CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-502

Bioequivalence Review(s)

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANTS

ANDA: 75-502 APPLICANT: Altana, Inc.

DRUG PRODUCT: Clotrimazole/Betamethasone Dipropionate Cream, USP, 1%/0.05%

The Division of Bioequivalence has completed its review of your submission(s) acknowledged on the cover sheet and has no further questions at this time.

Please also 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 regulatory reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation in not approvable.

Sincerely yours,

for

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

31

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

Clotrimazole/Betamethasone Dipropionate Cream, USP 1%/0.05%
ANDA #75-502
Reviewer: James E. Chaney
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Altana, Inc.
Melville, N.Y.
Submission Date
November 29, 2000
February 16, 2001

Review of a Pilot Dose Response Study, a Pivotal Pharmacodynamic and a Bioequivalence Study

I. Introduction

Altana, Inc. is seeking approval to market its clotrimazole/betamethasone dipropionate cream 1%/0.05%, and has submitted pilot dose-response and pivotal in vivo bioequivalence vasoconstriction studies for the corticosteroid component, and a clinical study to establish bioequivalence of this product. The clinical study was previously reviewed and found acceptable by the Medical Officer, Office of Generic Drugs (Attachment 1).

Type of Submission: Original ANDA

NOTE: The amendment dated February 16, 2001 provides the expiration date of the RLD which was requested by the Division of Bioequivalence on February 13, 2001. This information had been omitted from the original submission, wherein reference was merely made to the crimp for the expiration date. The crimp was not available to the reviewer.

Reference Listed Drug: Lotrisone® (NDA #18-827 approved July 10, 1984, manufactured by Schering/Key Pharm.)

II. Background

Clotrimazole and Betamethasone Dipropionate Cream, USP contains a combination of clotrimazole, USP, a synthetic antifungal agent, and betamethasone dipropionate, USP, a synthetic corticosteroid, for dermatologic use. The cream is indicated for the topical treatment of the following dermal infections: tinea pedis, tinea cruris, and tinea corporis.

III. Pilot Study – Dose-Response Study of Clotrimazole/ Betamethasone Dipropionate Topical Creams (Vasoconstrictor Assay: Study No. 97-263-001-L01)

A. Objective:

To estimate the ED50 of the vasoconstrictive dose-response relationship for topical Clotrimazole/Betamethasone Dipropionate (Lotrisone® Cream, 1%/0.05%).

B. Study Information:

Clinical Site: ClinSites/LeeCoast Research Center, Inc., Fort Myers, FL
Principal Investigator: Barrie M. Phillips, Ph.D.
Clinical Dates: September 12-13, 1997
Subjects: *Entered*: 15 normal healthy Caucasian female subjects between 18 and 49 years of age.
Completed: 15

Inclusion/Exclusion Criteria: Listed in Vol. 1.2, pp. 539-540.

Product information:

Drug Treatment:	Lotrisone® Cream (Clotrimazole/ Betamethasone Dipropionate, 1%/0.05%)
Manufacturer:	Schering/Key Pharm.
Lot No.:	#6NBN106
Expiration Date:	5/98

Study Design: One period, randomized, vasoconstrictor study.

Application and Removal:

The sponsor followed staggered application and synchronized removal methodology in this study as described in the guidance.

Eight circular (approximately diameter) application sites were designated on the flexor surface of each forearm between the wrist and the elbow. After duplicate baseline chromameter and visual readings, an open washer was positioned over each pre-designated site and taped to the forearm using hypo-allergenic paper tape on the sides of the washer so that the treated area was not occluded. Using a 250 µL glass Hamilton syringe, application of the study drug was applied to the assigned sites on each arm at times according to the randomization schedule (Vol. 1.2, p. 615). The applied cream was spread evenly over the skin surface at each site with the conical tip of a 1.5-mL microcentrifuge tube.

Baseline assessments were started approximately two hours prior to the first scheduled application. Lotrisone® cream was applied to seven sites on each arm. The treatments were applied at 180, 120, 80, 50, 30, 20, and 10 minutes prior to removal.

