)	30 (32%)	0.658[2]
	MILD	64 (33%)	61 (33%)	41 (44%)	
	MODERATE	44 (23%)	33 (18%)	18 (19%)	
	SEVERE	6 (3%)	12 (6%)	4 (4%)	
Pruritus	NONE	128 (66%)	114 (62%)	58 (62%)	0.917[2]
	MILD	41 (21%)	54 (29%)	24 (26%)	
	MODERATE	18 (9%)	16 (9%)	9 (10%)	
	SEVERE	6 (3%)	1 (1%)	2 (2%)	
Stinging/Burning	NONE	136 (70%)	145 (78%)	70 (75%)	0.282[2]
	MILD	37 (19%)	26 (14%)	15 (16%)	
	MODERATE	15 (8%)	13 (7%)	6 (6%)	
	SEVERE	5 (3%)	1 (1%)	2 (2%)	
Facial Edema	NONE	161 (83%)	151 (82%)	82 (88%)	0.177[2]
	MILD	26 (13%)	27 (15%)	10 (11%)	
	MODERATE	5 (3%)	6 (3%)	1 (1%)	
	SEVERE	1 (1%)	1 (1%)	0 (0%)	

[1] P-values for treatment comparisons from nonparametric Friedman's test.

[2] P-values for treatment comparisons from Cochran-Mantel-Haenszel row mean score test, adjusted for site.

Efficacy Outcomes

1. Primary Endpoints

The primary efficacy measures were the mean percent change from Baseline to Visit 5 (Day 85) in the number of total lesions (papules and pustules) and the proportion of

"cured" patients at Visit 5 (Day 85). The sponsor defined "cured" as an Investigator's Global Evaluation score of 5 (completely cleared) or 4 (excellent response). The Sponsor's primary efficacy outcomes are shown in Table VII.

In the sponsor's PP population analysis of lesion counts, the test group and the reference group were comparable in regard to mean percent reduction from Baseline to Visit 5; the mean percent reduction was 63% for test patients and 64% for reference patients, compared to 48% for vehicle patients. Altana's metronidazole cream, 0.75%, was determined to be clinically equivalent to Metrocream®, 0.75%, in the sponsor's PP analysis (90% confidence interval on difference between active treatments: (-0.0757, +0.0589), which is contained within +/- 20% of the reference product mean percent reduction of -12.93% to 12.93%) at Visit 5 (Day 85).

In the sponsor's MITT population analysis of lesion counts, the test group and the reference group were comparable in regard to mean percent reduction from Baseline to Visit 5; the mean percent reduction was 55% for test patients and 58% for reference patients, compared to 45% for vehicle patients. Both the test product and the reference product showed superiority over the vehicle in the MITT population at the Day 85 visit (both $p<0.05$).

In the sponsor's PP population analysis of the Investigator's Global Evaluation scores, the test group and the reference group were comparable in regard to the proportion of cured patients at Visit 5; 53% of test patients and 53% of reference patients were considered cured, compared to 40% of vehicle patients. Altana's metronidazole cream, 0.75%, was determined to be clinically equivalent to Metrocream®, 0.75%, in the PP analysis (90% confidence interval of the proportional difference between active treatments: (-0.1030, +0.0975) at Visit 5 (Day 85) per the sponsor's analysis.

In the sponsor's MITT population analysis of Investigator's Global Evaluation scores, the test group and the reference group were comparable in regard to the proportion of cured patients at Visit 5; 48% of test patients and 51% of reference patients were considered cured, compared to 34% of vehicle patients. Both the test product and the reference product showed superiority over the vehicle in the MITT population at the Day 85 visit (both $p<0.05$).

Reviewer's Comments:

- *A static score consistent with a condition of clear or almost clear was needed for success; therefore, only a score of 5 (completely cleared) was acceptable for "cured." Table VIII lists the distribution of patients' visits that should be considered treatment failure (IGE score of 4) in the MITT population. All of these visits should be included in the analyses. Table IX lists the patients that had an IGE score of 4 for Visit 5. These patients should be considered treatment failure in the PP population.*
- *Because the sponsor inappropriately included or excluded some patients from the MITT/PP populations analysis and inappropriately considered certain responses as "cured", the FDA statistician is consulted for reanalysis and verification of the*

sponsor's data.

- *The FDA statistician is also requested to perform a subset analysis that excluded all visits that were outside a visit window of +/- 4 days for all post baseline visits (Visit 2, 3, 4, and 5).*

Table VII - Sponsor's Primary and Supportive Efficacy Assessments

Pop.	Statistics	Metronidazole Cream, 0.75%	Metrocream®	Vehicle	90% CI Between Metronidazole and Metrocream®	p-value for Metronidazole vs. Vehicle	p-value for Metrocream® vs. Vehicle
Mean Percent Reduction from Baseline to Visit 5 (Day 85) in the Total Lesion Count							
PP	N	152	155	75	(-7.67, 5.89)[1a] Ref. LSmean=64.64 BE Limits: (-12.93, 12.93)	0.0031[b]	0.0021[b]
	Mean ± SD	62.9 ± 39.0	63.8 ± 34.3	47.7 ± 43.2			
	Min - Max	-100.0 - 100.0	-62.5 - 100.0	-80.0 - 100.0			
MITT	N	193	185	93	(-10.9, 5.74)[1b] Ref. LSmean=58.95 BE Limits: (-11.79, 11.79)	0.0021[a]	0.0011[a]
	Mean ± SD	55.3 ± 52.3	58.0 ± 47.5	45.1 ± 42.6			
	Min - Max	-300.0 - 100.0	-285.7 - 100.0	-80.0 - 100.0			
Proportion of Cured at Visit 5 (Day 85)							
PP	N (%)	80 (53%)	82 (53%)	30 (40%)	(-10.30%, 9.75%)[2a]	0.0993[b]	0.0902[b]
MITT	N (%)	93 (48%)	94 (51%)	32 (34%)	(-11.61%, 6.36%)[2b]	0.0382[a]	0.0143[a]

[1] Confidence intervals from two-way analysis of variance model. P-values for treatment comparisons from nonparametric Friedman's test. Bioequivalence (BE) conclusions based on the comparisons of the 90% confidence intervals with the BE limits.

[2] Confidence intervals from Wald's method with Yates' continuity correction. P-values for treatment comparisons from two-sided Z-test with Yates' continuity correction.

Table VIII - Number of Patients with "excellent response" for proportion of "cured" in the MITT population (per reviewer)

(These patients need to be analyzed as treatment Failure)

Total	Test	Reference	Vehicle
157	60	68	29

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Table IX - Patients with "excellent response" for IGE in the PP population (per reviewer)
(These patients need to be analyzed as treatment Failure)

Population	Total	Test	Reference	Vehicle
Included in PP population	135	53 (1-10, 1-12, 1-488, 1-490, 1-494, 1-498, 1-505, 1-508, 1-512, 2-423, 2-427, 3-46, 3-58, 3-405, 3-406, 4-65, 5-90, 6-105, 6-107, 6-119, 6-463, 7-128, 7-284, 9-165, 9-166, 9-172, 10-186, 10-191, 10-197, 10-200, 11-206, 11-209, 12-223, 13-241, 13-259, 14-263, 14-272, 14-277, 14-444, 14-452, 14-455, 15-287, 16-315, 17-328, 17-330, 17-334, 17-336, 17-607, 18-343, 18-345, 18-349, 19-364, 19-375)	60 (1-7, 1-11, 1-489, 1-492, 1-503, 1-506, 1-518, 2-27, 2-431, 2-432, 3-53, 3-57, 3-402, 3-407, 4-61, 4-67, 4-72, 4-77, 5-87, 5-92, 6-108, 6-113, 6-567, 7-126, 7-583, 7-590, 9-161, 9-162, 9-175, 10-184, 10-188, 11-210, 11-211, 12-225, 13-252, 13-536-, 14-261, 14-274, 14-278, 14-279, 14-442, 14-449, 14-454, 15-285, 15-288, 15-289, 15-295, 15-299, 15-548, 16-302, 16-310, 16-314, 17-322, 17-329, 18-341, 18-342, 18-355, 19-362, 19-363, 19-373)	22 (3-404, 4-71, 5-81, 5-95, 6-472, 9-164, 10-192, 11-208, 12-222, 13-247, 14-266, 14-271, 14-441, 14-448, 15-290, 15-541, 15-547, 17-327, 17-332, 18-356, 19-365, 19-379)
Excluded from PP population	14	6 (3-51, 6-111, 6-114, 6-478, 18-353, 19-374)	8 (1-520, 2-48, 11-207, 13-256, 15-550, 15-545, 17-326, 17-611)	0
Total	149	59	68	22

Patients are identified in parenthesis by site number followed by patient number. (e.g. 13-242)

2. Secondary Endpoints

For each of the secondary variables, treatment comparisons were made by the sponsor for both the PP and the MITT populations by a nonparametric Friedman's test because the assumptions of ANOVA were not satisfied. All pairwise comparisons were summarized by two-sided tests with a significance level of 5%.