The washers were detached and the residual surface treatment was removed by gently wiping several times with a cotton ball. The untreated site on each arm was similarly wiped with a clean cotton ball. Time zero was the time of drug product removal.

Confinement/Restrictions: Described on page 518, Vol. 1.2.

Dermal Assessment:

Chromameter operators and visual evaluators assessed the degree of blanching response at each site prior to treatment and at 2, 4, 6, 8, 10, 12, 20, and 24 hours after removal. The chromameter operators and visual evaluators were blinded as to the duration of application at each site. Chromameter assessments were based on the a-scale response. visual scoring used the following rating scale:

0 = No pallor; no change from surrounding area.
1 = Mild pallor; slight or indistinct outline of application site.
2 = Moderate pallor; discernable outline of application site.
3 = Intense pallor; clean, distinct outline of application site.

Data Evaluation:

The post-dose chromameter a-scale reading at each site and assessment time was first adjusted by subtracting the average value of the duplicate pre-dose (baseline) readings at the site. This baseline adjustment normalized the chromameter readings for variations in skin tone between the different sites on each subject's forearms. To compensate for skin tone changes that occur over time, the baseline-adjusted value for the untreated site

on each arm was subtracted from the baseline-adjusted chromameter value for each site on the same arm at each assessment time. These corrected baseline-adjusted chromameter values were used in all subsequent analysis.

The sponsor has calculated chromameter areas-under-the-effect curve (AUEC) from 0-24 hours from the corrected, baseline-adjusted readings by the linear trapezoidal method.

The AUEC for the visual assessments were determined directly from the raw blanching scores.

C. Study Results

Protocol Deviations: Subject #3 took acetaminophen on two occasions on 9/13/97. These deviations were considered not to have an impact on the outcome of the study.

Adverse Events: A total of five mild adverse events were reported for three subjects (including headaches, neck ache, nausea and injured finger). There was one headache of moderate severity. (Vol. 2, p 526)

Precision of Chromameter (Method Validation):
The precision of the chromameter operators were evaluated from replicate evaluations (five readings, at least 30 minutes apart) at four untreated skin sites on each arm of four different subjects. The between-site CV was less than 15% and the within-site CV was less than 10% (pp 707-722 of Vol. 2).

Pharmacodynamic Data Analysis:
Estimates by the firm of ED50 (duration at which half-maximal response occurs) and Emax (maximum vasoconstrictive response) were obtained by population fit of the results from chromameter and visual data using the P-Pharm program. (See Attachment 2 for the plot of the chromameter results).

The Division of Bioequivalence analyzed the AUEC vs. dose duration data based on the non-linear mixed effect modeling method using P-Pharm. (See Attachment 3 for the firm's presentation).

The firm's and the Division's estimated Emax and ED50 parameters for Lotrisone® Cream (clotrimazole/betamethasone Dipropionate, 1%/0.05%) using nonlinear mixed effect modeling are:

	Firm's Estimation	Division's Estimation
Emax	-26.942	-26.925
ED50	49.67	49.58

D. Conclusion:

The estimated value of ED50 reported by the firm from the chromameter results was 50 minutes. The estimated value of ED50 reported by the firm from its visual results was 82 minutes. Based on the pilot study results, the sponsor chose a dose-duration of 60 minutes for the pivotal bioequivalence study. The Division of Bioequivalence has previously accepted pilot studies on betamethasone dipropionate with ED50 values greater than 60 minutes.

E. Comment:

The ED50 duration (60 min) and the use of D1 (30 min) and D2 (120 min) are acceptable.

IV. Pivotal Study: Bioequivalence of Clotrimazole/Betamethasone Dipropionate Cream, (Study No. 97-263-001-L01)

A. Objective

To demonstrate *in vivo* bioequivalence of the corticosteroid component between Altana, Inc.'s clotrimazole/betamethasone dipropionate cream, 1%/0.05% and Schering/Key's Lotrisone® Cream, 1%/0.05%.

B. Study Information

Clinical Site: ClinSites/LeeCoast Research Center, Inc., Fort Myers, FL
Principal Investigator: Barrie M. Phillips, Ph.D.
Dosing Dates:

Group 1: November 1, 1997 (Subject # 01-20)
Group 2: November 8, 1997 (Subject # 21-40)
Group 3: December 15, 1997 (Subject # 41-60)
(Vol.1.1, p. 12)

Subjects: 60 normal healthy female subjects between 18 and 41 years of age.

Inclusion/Exclusion Criteria: Same as given for the pilot study (Vol. 1.1, pages 29-30).

Product Information: The following drug products were used in this study:
Test: Clotrimazole/betamethasone dipropionate 1%/0.05%, topical cream, Altana, Inc., Lot # 8077; Batch Size Maximum production batch is kg.
Reference: Same as that used in the pilot study

Study Design: The pivotal study was conducted as a one-period study involving randomized applications of the test formulations to both arms along with the replicate applications of the calibrator doses (D1 and D2) of the reference product. The treatment randomization providing complementary applications on left and right arms is listed in Vol. 1.1, pp. 104-105.

Application and Removal:

- Eight circular (approximately diameter) application sites were designated on the flexor surface of each forearm between the wrist and the elbow. The study drugs were applied to 12 of the 16 forearm sites according to the randomization schedule. Two sites on each arm were randomized as untreated chromameter reference sites.
- After duplicate baseline chromameter readings and visual readings, an open washer was positioned over each site and taped to the forearm using hypo-allergenic paper tape on the sides of the washer so that the treated area was not occluded. Using a 250 µL glass Hamilton syringe, *a* application of the study drug was applied to the assigned sites on each arm according to the randomization schedule. The applications were spread evenly over the skin surface at each site with the conical tip of a 1.5 mL polypropylene microcentrifuge tube.

- Baseline assessments were started approximately 2 hours prior to the first application. The test and reference creams were applied to 6 sites on each arm for 30-minutes, 60-minutes or 120-minutes prior to scheduled removal. All sites were on, or staggered about the midline axis of the subject's forearm.
- All applications were removed at the same time point (0 hour). The washers were detached and the residual surface treatment was removed by gently wiping several times with a cotton ball. The untreated site on each arm was similarly wiped with a clean cotton ball.

Housing and Meals: Same as in the pilot study.
Restrictions: Same as in the pilot study.
Dermal Assessment:
Same as in the pilot study. The degree of skin blanching was determined both by chromameter and visual assessments at each site prior to treatment application and at 0, 2, 4, 6, 8, 10, 12, 20 and 24 hours after drug removal.
Data Evaluation:

- The post-dose chromameter a-scale reading at each site and assessment time was obtained as described in the pilot study.
- Chromameter areas under the effect curve (AUEC) from 0-24 hours were calculated from the corrected, baseline-adjusted readings by the linear trapezoidal method. The reviewer verified the firm's calculations.
- The firm also submitted visual scores data. The OGD guidance does not require documentation of bioequivalence based on both chromameter and visual assessment of vasoconstriction. Therefore, the visual assessment data were not used in evaluation of the application.
- The ratio of the mean area under the response curve for the reference 2-hour duration (D2) to that of the 30-minute duration (D1) was calculated for each subject. Subjects whose D2/D1 ratio was at least 1.25 were considered qualified for inclusion in the statistical analysis.
- Locke's method for calculating confidence intervals was applied to the chromameter area results from qualifying subjects.

C. Study Results

Protocol Deviations: None

Adverse Events: A total of six mild adverse events were reported for four subjects (including leg cramps, headaches, nausea, and retching). There was one headache of moderate severity (Vol. 1.1, p. 20).

Pharmacodynamic Data Analysis:
An example of the reviewer's verification of AUEC calculations are shown in Table 1.

Based on the D2/D1 ratio criterion of 1.25, 31 subjects qualified as detectors for the chromameter results and 26 subjects qualified as detectors for the visual results. The D2, D1 and D2/D1 ratios for the subjects who qualified as detectors for the chromameter results are shown in Table 2.