According to the sponsor's analysis, the test group and the reference group were comparable in regard to mean percent reduction in papules from Baseline to Visit 5 (Day 85) for the MITT population; the mean percent reduction was 55% for test patients and 58% for reference patients, compared to 43% for vehicle patients. Altana's metronidazole cream, 0.75%, did not differ from Metrocream®, 0.75%, in the MITT analysis at Visit 5 (p=0.966). Both the test product and the reference product showed superiority over the vehicle in the MITT population at the Day 85 visit (both p=0.001).

In the sponsor's PP analysis, the test group and the reference group were comparable in regard to mean percent reduction in papules from Baseline to Visit 5 (Day 85); the mean percent reduction was 62% for test patients and 64% for reference patients, compared to 46% for vehicle patients. Altana's metronidazole cream, 0.75%, did not differ from

Metrocream®, 0.75%, in the PP analysis at Visit 5 (p=0.852). Both the test product and the reference product showed superiority over the vehicle in the PP population at the Day 85 visit (both $p<0.05$).

With respect to mean percent reduction in pustules from Baseline to Visit 5 (Day 85) for the MITT population, data were spread widely for all treatment groups according to the sponsor's analysis, with standard deviations of at least ten times the mean values. No significance was shown for any pairwise comparisons. Altana's metronidazole cream, 0.75%, did not differ from Metrocream®, 0.75%, (p=0.515). Neither the test product nor the reference product showed superiority over the vehicle (both $p>0.05$).

In the sponsor's PP analysis, with respect to mean percent reduction in pustules from Baseline to Visit 5 (Day 85), data also were scattered over a wide range for all treatment groups. However, the test group and the reference group were still comparable; the mean percent reduction was 20% for test patients and 17% for reference patients, compared to 4% for vehicle patients. Altana's metronidazole cream, 0.75%, did not differ from Metrocream®, 0.75% (p=0.386). Both the test product and the reference product showed superiority over the vehicle (both $p<0.05$).

The mean percent reduction in number of papules improved over time for all treatment groups according to the sponsor's analysis. Altana's metronidazole cream, 0.75%, and Metrocream®, 0.75%, had a comparable amount of reduction at all visits, and they both reduced the number of papules faster than the vehicle. With respect to mean percent reduction in number of pustules, there were no clear trends.

According to the sponsor, similar results were found for the PP population.

Adverse Events:

Of the 495 ITT patients, 228 experienced one or more treatment-emergent adverse events (AEs) during the study. The AEs that occurred in more than 5% of patients per treatment group were dry skin, pruritus, rosacea, and smarting. According to the sponsor, most AEs were mild or moderate in severity. Six patients (5 reference and 1 vehicle) experienced AEs that were classified as serious by FDA definition. Patient 06-102 had blood in the stool, Patient 07-136 had surgery to repair a torn heart valve, Patient 10-189 had an abnormal lung X-ray (i.e., Lung Cancer), Patient 12-228 had open heart surgery, Patient 15-296 had hernia surgery and testicle cyst removal, and Patient 19-380 experienced facial numbness. None were considered related to the study medication. No deaths were reported. According to the sponsor, 20 patients (10 test, 7 reference, and 3 vehicle) discontinued due to adverse events. According to OGD's analysis, 26 patients discontinued the study due to adverse events (11 test, 11 reference, and 4 vehicle). Of the 26 patients, 19 experienced skin related adverse events (9 test, 7 reference, and 3 vehicle). The sponsor reports that skin irritation was similar for all three treatment groups. OGD's analysis shows that 150 patients experienced skin related adverse events (62 test (31%), 56 reference (28.6%), 32 vehicle (32.7%)).

Reviewer's comment: *The test product contains the same active and inactive ingredients as the RLD and in nearly identical amounts.*

V. Formulation

Ingredients	Test (%w/w)	Reference (%w/w)
Metronidazole USP	0.75	0.75
Emylsifying Wax NF	[redacted]	[redacted]
Sorbitol Solution USP		
Glycerin USP		
Isopropyl Palmitate NF		
Benzyl Alcohol NF		
*Lactic Acid USP		
*Sodium Hydroxide NF	pH adjustment	pH adjustment
Purified Water USP	[redacted]	[redacted]

*May also be used for pH adjustment if required.

The regulatory Branch review indicates that all inactive ingredients are acceptable for filling. (vol. 1.1)

Retention Samples

Randomly selected samples of each of the three study medications, including the vehicle-only placebo, sufficient to satisfy regulatory requirements was retained in secure storage on the premises of [redacted] until such time as notification is received from the sponsor that the samples are no longer required.

Reviewer's comments: *The sponsor does not specify when the retention samples were set aside (e.g. prior to dispensing to patients, during dispensing or after all patients were dispensed).*

VI. Review of Division of Scientific Investigation (DSI) report

DSI concluded that the inspected clinical study sites did not meet regulatory requirements regarding bioequivalence testing samples (21 CFR Parts 320.38 and 320.63) and issued deficiencies with Voluntary Action Indicated (VAI). DSI commented that these sites were not aware of their responsibilities to retain reserve samples and they proposed to correct this deficiency in the future.

DSI also commented that these sites failed to maintain the CRFs with the tear-off drug labels, which contained the scatch-off treatment codes, as part of the study records. However, the CRFs were returned to the sites after the FDA investigator announced his intent to inspect the sites. DSI concluded that the integrity of the study data should not be affected by this deficiency.

Lastly, one of the sites ([redacted]), failed to provide contact information in the informed consent form. DSI commented that the investigator proposed to correct this deficiency in the future.

Reviewer's Comments:
Besides the retention sample issues, no major flaws in the study were addressed in the DSI report. Given that DSI noted that these sites were not aware of their responsibilities to retain reserve samples and categorized this deficiency as VAI (voluntary action indicated), the data from this study need not be discarded due to this deficiency. However, it is the sponsor's responsibility to assure that the clinical sites for all future BE studies comply with the requirements for retention of study drugs as per 21 CFR 320.38 and 320.63. If the sponsor fails to comply with the Agency's regulation in any subsequent study, the study may be found unacceptable and a new bioequivalence study may be requested.

VII. Review of the FDA Statistical Report (Dated 5/3/04)

The FDA statistical analyses support the bioequivalence of the test and the reference products. The 90% CI of both the mean percent change from baseline of total lesion count and the rate of cure for the evaluable population (the PP population) at the primary endpoint (visit 5, Day 85) is within -.20 and +.20. The FDA statistical analyses were performed using both +/- 10 days and +/- 4 days visit window for the visit 5 (Day 85). The test and the reference products also demonstrate superiority ($p<0.05$) over Placebo in the MITT population for both the mean percent change from baseline of total lesion count and the rate of cure at visit 5.

The FDA statistician summarized the primary endpoint analyses as follows:

The percent change from baseline of total lesion count at visit 5

Efficacy - FDA's MITT analysis dataset (raw and rank^ values)

	Test vs. placebo			Ref. vs. placebo		
Variable	Test Drug LS Mean	Placebo LS Mean	p-value*	Ref. Drug LS Mean	Placebo LS Mean	p-value*
Raw	55.2	45.5	0.1255	58.7	45.5	0.0251
Rank	n/a	n/a	**0.0076**	n/a	n/a	**0.0018**

*: two-sided p-value from Fisher's Exact Test
^: The percent change from baseline for total lesion count was skewed strongly enough that the assumption of normality of distribution was likely not the most appropriate for these data. The efficacy and equivalence analyses was conducted based on the rank value.

Equivalence - FDA's PP analysis dataset

	Raw				Rank	
Population	Test LS mean	Ref. LS mean	90% Confidence Interval (%)	Pass/Fail	90% Confidence Interval (%)	Pass/Fail
PP	61.2	64.2	85.0, 106.9	Yes	93.3, 105.9	**Yes**
PPw5^	65.2	63.6	90.4, 116.3	Yes	94.5, 111.2	**Yes**

^: FDA's PP population using +/-4 days visit window for Visit 5

The success/cure rate at visit 5

Efficacy and Equivalence - FDA's MITT and PP analyses dataset

Population	Test* % successes (No. of successes/total)	Reference* % successes (No. of successes/total)	Placebo* % successes (No. of successes/total)	p-value# for Test vs. Placebo	p-value# for Reference vs. Placebo	90% Confidence interval for Test vs. Ref. (%)	90% CI is within (-20%, 20%)
MITT	17.7 (34/192)	13.7 (25/183)	4.4 (4/92)	**0.0014**	**0.021**		
PP	18.3 (28/153)	13.7 (21/153)	5.4 (4/74)			-2.9, 12.1	**Yes**
PPw5	20.4 (21/103)	11.3 (11/97)	4.2 (2/48)			-0.4, 18.5	**Yes**

*: The rate of success equals the number of successes divided by the total number, then multiplied by 100.
#: The p-values were from Fisher's exact test (2-sided).

VIII. Conclusion

The data presented in this ANDA demonstrate that Altana Inc.'s Metronidazole Topical Cream USP, 0.75% is bioequivalent to the reference listed drug, Metrocream®. The FDA Statistical review confirms that the 90% CI of the proportional difference in the percent change from baseline of total lesion count and the cure rate between the test and reference products at visit 5 (Day 85) are within (-.20, +.20).

IX. Recommendation

The data submitted to ANDA 76-408, using the primary endpoint of percent change from baseline of total lesion count and cure rate at visit 5 (Day 85) are adequate to demonstrate bioequivalence of Altana Inc.'s Metronidazole Topical Cream USP, 0.75% with the reference listed drug, Metrocream®. This application is recommended for approval from a clinical bioequivalence standpoint.

Sarah Ho, Pharm.D.
Clinical Reviewer
Office of Generic Drugs

5/10/04
Date

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

5/10/04
Date

Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence

5/18/04
Date

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA:76-408 APPLICANT: Altana Inc.

DRUG PRODUCT: Metronidazole Topical Cream, 0.75%

The Division of Bioequivalence has completed its review and has no further questions at this time.

The data submitted to ANDA 76-408, using the primary endpoint of mean percent change from baseline of total lesion count and cure rate at the follow-up visit (day 85), are adequate to demonstrate bioequivalence of Altana Inc.'s Metronidazole Topical Cream, 0.75% with the reference listed drug, Galderman Laboratories, Inc.'s Metrocream®.

It is the sponsor's responsibility to assure that the clinical sites for all future BE studies comply with the requirements for retention of study drugs as per 21 CFR 320.38 and 320.63. If the sponsor fails to comply with the Agency's regulation in any subsequent study, the study may be found unacceptable and a new bioequivalence study may be requested.

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

CC: ANDA 76-408
ANDA DUPLICATE
DIVISION FILE
HFD-651/ Bio Drug File
HFD-600/ S. Ho
HGD-600/ D. Hixon

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Endorsements: (Final with Dates)
HFD-600/S. Ho 5/10/04
HFD-600/D. Hixon 5/10/04
HFD-650/D. Conner 5/18/04

BIOEQUIVALENCY - ACCEPTABLE

submission dates:
May 3, 2002
February 14, 2003
October 15, 2003

1. Bioequivalence Study (STU); May 3, 2002 Strengths: 0.75%
Outcome: AC

2. Study Amendments (STA); February 14, 2003 Strengths: ALL
October 15, 2003 **Outcome: AC**

Outcome Decisions: **AC** - Acceptable
WC - Without charge
IC - Incomplete
UC - Unacceptable

APPEARS THIS WAY ON ORIGINAL

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA # : 76-408 SPONSOR : Altana Inc.

DRUG AND DOSAGE FORM : Metronidazole Topical Cream, 0.75%

STRENGTH(S) : 0.75%

TYPES OF STUDIES : Clinical Endpoint

CLINICAL STUDY SITE(S) : multiple sites in United States

ANALYTICAL SITE(S) : N/A

STUDY SUMMARY: Study is acceptable

DISSOLUTION : N/A

DSI INSPECTION STATUS

Inspection needed: YES / NO	Inspection status: Complete	Inspection results: VAI, acceptable
First Generic _____ New facility __X__ For cause _____ other _____	Inspection requested: (date) 10/31/2003 Inspection completed: (date) 2/27/2004	

PRIMARY REVIEWER: Sarah Ho, Pharm. D.

INITIAL : _____ DATE : 5/10/04

ASSOCIATE DIRECTOR FOR MEDICAL AFFAIRS: Dena R. Hixon, M.D.

INITIAL : Dena R. Hixon MI DATE : 5/10/04

DIRECTOR, DIVISION OF BIOEQUIVALENCE : Dale P. Conner, Pharm. D.

INITIAL : _____ DATE : 5/18/04

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-408

STATISTICAL REVIEW

ANDA 76-408
Drug Product: Metronidazole Topical Cream USP, 0.75%
Sponsor: Altana Inc.
Reference Listed Drug: Metrocream®, Galderma Laboratories, Inc., NDA 20531
Submission date: 5/3/02, 2/14/03, 11/12/03
V:/firmsam/altana/ltrs&rev/76408st.doc

Reviewer: **Huaixiang Li, Ph.D., QMRS/OB/CDER**
Requestor: **Dena Hixon, MD, Sarah Ho, Pharm.D., OGD/CDER, 3/16/04**

Objectives of the study

The primary objective of the study was to establish the bioequivalence of the test product, Altana Inc., Metronidazole topical cream USP, 0.75%, and the reference product, Galderma Laboratories, Inc., Metrocream® cream, and to show superiority of the two active treatments to the placebo, a cream vehicle, in the treatment of rosacea.

Remarks

The sponsor submitted SAS datasets and programs to the Electronic Document Room (EDR), CDER on February 14, 2003. The statistical analyses used information from two datasets: 'dataorig.xpt' and 'datalocf.xpt' contained in the 'primarydata.xpt' file.

The following adjustments to these submitted datasets were made in accordance with recommendations of the FDA medical reviewers and our (medical and statistical reviewers) best judgment.[1]

Exclusion/inclusion from the FDA's Intent-to-treat (FITT)/Per protocol (FPP/FPPw5) populations

1) Four patients,

   01-490 (test group) used a prohibited concomitant medication
   17-610 (reference group) violated exclusion criteria
   06-112 (placebo group) without last visit
   18-350 (reference group) without last visit,

   were excluded from the FITT and FPP populations.

2) Two patients, 13-251 and 13-253, in the test treatment group, who discontinued early due to treatment failure, were included in the FPP population as treatment failures.

[1] Please see the details in the FDA medical reviewer's report and summary table on page 5 of this report. Three patients, 02-431, 11-202, and 11-208, were excluded from the sponsor's PP and the FDA's PP populations due to out of the visit window at visit 5 (85±10 days) based on the further check.

3) The visit window at visit 5, 85±10 days, for the FPP population was narrowed down to 85±4 days for the FPPw5 population.

Re-evaluation/revision of the success/cure rate at visit 5 (Day 85)
Success/cure was re-defined as an Investigator's Global Evaluation (IGE) score of 5 only (completely cleared) at visit 5 (Day 85) instead of the definition of the sponsor – IGE score of 4 or 5 (excellent response or completely cleared).

Study Design

This was a 3 arm parallel double-blind study for patients with signs and symptoms of rosacea. The three creams were the test product, Altana Inc., Metronidazole topical cream USP, 0.75%, the reference product, Galderma Laboratories, Inc., Metrocream® cream, and the placebo, a cream vehicle.