Mean AUEC (0-24) values from chromameter measurements for the 31 evaluable subjects for the test and reference products are shown in Table 3.

The Division applied Locke's method for calculating confidence intervals to the chromameter data from the qualifying subjects. The results follow:

N	Mean Area Under Response Curve Test	Reference	T/R	Confidence Interval
31	-12.14	-12.11	1.002	85.1-116.3

Chromameter results based on calculations by Locke's method performed by the sponsor follow (Vol. 1.1, p. 21):

Assessment Method	N	Mean Area Under Response Curve Test	Reference	T/R	Confidence Interval
Chromameter	31	-12.14	-12.11	1.002	85.1-116.3
Visual	26	9.66	11.66	0.828	70.1-94.3

V. Formulation. Components and composition of the test and the reference products are given in Table 4.

VI. Overall Comments

1. The firm has conducted acceptable pilot dose-response and pivotal in vivo bioequivalence vasoconstriction studies according to OGD 1995 Guidance (June 2, 1995) on topical corticosteroids.

2. Based on the chromameter evaluation of skin blanching, the AUEC(0-24) of the test product was 0.2% higher than the reference product. The 90% confidence intervals for the chromameter results are within the 80-125% range. The study is acceptable.

3. No severe medical event reported during pilot and pivotal studies.

4. The clinical study was found acceptable. See Attachment 1 (OGD's Medical Officer's Summary dated October 14, 1999).

5. The ED50 data is highly variable (See Attachment 3).

VII. Recommendations

The *in vivo* bioequivalence studies - based on the vasoconstrictor and clinical assays - conducted by Altana, Inc. on its clotrimazole/betamethasone dipropionate cream, 1%/0.05% (Lot 8077) comparing it to the reference product, Lotrisone 1%/0.05% cream (clotrimazole/betamethasone dipropionate 1%/0.05%), Lot #6NBN106, have been found acceptable by the Division of Bioequivalence. The results of these vasoconstriction and clinical studies demonstrate that Altana, Inc.'s Clotrimazole/Betamethasone Dipropionate cream, 1%/0.05% formulation is bioequivalent to the reference product, Lotrisone 1%/0.05% cream (clotrimazole/betamethasone dipropionate 1%/0.05%) manufactured by Schering/Key Pharm.

James E. Chaney, Ph.D.
Division of Bioequivalence
Review Branch I

RD INITIALED YCHuang
FT INITIALED YCHuang Date 7/26/2001

Concur: Date 2/27/2001
Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence

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Clotrimazole/
Betamethasone Dipropionate Cream, USP
1%/0.05%

Altana, Inc. Pharmaceuticals, Inc.

Table 1. An Example of Verification of the AUEC Calculations from the Pivotal Study Reported By The Firm

Sub	TRT	Arm	Hours After Drug Removal 0	2	4	6	8	10	12	20	24	FDA AUEC	Firm AUEC	FDA/ Firm
	D1	LT										20.35	-20.35	1.00
	D2	LT										-15.86	-15.86	1.00
	REF1	LT									9	9.21	9.21	1.00
	REF2	LT									9	-23.61	-23.61	1.00
	TEST1	LT	-								7	-19.15	-19.15	1.00
	TEST2	LT									08	-1.73	-1.73	1.00

Table 2. Mean Individual D1 (Lotrisone Area at 30 Minutes) and D2 (Lotrisone Area at 120 Minutes) and D2/D1 Ratios for Qualifying Subjects (Chromameter Results)

S ct #	Mean D2	Mean D1	Mean-D2/ Mean-D1
	-16.43	-12.93	1.27
	-13.64	-5.06	2.7
	-29.15	-20.88	1.4
	-25.68	-15.55	1.65
	-4.92	-0.51	9.65
	-23.77	-17.49	1.36
	-39.49	-20.22	1.95
	-5.54	-1.98	2.8
	-7.4	-3.26	2.27
	-21.84	-9.44	2.31
	-14.68	-1.27	11.56
	-19.07	-10.34	1.84
	-24.09	-8.16	2.95
	-26.73	-12.39	2.16
	-36.01	-16.56	2.17
	-15.21	-1.09	13.95
	-35.28	-9.86	3.58
	-10.46	-2.86	3.66
	-3.89	-2.31	1.68
	-20.55	-9.11	2.26
	-41.3	-23.77	1.74
	-8.87	-4.15	2.14
	-8.63	-0.82	10.52
	-24.76	-13.23	1.87
	-10.49	-6.39	1.64
	-12.42	-3.6	3.45
	-31.28	-19.83	1.58
	-9.71	-3.01	3.23
	-14.22	-8.17	1.74
	-22.39	-11.39	1.97
	-21.31	-13.54	1.57