A total of 495 patients were enrolled and randomly assigned to three treatment groups in the study with a ratio of 2:2:1 (test:reference:placebo). At the baseline visit (Day 1), each sign/symptom – erythema, telangiectasis, dryness, pruritus, stinging/burning, edema, was scored as (0=none, 1=mild, 2=moderate, and 3=severe), and the lesion counts – papules and pustules - each were made. For inclusion in the study, the patient had to have a minimum of 6, but no more than 25, total (papules and pustules) lesion count, and moderate or severe erythema (score=2 or 3). The eligible patient was instructed to apply the study cream onto the face twice daily for 84 days. Patients returned for clinical evaluations at visit 2 (Day 22), visit 3 (Day 43), visit 4 (Day 64), and visit 5 (Day 85).

Outcome Variables at Visit 5 (Day 85)

The dual primary efficacy variables at visit 5 were: 1) the percent change from baseline of total (papules and pustules) lesion count, 2) the success/cure rate. As noted above, success/cure has been re-defined as an Investigator's Global Evaluation (IGE) score of 5 only (completely cleared)[2].

Statistical Analysis Methods

Remark for center effect

This study was carried out in eighteen (18) centers with varying numbers of patients per each center. The table below shows the distribution of the numbers of patients in the centers.

[2] One of the entrance criteria required the total (papules and pustules) lesion count to be within (6, 25), but no requirement for either papules or pustules lesion count separately. There were 221 enrolled patients with zero pustules at baseline. Consequently, there was a tremendous amount of variability for the percent change from baseline of the pustules lesion count. In accordance with the FDA medical reviewer comments, the secondary endpoints – the percent changes from baseline of the papules and pustule count (separately) were dismissed in this statistical review.

Center	1	2	3	4	5	6	7	9	10	11	12	13	14	15	16	17	18	19
Test	24	20	9	8	7	19	12	6	10	5	6	16	14	13	6	10	7	8
Ref.	24	20	9	8	7	19	12	6	10	5	6	16	14	12	6	11	6	8
Placebo	12	10	4	4	3	9	6	3	4	2	3	8	8	6	4	5	4	3

Although there was some evidence of a center effect for some of the total lesion count endpoint comparisons, the statistical analyses presented below were performed by pooling all patients across the centers. For the total lesion count percent change from baseline endpoint, the conclusions for efficacy and equivalence are unchanged if a Center effect is included in the statistical model.

The percent change from baseline of total lesion count at visit 5

Efficacy Analysis

All treatment arms should be similar for signs/symptoms scores and lesion counts at the enrollment visit.

The comparisons for the percent change from baseline of total (papules and pustule) lesion count were made between treatment arms at the (two-sided) 5% level of significance. The efficacy analysis for each active treatment was tested separately by comparing with the placebo. The active treatment should be more distinguishable from placebo as the study progresses.

Equivalence Analysis

The compound hypothesis to be tested is:

H_0: $\mu_T/\mu_R < \theta_1$ or $\mu_T/\mu_R > \theta_2$

versus

H_A: $\theta_1 \leq \mu_T/\mu_R \leq \theta_2$

In accordance with the standard in OGD for equivalence analyses for continuous endpoints, α=0.05, θ_1=0.80, and θ_2=1.25. Consequently, for "Raw" (i.e. untransformed) endpoints the 90% confidence interval (corresponding to two 1-sided tests at level α=0.05, as described by Sasabuchi) based on Fieller's method is calculated for the equivalence test. The null hypothesis H_0 is rejected if the 90% confidence interval for μ_T/μ_R is contained in the [0.80, 1.25] interval. Rejection of the null hypothesis H_0 supports the conclusion of equivalence of the two products. Calculation of the 90% confidence intervals, using Fieller's method, was facilitated by using the GLM procedure in SAS®, including the variable treatment only in the model.

Rank Transformation analyses: We found that the percent change from baseline for total lesion count was strongly enough skewed that the assumption of normality of distribution was likely not the most appropriate for these data. We conducted the efficacy and equivalence analyses based on the rank value. The results were obtained from rank

assignment by using the SAS® RANK procedure and the general linear model, containing the variable treatment only, by using the SAS® GLM procedure.

The success/cure rate at visit 5

Efficacy Analysis

The efficacy analyses for the success/cure rate were carried out by using Fisher's exact test. The efficacy analysis for each active treatment was tested separately by comparing with the placebo.

Equivalence Analysis

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

The compound hypothesis to be tested is:

H_0: $p_T - p_R < -.20$

or $p_T - p_R > .20$

versus

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

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

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

$$L = (\hat{p}_T - \hat{p}_R) - 1.645\ se - (1/n_T + 1/n_R)/2$$

$$U = (\hat{p}_T - \hat{p}_R) + 1.645\ se + (1/n_T + 1/n_R)/2$$

We reject H_0 if $L \geq -.20$ and $U \leq .20$

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

Analysis Populations

Two analysis populations were defined in the FDA medical reviewer's report:

Intent-to-treat population (ITT) – All subjects randomized to treatment and treated, with at least one post-baseline visit.
Per protocol population (PP) – All subjects in the ITT population who completed the study and were evaluable for the analyses based on the protocol and FDA medical reviewer's best judgment.

According to best judgment of the FDA medical and statistical reviewers , the determination of clinical equivalence of the two active treatments was to be assessed using the FDA's Per Protocol populations (FPP and FPPw5), while the superiority comparison of the two active treatments to placebo was to be assessed using the FDA's Intent-to-treat population (FITT).

Statistical Analysis Results

A total of 495 patients were enrolled. The FITT population included 467 patients. The FPP included 380 patients. There were 248 patients in the FPPw5 population when using the narrower visit window (85±4 days) at visit 5.

The following table shows the number of patients in each population per treatment arm

	Metronidazole	Metrocream®	Placebo	Total
Enrollment	**200**	**197**	**98**	**495**
Did not return after baseline visit	6	11	5	22
Violated inclusion/exclusion criteria	1	1	0	2
On prohibited medication/did not meet exclusion criteria/did not have 12 weeks data	1	2	1	4
Total exclusion from FDA's ITT population	8	14	6	28
FDA's ITT population	**192**	**183**	**92**	**467**
Sponsor's MITT population	*193*	*185*	*93*	*471*
Did not comply with minimum treatment/ other violation of protocol	18	14	9	41
Missing more than 2 consecutive visits/visit 5	9	5	3	17
Non-compliance	0	4	2	6
Out of visit window (85±10 days) at visit 5	4	5	1	10
Used prohibited medication	8	2	3	13
Total exclusion from FDA's PP population	39	30	18	87
FDA's PP population	**153**	**153**	**74**	**380**
Sponsor's PP population	*152*	*155*	*75*	*382*
FDA's PPw5 population using visit window (85 ± 4 days) at visit 5	103	97	48	248

Demographics and baseline

The mean age was 49.8 years and the age ranged from 20 to 83 years old in the FITT population. The table below shows the sex and race distribution for the FITT population. The age, sex, and race of patients were comparably distributed among the three treatment groups for the FITT and FPP populations.

	Metronidazole	Metrocream®	Placebo	Total
Sex				
Female	130	125	63	318
Male	62	58	29	149
Race				
White	176	167	85	428
Black	0	1	1	2
Hispanic	1	1	2	4
Others	15	14	4	33

An analysis of the frequencies and chi-square tests for homogeneity of signs/symptoms scores and lesion counts for the FITT and FPP populations at the enrollment visit was performed. There were no significant differences between treatment arms for all the signs/symptoms scores and lesion counts for both populations at the enrollment visit except telangiectasis (not essential sign score for the study).

Efficacy and equivalence Analyses

We analyzed the data for efficacy and equivalence for the percent change from baseline of total lesion count and the success/cure rate at visits 5 (Day 85).

The percent change from baseline of total lesion count at visit 5

Table 1.1: Efficacy analysis for the percent change from baseline of total lesion count (raw and rank values) for the FITT population at visit 5

	Test vs. placebo			Ref. vs. placebo		
Variable	Test Drug LS Mean	Placebo LS Mean	p-value	Ref. Drug LS Mean	Placebo LS Mean	p-value
Raw	55.2	45.5	0.1255	58.7	45.5	0.0251
Rank	n/a	n/a	0.0076	n/a	n/a	0.0018

For the percent change from baseline of total lesion count for the FITT population at visit 5, rank value: the test and reference treatments were significantly better than placebo; raw value: the reference treatment was significantly better than placebo, the test treatment was better, but not significantly better than placebo.

Table 1.2: Equivalence Analysis for the percent change from baseline of total lesion count (raw and rank values) for the FPP and FPPw5 populations at visit 5

	Raw				Rank	
Population	Test LS mean	Ref. LS mean	90% Confidence Interval (%)	Pass/Fail	90% Confidence Interval (%)	Pass/Fail
FPP	61.2	64.2	85.0, 106.9	Yes	93.3, 105.9	Yes
FPPw5	65.2	63.6	90.4, 116.3	Yes	94.5, 111.2	Yes

The equivalence test passed for the raw and rank values of the percent change from baseline of total lesion count for the FPP and FPPw5 populations at visit 5.

The success/cure rate at visit 5

Table 2: Efficacy and equivalence analyses for the success/cure rate at visit 5

Population	Test* % successes (No. of successes/total)	Reference* % successes (No. of successes/total)	Placebo* % successes (No. of successes/total)	p-value# for Test vs. Placebo	p-value# for Reference vs. Placebo	90% Confidence interval for Test vs. Ref. (%)	90% CI is within (-20%, 20%)
FITT	17.7 (34/192)	13.7 (25/183)	4.4 (4/92)	0.0014	0.021		
FPP	18.3 (28/153)	13.7 (21/153)	5.4 (4/74)			-2.9, 12.1	Yes
FPPw5	20.4 (21/103)	11.3 (11/97)	4.2 (2/48)			-0.4, 18.5	Yes

*: The rate of success equals the number of successes divided by the total number, then multiplied by 100.
#: The p-values were from Fisher's exact test (2-sided).

The two active treatments were significantly better than placebo ($p \leq 0.021$) for the FITT population and the equivalence test was passed for the FPP and FPPw5 populations for the total success/cure rate at visit 5.

Comments on the Sponsor's Analysis

The analyses using the original datasets were performed for the sponsor's MITT/PP populations and endpoints without adjustment (see Remarks, page 1 of this review). The results were the same as the sponsor's.

The differences between our results and the sponsor's were due to the adjustment to the datasets in accordance with recommendations of the OGD medical reviewer and our (medical and statistical reviewers) best judgment.

Safety

Please see the details in the OGD medical reviewer's report.

Conclusion

The percent change from baseline of total lesion count at visit 5

For the FITT population, rank value: the test and reference treatments were significantly better than placebo; raw value: the reference treatment was significantly better than placebo, the test treatment was better, but not significantly better than placebo.

The equivalence test passed for the raw and rank values for the FPP and FPPw5 populations.

The success/cure rate at visit 5

The two active treatments were significantly better than placebo for the FITT population and the equivalence test was passed for the FPP and FPPw5 populations.

Huaixiang Li 5/3/04

Huaixiang Li, Ph.D.
Mathematical Statistician, QMR

Donald J. Schuirmann 4/30/04

Donald J. Schuirmann
Expert Mathematical Statistician, QMR

Stella G. Machado 4/30/04

Stella G. Machado, Ph.D.
Director, QMR
cc:
HFD-600 Dena R Hixon, Carol Y Kim, Krista Scardina
HFD-705 Stella G. Machado, Donald J. Schuirmann, Huaixiang Li
HFD-705 QMR Chron

APPEARS THIS WAY ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-408

ADMINISTRATIVE DOCUMENTS

76.408 1.1

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE : June 20, 2002

TO : Director
Division of Bioequivalence (HFD-650)

FROM : Chief, Regulatory Support Branch
Office of Generic Drugs (HFD-615) 20-JUN-2002

SUBJECT: Examination of the bioequivalence study with clinical endpoints submitted with an ANDA for Metronidazole Topical Cream, 0.75% to determine if the application is substantially complete for filing.

Altana Inc. has submitted ANDA 76-408 for Metronidazole Topical Cream, 0.75%. The ANDA contains a first generic. In order to accept an ANDA that contains a first generic, the Agency must formally review and make a determination that the application is substantially complete. Included in this review is a determination that the Bioequivalence study is complete, and could establish that the product is bioequivalent.

Please evaluate whether the bioequivalence study with clinical endpoints submitted by Altana on May 3, 2002 for its Metronidazole product satisfies the statutory requirements of "completeness" so that the ANDA may be filed.

A "complete" bioavailability or bioequivalence study is defined as one that conforms with an appropriate FDA guidance or is reasonable in design and purports to demonstrate that the proposed drug is bioequivalent to the "listed drug".

In determining whether a bio study is "complete" to satisfy statutory requirements, the following items are examined:

1. Study design

   (a) Appropriate number of subjects
   (b) Description of methodology

2. Study results

   (a) Individual and mean data is provided
   (b) Individual demographic data
   (c) Clinical summary

The issue raised in the current situation revolves around whether the study can purport to demonstrate bioequivalence to the listed drug.

We would appreciate a cursory review and your answers to the above questions as soon as possible so we may take action on this application.

DIVISION OF BIOEQUIVALENCE:

✓ Study meets statutory requirements (clinical end point study)

_____ Study does **NOT** meet statutory requirements

Reason:

_____ Waiver meets statutory requirements

_____ Waiver does **NOT** meet statutory requirements

Reason:

CONCUR:

7/2/2002

Director, Division of Bioequivalence

7/3/02
Date

BIOEQUIVALENCE CHECKLIST FOR APPLICATION COMPLETENESS
First Generic ANDA

ANDA# 76-408 FIRM NAME Altana

DRUG NAME Metronidazole, 0.75%

DOSAGE FORM Topical Cream

Requested by: _____
Chief, Regulatory Support Team, (HFD-615)

Summary of Findings by Division of Bioequivalence

☑ **Study meets statutory requirements**

☐ **Study does NOT meet statutory requirements**
Reason:

☐ **Waiver meets statutory requirements**

☐ **Waiver does NOT meet statutory requirements**
Reason:

RECOMMENDATION: ✓ COMPLETE ___ INCOMPLETE

Reviewed by:

PRADEEP SATHE, Sathe Date: 6/27/02
Reviewer

Team Leader Date: 7/2/2002

Director, Division of Bioequivalence Date: 7/8/02

Item Verified:	Yes	No	Required Amount	Amount Sent	Comments
Protocol	✓				
Assay Methodology					
Procedure SOP	✓				
Methods Validation					
Study Results Ln/Lin					
Adverse Events	✓				
IRB Approval	✓				
Dissolution Data					
Pre-screening of Patients	✓				
Chromatograms	✓				
Consent Forms	✓				
Composition	✓				
Summary of Study	✓				
Individual Data & Graphs, Linear & Ln					
PK/PD Data Disk (or Elec Subm)					
Randomization Schedule					
Protocol Deviations					
Clinical Site	✓				
Analytical Site	✓				
Study Investigators	✓				
Medical Records	✓				
Clinical Raw Data	✓				
Test Article Inventory	✓				

BIO Batch Size	✓				
Assay of Active Content Drug	✓				
Content Uniformity	✓				
Date of Manufacture	✓				
Exp. Date of RLD	✓				
BioStudy Lot Numbers	✓				
Statistics	✓				
Summary results provided by the firm indicate studies pass BE criteria					
Waiver requests for other strengths / supporting data		✓			

Additional Comments regarding the ANDA:

The firm has conducted a multi-center, double-blind, randomized, vehicle controlled, parallel group, clinical end point study to determine therapeutic equivalence of two metronidazole 0.75% topical cream formulations. The study was conducted in patients for the treatment of rosacea.