Table 3. Mean AUEC (0-24) For The Test And Reference Products (N=31)			
SUBJECT	TEST	REF	TEST/REF
	-12.688	-10.738	1.18
	-8.91	-8.74	1.02
	-14.353	-11.623	1.23
	-18.258	-11.043	1.65
	-9.25	-4.185	2.21
	-5.448	-18.627	0.29
	-34.203	-28.883	1.18
	-6.058	-10.075	0.60
	-6.558	-9.768	0.67
	-18.045	-8.703	2.07
	-6.743	-6.895	0.98
	-4.848	-7.225	0.67
	-3.708	-13.383	0.28
	-10.578	-13.803	0.77
	-19.035	-25.42	0.75
	-1.588	-7.265	0.22
	-24.075	-16.223	1.48
	-6.518	-11.808	0.55
	-4.18	-4.048	1.03
	-5.84	-7.743	0.75
	-29.535	-22.622	1.31
	-10.095	-6.875	1.47
	-6.763	-5.548	1.22
	-7.265	-13.783	0.53
	-9.825	-0.54	18.19
	-10.175	-5.133	1.98
	-39.68	-36.928	1.07
	-3.235	-9.03	0.36
	-15.023	-14.343	1.05
	-14.855	-5.918	2.51
	-8.913	-18.505	0.48

Table 4. Comparative Formulation (%w/w) (NOT TO BE RELEASED UNDER FOI):		
Composition	**Test Product**	**Reference, %w/w***
Clotrimazole	1.00	1.00
Betamethasone Dipropionate		
Propylene Glycol		
White Petrolatum		
Cetostearyl Alcohol		
Mineral Oil		
Ceteareth		
Benzyl Alcohol		
Monobasic Sodium Phosphate, Monohydrate		
Purified Water		
Phosphoric Acid		
Sodium Hydroxide	--	

DEC 27 1999

BIOEQUIVALENCY DEFICIENCIES

ANDA: 75-502 APPLICANT: Altana, Inc.

DRUG PRODUCT: Clotrimazole 1% and Betamethasone Dipropionate 0.05% Cream, USP

The Division of Bioequivalence has completed its review of your submission(s) acknowledged on the cover sheet. The following deficiencies have been identified:

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

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

Sincerely yours,

Dale P. Conner

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

Clotrimazole, 1% and
Betamethasone Dipropionate 0.05% Cream, USP
ANDA #75-502
Reviewer: James E. Chaney
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Altana, Inc.
Melville, N.Y.
Submission Date
November 11, 1998

Review of a Clinical Bioequivalence Study and a Potency Ranking Study

The firm has submitted a clinical study on its clotrimazole 1% and betamethasone dipropionate 0.05% topical cream in support of the activity of the clotrimazole component. Regarding the corticosteroid component (betamethasone dipropionate) the sponsor reported in the same submission the results of a potency ranking study based on the single-point (16 hr) skin blanching assay.

RECOMMENDATIONS

1. The bioequivalence study was based on clinical endpoints relevant to the action of clotrimazole. The study has been found acceptable. (See attached review of October 14, 1999 by Dr. Mary Fanning.)

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

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

The firm should be informed of recommendations 2 and 3.

James E. Chaney

James E. Chaney, Ph.D.
Division of Bioequivalence
Review Branch I

RD INITIALED YCHuang
FT INITIALED YCHuang _____ Date 12/8/99

Concur: _____ Date 12/13/99
Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence

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