OGD APPROVAL ROUTING SUMMARY

ANDA # 76-408 **Applicant: Altana, Inc.**
Drug: Metronidazole Topical Cream **Strength(s): 0.75%**

PROVAL ■ TENTATIVE APPROVAL ☐ SUPPLEMENTAL APPROVAL (NEW STRENGTH) ☐ OTHER ☐

REVIEWER:	DRAFT Package	FINAL Package
1. Martin Shimer Chief, Reg. Support Branch	Date 3 May 2004 Initials MS	Date 5/28/04 Initials

Contains GDEA certification: Yes ☑ No ☐ (required if sub after 6/1/92)
Determ. of Involvement? Yes ☐ No ☒
Pediatric Exclusivity System
RLD = NDA# 20831
Patent/Exclusivity Certification: Yes ☑ No ☐
Date Checked 5/28/04
If Para. IV Certification- did applicant Nothing Submitted ☒
Notify patent holder/NDA holder Yes ☐ No ☐ Written request issued ☐
Was applicant sued w/in 45 days: Yes ☐ No ☐ Study Submitted ☐
Has case been settled: Yes ☐ No ☐ Date settled:
Is applicant eligible for 180 day
Generic Drugs Exclusivity for each strength: Yes ☐ No ☐
Type of Letter:
Comments: No patents/exclusivities ∴ eligible for FA MS

2. Project Manager, **Wanda Pamphile** Team 5 Review Support Branch	Date 5-1-04 Initials WP	Date 5-19-04 Initials WP

Original Rec'd date 5-3-02
Date Acceptable for Filing 5-7-02 ✓
Patent Certification (type) II
Date Patent/Exclus.expires NA
Citizens' Petition/Legal Case Yes ☐ No ☒
(If YES, attach email from PM to CP coord)
First Generic Yes ☒ No ☐
Acceptable Bio reviews tabbed Yes ☒ No ☐
Suitability Petition/Pediatric Waiver
Pediatric Waiver Request Accepted ☐ Rejected ☐ Pending ☐

EER Status Pending ☐ Acceptable ☒ OAI ☐
Date of EER Status 6-25-03
Date of Office Bio Review 5-18-04
Date of Labeling Approv. Sum 5-16-03
Date of Sterility Assur. App. N/A
Methods Val. Samples Pending Yes ☐ No ☐
MV Commitment Rcd. from Firm Yes ☒ No ☐ 2/3/04
Modified-release dosage form: Yes ☐ No ☒
Interim Dissol. Specs in AP Ltr: Yes ☐

Previously reviewed and tentatively approved ☐ Date
Previously reviewed and CGMP def. /NA Minor issued ☐ Date
Comments:

3. David Read **(PP IVs Only)** Pre-MMA Language included ☐ OGD Regulatory Counsel, Post-MMA Language Included ☐ Comments: N/A.		Date Initials

4. Div. Dir./Deputy Dir. Chemistry Div. I II OR III Comments: CMC is OK		Date 5/26/04 Initials RS

REVIEWER: **FINAL ACTION**

5. Frank Holcombe **First Generics Only** Date 5/26/04
Assoc. Dir. For Chemistry Initials
Comments: (First generic drug review) SATISFACTORY

6. Vacant RLD = HetroCream 0.75% Topical Cream Date
Deputy Dir., DLPS Initials
Galderma Laboratories LP NDA 20-531

7. Peter Rickman Date 5/28/04 for
Director, DLPS Initials
Para.IV Patent Cert: Yes ☐ No ☐; Pending Legal Action: Yes ☐ No ☐; Petition: Yes ☐ No ☐
Comments: Acceptable GES dtd 6/25/03 (Verified 5/28/04). No OAI labels noted. PP found acceptable 5/16/03. CMC found acceptable 5/18/04. Methods validation will not be requested - does not meet current criteria. Bioequivalence study (limited-confirmatory with clinical endpoint) found acceptable 5/18/04. DSI inspectional comments have been addressed. Statistical review also finds data to be acceptable. Office-level bio endorsed 5/18/04. First-generic CMC audit has been completed.

8. Robert L. West Date 5/28/2004
Deputy Director, OGD Initials
Para.IV Patent Cert: Yes ☐ No ☒; Pending Legal Action: Yes ☐ No ☒; Petition: Yes ☐ No ☐
Comments: there are no unexpired patents or exclusivity listed in the current Orange Book for this drug product.

This ANDA is recommended for approval.

9. Gary Buehler Date 5/28/04
Director, OGD Initials GB
Comments:
First Generic Approval ☒ PD or Clinical for BE ☒ Special Scientific or Reg.Issue ☐

10. Project Manager, **Wanda Pamphile**
Team 5
Review Support Branch Date 5/28/04
N/A Date PETS checked for first generic drug (just prior to notification to firm) Initials WP
Applicant notification:
9:55 Time notified of approval by phone 10:03 Time approval letter faxed
FDA Notification:
5/28 Date e-mail message sent to "CDER-OGDAPPROVALS" distribution list.
5/28 Date Approval letter copied to \\CDS014\DRUGAPP\ directory.

File V:/division/dlps/approvrou8.doc

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-408

CORRESPONDENCE

ALTANA

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

May 3, 2002 *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

505(j)(2)(A) OK
02-JUL-2002
Gregory S. Davis

Original Submission
Abbreviated New Drug Application
Metronidazole Topical Cream, 0.75%

Dear Sir or Madam:
Pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act and in accordance with the provisions under 21 CFR §314.94, Altana Inc. is submitting this Abbreviated New Drug Application to market a new drug, **Metronidazole Topical Cream, 0.75%**.

The Reference Listed Drug (RLD) that is the basis for this submission is **MetroCream™ (metronidazole) topical cream 0.75%** manufactured by Galderma Laboratories, Inc., NDA 20-531. The proposed drug, Metronidazole Topical Cream, 0.75% contains the same active ingredient and is identical in strength, dosage form and route of administration to the RLD. All inactive ingredient amounts conform to the ranges as listed in the Inactive Ingredient Guide (January 1996).

The exhibit batch, Batch #E906, included in this application was fully packaged utilizing the 45 gram presentation for which approval is currently requested. The number of units filled for this 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 356, is the required Patent Status 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; Container/Closure System; controls for the Finished Dosage Form, Analytical Methods; Stability of the Finished Dosage Form; Environmental Assessment and Certification Requirements of the Generic Drug Enforcement Act of 1992.

All regulatory correspondence related to this Abbreviated New Drug Application should be addressed to the following:

Ms. Audrey Bialeski
Manager, Regulatory Affairs
Altana, Inc.
60 Baylis Road
Melville, NY 11747
Telephone: (631) 454-7677 X 3007
Facsimile: (631) 756-5114

A certified copy of the technical section and a copy of the Methods Validation package, are being sent to the New York District Office under separate cover.

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

Sincerely,
ALTANA INC.

for Audrey Bialeski

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

RJA/ap

Enclosures

TELEFAX DATED: June 26, 2002

ALTANA

Altana Inc. 60 Baylis Road, Melville, NY 11747 631-454-7677 Fax: 631-756-5114

BYK GULDEN PHARMA GROUP

TO: Paras Patel FAX NO: 301-594-1174

FROM: Jacqueline Bazata

OF PAGES (including this page): 4

ANDA 76-408
Metronidazole Topical Cream, 0.75%
Telephone Amendment

NC
NEW CORRESP

Dear Mr. Patel:

As requested, enclosed is the cGMP Certification for the Altana Inc. Hicksville facility. We have also included a Form FDA 356h. A hard copy of this submission will be sent via Federal Express.

If you have any questions or require additional information, please contact me at (631) 454-7677 extension 3007. Fax communications can be made to (631) 756-5114.

Sincerely,

ALTANA INC.

Audrey Bialeski for

Audrey Bialeski
Manager, Regulatory Affairs

ANDA 76-408

Altana Inc.
Attention: Robert J. Anderson
60 Baylis Road
Melville, NY 11747

JUL 8 2002

Dear Sir:

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

Reference is made to the telephone conversation dated June 26, 2002 and to your correspondence dated June 26, 2002.

NAME OF DRUG: Metronidazole Cream, 0.75%

DATE OF APPLICATION: May 3, 2002

DATE (RECEIVED) ACCEPTABLE FOR FILING: May 7, 2002

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:

Tim Ames
Project Manager
(301) 827-5848

Sincerely yours,

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

ANDA 76-408
cc: DUP/Jacket
Division File
Field Copy
HFD-610/R.West
HFD-610/P.Rickman
HFD-92
HFD-615/M.Bennett
HFD-600/
Endorsement:
HFD-615/GDavis,Chief, RSB Davis 02-JUL-2002 date
HFD-615/PPatel,CSO Patel date 7/2/02
Word File V:\Firmsam\Altana\ltrs&rev\76408.ACK
F/T EEH 07/02/02
ANDA Acknowledgment Letter!

APPEARS THIS WAY
ON ORIGINAL

*2.1

Pharma

ALTANA

9/23/02

NEW CORRESP
NC

BIOAVAILABILITY

ALTANA Inc
60 Baylis Road
Melville, NY 11747
USA
T +1 (631) 454-7677
www.altanainc.com

September 18, 2002

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

VIA FEDERAL EXPRESS

ANDA 76-408
METRONIDAZOLE CREAM, 0.75%
NEW CORRESPONDENCE BIOEQUIVALENCE

Dear Sir or Madam:

Reference is made to the Altana Inc. Abbreviated New Drug Application dated May 3, 2002, submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act for Metronidazole Cream, 0.75% and accepted for filing on May 7, 2002.

Altana Inc. is hereby submitting the data diskettes for the bioequivalence study conducted to support the ANDA 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 communication may be made to (631) 756-5114.

Sincerely,

ALTANA INC.

for Audrey Bialeski

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

RJA:tw

Enc.

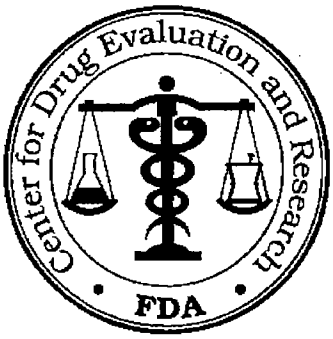
RECEIVED
SEP 19 2002
OGD / CDER

MINOR AMENDMENT

ANDA 76-408

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

OCT 24 2002



TO: APPLICANT: Altana Inc. TEL: 631-454-7677 ext. 2085

ATTN: Robert J. Anderson, Esq. FAX: 631-756-5114

FROM: Wanda Pamphile PROJECT MANAGER: 301-827-5848

Dear Sir:

This facsimile is in reference to your abbreviated new drug application dated May 3, 2002, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Metronidazole Topical Cream, 0.75%.

The application is deficient and, therefore, Not Approvable under Section 505 of the Act for the reasons provided in the attachments (3 pages). This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all of the deficiencies listed. Facsimiles or partial replies will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this facsimile will be considered to represent a MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. The designation as a MINOR AMENDMENT should appear prominently in your cover letter. You have been/will be notified in a separate communication from our Division of Bioequivalence of any deficiencies identified during our review of your bioequivalence data. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

SPECIAL INSTRUCTIONS:
Chemistry comments included.

WP 10/24/02

Redacted 2 page(s)

of trade secret and/or

confidential commercial

information from

10/24/2002 FDA FAX

c. [redacted]

d.

e.

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

1. We require an acceptable Methods Validation to support the ANDA and will schedule the study after all testing issues are resolved. Please 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.

2. Please submit accrued stability data.

3. All facilities referenced in the ANDA should have a satisfactory compliance evaluation at the time of approval. We have requested an evaluation from the Office of Compliance.

4. The bioequivalence portion of the submission is pending review. Deficiencies, if any will be communicated separately.

5. The labeling portion of the submission is pending review. Deficiencies, if any will be communicated separately.

Sincerely yours,

Paul Schwartz

Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

Pharma

ALTANA

February 3, 2003

ORIG AMENDMENT
N/AM

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www.altanainc.com

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

VIA FEDERAL EXPRESS

ANDA 76-408
Metronidazole Topical Cream, 0.75%
MINOR AMENDMENT

Dear Sir or Madam:

Reference is made to the Abbreviated New Drug Application dated May 3, 2002 submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act and in accordance with the provisions under 21 CFR §314.94 for Metronidazole Topical Cream, 0.75%.

Reference is also made to the FDA correspondence dated October 24, 2002 that included 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. [redacted]

RECEIVED
FEB 04 2003
OGD / CDER

2/3/03

Redacted 4 page(s)

of trade secret and/or

confidential commercial

information from

2/3/2003 ALTANA LETTER

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

1. **We require an acceptable Methods Validation to support the ANDA and will schedule the study after all testing issues are resolved. Please provide a commitment to work with us expeditiously to resolve any deficiencies from the Methods Validation study if the ANDA is approved prior to its completion.**

   Altana commits to work with FDA to respond to the request for Methods Validation Samples and work expeditiously to resolve any deficiencies from the Methods Validation Study.

2. **Please submit accrued stability data.**

   Altana has submitted updated Controlled Room Temperature Stability Data. See **Attachment XIII.**

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

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

4. **The bioequivalence portion of the submission is pending review. Deficiencies, if any will be communicated separately.**

   Altana acknowledges the bioequivalence portion of the submission is pending review and deficiencies, if any will be communicated separately.

5. **The labeling portion of the submission is pending review. Deficiencies, if any will be communicated separately.**

   Altana acknowledges the labeling portion of the submission is pending review and deficiencies, if any will be communicated separately.

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

Sincerely,

ALTANA INC. for

Audrey Zaweski

Robert J. Anderson. Esq.
Senior Director, Scientific Affairs
RJA/jb

Pharma

ALTANA

February 14, 2003

Dale Conner, Pharm.D.
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

N/AB

ALTANA Inc
60 Baylis Road
Melville, NY 11747
USA
T +1 (631) 454-7677
www.altanainc.com

VIA FEDERAL EXPRESS

ANDA 76-408
Metronidazole Topical Cream, 0.75%
BIOEQUIVALENCE AMENDMENT

Dear Dr. Conner:

Reference is made to the Abbreviated New Drug Application dated May 3, 2002 submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act and in accordance with the provisions under 21 CFR §314.94 for Metronidazole Topical Cream, 0.75%.

This Amendment contains a re-organization of the clinical study data analysis used to support the bioequivalence of the Altana product. The data analysis was re-organized in accordance with recommendations Altana has received from the Division of Bioequivalence for several other ANDA submissions. This information is provided in an effort to better facilitate the review of the application.

Altana requests that the Division of Bioequivalence conduct its review of the bioequivalence of the Metronidazole Topical Cream using the clinical study report and associated data files contained in this submission.

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

Sincerely,

ALTANA INC.

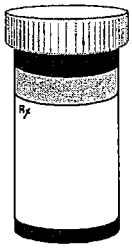
Audrey Zaweski for

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

RJA/cd

RECEIVED
FEB 21 2003
OGD / CDER

Fax Cover Sheet



Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Generic Drugs
Rockville, Maryland

To: Robert J. Anderson, Esq.
Altana Inc.
Fax: 631-756-5114 **Phone:** 631-454-7677 x2085

From: Ruby Wu
Fax: 301-443-3847 **Phone:** 301-827-5846

Number of Pages (including cover sheet): 2 **Date:** April 30, 2003

Comments:

Labeling comments provided for ANDA 76-408 for Metronidazole Cream, 0.75%.

When you send your amendment, please send a courtesy desk copy to my attention (please clearly identify it as DESK COPY FOR LABELING REVIEWER on the cover sheet).

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

ANDA Number:	76-408
Date of Submission:	May 3, 2002 (Original Submission)
Applicant's Name:	Altana Inc.
Established Name:	Metronidazole Cream, 0.75%

Labeling Deficiencies:

1. **CONTAINER** – 45 gram tubes
   Storage Recommendation: Add "(See USP)"

2. **CARTON** – (1 x 45 g tube)
   A. TO OPEN statement: "...reverse the cap..." ["the" instead of "he"]
   B. Add "Rx Only" to the main panel
   C. Refer to comment 1.

3. **INSERT** –
   A. DESCRIPTION, chemical name: Revise to read "...2-Methyl-5-nitroimidazole-1-ethanol."
   B. HOW SUPPLIED: See Comment 1

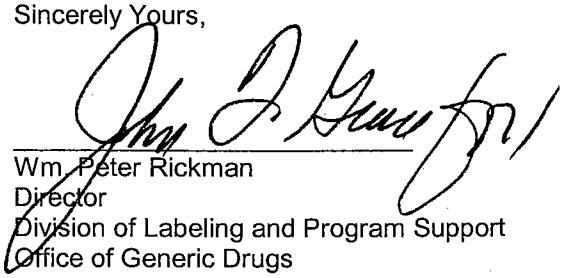
Please revise your labels and labeling, then prepare and submit 12 copies of final print.

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address -

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.

Sincerely Yours,



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

Pharma

ALTANA

May 7, 2003

ALTANA Inc
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www.altanainc.com

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

VIA FEDERAL EXPRESS

ANDA 76-408
Metronidazole Topical Cream, 0.75%
LABELING AMENDMENT

ORIG AMENDMENT
N/AA

Dear Sir or Madam:

Reference is made to the Abbreviated New Drug Application dated May 3, 2002 submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act and in accordance with the provisions under 21 CFR §314.94 for Metronidazole Topical Cream, 0.75%.

Reference is also made to the FDA correspondence dated April 30, 2003 that included Labeling comments. This correspondence is designated as a **LABELING AMENDMENT** and appears prominently in this cover letter.

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

Labeling

Deficiencies:

1. **CONTAINER – 45 gram tubes**

   Storage Recommendation: Add "(See USP)"

   Altana Inc. has revised the 45 gram tube label to add "(See USP)" after the storage recommendation.

2. **CARTON – (1 x 45 g tube)**

   A. TO OPEN statement: "...reverse the cap..." ["the" instead of "he"]

   Altana Inc. has revised the TO OPEN statement: "...reverse the cap..." ["the" instead of "he"].

B. Add "Rx Only" to the main panel

Altana Inc. has added "Rx Only" to the main panel.

C. Refer to comment 1

Altana Inc. has revised the carton labeling to add "(See USP)" after the storage recommendation.

3. **INSERT –**

A. DESCRIPTION, chemical name: Revise to read "...2-Methyl-5-nitroimidazole-1-ethanol."

Altana Inc. has revised the chemical name in the DESCRIPTION section to read "...2-Methyl-5-nitroimidazole-1-ethanol."

B. HOW SUPPLIED: See Comment 1

Altana Inc. has revised the insert labeling to add "(See USP)" after the storage recommendation.

Please revise your labels and labeling, then prepare and submit 12 copies of final print.

Altana Inc. has revised the labels and labeling as instructed and 12 copies of final printed labeling are included in **Attachment I.**

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address –

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

Altana Inc. acknowledges that prior to approval, it may be necessary to revise the labeling subsequent to approved changes for the reference listed drug. In order to keep ANDA labeling current, Altana has subscribed to the daily updates of new documents posted on the CDER web site at the following address.

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.

To facilitate review of this submission, and in accordance with 21 CFR 314.94(a)(8)(iv), a side-by-side comparison has been provided of the proposed labeling with the last submission with all differences annotated and explained. The side–by-side comparisons are included in **Attachment II.**

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

Sincerely,

ALTANA INC.

Audrey Zaweski for

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

RJA/jb

Pharma

ALTANA

October 15, 2003

ORIG AMENDMENT
NIAM

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www.altanainc.com

Sarah Ho
Senior Project Manager
Division of Labeling and Program Support
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

VIA FEDERAL EXPRESS

ANDA 76-408
Metronidazole Topical Cream, 0.75%
TELEPHONE AMENDMENT

Dear Ms. Ho:

Reference is made to the Abbreviated New Drug Application dated May 3, 2002 submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act for Metronidazole Topical Cream, 0.75%.

Reference is also made to the October 14th FDA telephone request that Altana Inc. submit a second copy of the bioequivalence study data disk. A CD containing all of the bioequivalence study data files has been provided with this submission, as requested.

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

Sincerely,

ALTANA INC.

Audrey Zaweski for

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

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RJA/az

Pharma

ALTANA

November 12, 2003

ORIG AMENDMENT
HFD/AP3

NEW CORRESP
NC

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Office of Generic Drugs (HFD-600)
Center for Drug Evaluation and Research
Food and Drug Administration
7500 Standish Place, Room 150
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VIA FEDERAL EXPRESS

ANDA 76-408
Metronidozole Topical Cream, 0.75%
BIOEQUIVALENCE AMENDEMNT – RESUBMISSION OF ELECTRONIC FILES

Dear Sir or Madam:

Reference is made to the Abbreviated New Drug Dated Application dated May 3, 2002 submitted pursuant to Section 505 (j) of the Federal Food, Drug and Cosmetic Act for Metronidozole Topical Cream, 0.75%. Reference is also made to the Altana Amendment dated October 15, 2003, which contained a re-organization of the clinical study data analysis used to support the bioequivalence of the Altana product.

On October 24, 2003 Altana received correspondence from the FDA's Electronic Document Room indicating that some of the data files included in the October 15, 2003 Amendment were submitted in non-archival format. Altana has subsequently re-formatted the data files affected and prepared a new CD-rom for inclusion in the October 15, 2003 Amendment. Altana respectfully requests that the FDA destroy the previously submitted CD-rom.

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

Sincerely

ALTANA INC.

Audrey Zaweski for

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

RJA:ic

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Enclosure

Pharma

ALTANA

March 11, 2004

ALTANA Inc
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Gary Buehler
Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North I
7520 Standish Place
Rockville, Maryland 20855

NEW CORRESP

NC

VIA TELEFAX AND
FEDERAL EXPRESS

NAT 3/23/04
This should be an NC.

ANDA 76-408
Metronidazole Cream
Application Review

Dear Mr. Buehler:

Reference is made to the Altana Inc. Abbreviated New Drug Application for Metronidazole Cream submitted on May 15, 2002 pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act.

FDA Action Requested

Altana requests that the FDA immediately approve its Abbreviated New Drug Application for Metronidazole Cream. Altana has met the requirements of Section 505(j) having submitted an application for a drug product that is qualitatively and quantitatively the same as the Reference Listed Drug. The Altana product is identical in its strength, labeling and indications for use. Altana has also submitted a bioequivalence study that demonstrates the proposed drug is bioequivalent to the Reference Listed Drug.

Application History

The application was submitted on May 15, 2002. The CMC and labeling reviews were completed and found to be acceptable in July 2003. FDA informed Altana that the review of the bioequivalence study was not conducted in parallel but was initiated after a delay of more than one year pending completion of the CMC and labeling reviews.

In July 2003 the Division of Bioequivalence assured Altana that this application was a high priority review. In spite of its "high priority" review status and the Division's estimated average two-week review period for clinical endpoint studies, the clinical review has still not been completed.

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FDA Action Requested

The Reference Listed Drug, MetroCream®, has been off patent for more than two years with no generic competition to reduce healthcare costs for the American public. FDA seems to be unreasonably delaying the approval of Altana's application to allow same-day approval for multiple applications. Feedback from Altana's customers indicates that two other applicants are expecting imminent approval.

Altana's Abbreviated New Drug Application for Metronidazole Cream has satisfied the requirements of Section 505(j). Altana requests that FDA approve this application without further delay.

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

Sincerely,

ALTANA INC.

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

RJA/az

ORIGINAL

Pharma

ALTANA

May 3, 2004

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VIA FACSIMILE (301) 594-0180 AND FEDERAL EXPRESS

ANDA 76-408
Metronidazole Topical Cream USP, 0.75%
Telephone Amendment - Request for Information
Withdrawal of Proposed Contract Testing Laboratories

Dear Dr. Patel:

Reference is made to the Altana Inc. Abbreviated New Drug Application submitted on May 3, 2002 pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act for Metronidazole Topical Cream USP, 0.75%.

Reference is also made to the May 1, 2004 FDA telephone request for information regarding the use of _____ as a contract laboratory.

Withdrawal of Proposed Contract Testing Laboratories

Altana Inc. is submitting this Telephone Amendment to withdraw the following contract laboratories listed in Section 10 of the original Abbreviated New Drug Application. These proposed laboratories were not used for any testing in support of this ANDA.

[redacted]

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

Sincerely,
ALTANA INC.

Audrey Zaweski for/
Robert J. Anderson, Esq.
Sr. Director, Scientific Affairs

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