CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 75-430

BIOEQUIVALENCE REVIEW(S)

(3)

Office of Generic Drugs

DIVISION OF BIOEQUIVALENCE

ANDA 75-430 Sponsor: Altana Inc.
Drug and Dosage form: Clobetasol Propionate Cream USP (Emollient)
Strength: 0.05%
Type of Study: Skin Blanching PD Study

Study Summary Pilot Study Acceptable
Pivotal Study Acceptable

A population ED_{50} of 19 minutes was determined in the pilot study.
A D1 duration of 10 min and a D2 duration of 40 min were used to test the detector subjects in the pivotal study.
Locke's exact 90% CI was 88.5-116% for $AUEC_{0.25-24h}$
The mean ratio, test to reference $AUEC_{0.25-24h}$, was 1.01.

Initial:_____ Date:_____
Primary Reviewer: Farah Nouravarsani Branch: III

Initial: /S/ Date: 3/4/99
Team Leader: Barbara Davit Branch: III

Initial: /S/ Date: 3/4/99
Director, Division of Bioequivalence

Initial:_____ Date:_____
Director, Office of Generic Drugs

2.1
Woodlawn

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 75-430 APPLICANT: Altana Inc.

DRUG PRODUCT: Clobetasol Propionate Cream USP, 0.05% (Emollient)

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

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,

/S/

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

Clobetasol Propionate
Emollient Cream, 0.05%
ANDA #75-430
Reviewer: F. Nouravarsani
WP: 75430STU.898

Altana Inc.
Melville, NY
Submission Dates:
August 05, 1998
December 10, 1998(diskettes)
February 08, 1999

REVIEW OF A PILOT DOSE DURATION-RESPONSE STUDY AND A PHARMACODYNAMIC BIOEQUIVALENCE STUDY

I. INTRODUCTION:

-Altana Inc. has submitted the following studies:
1. Pilot Dose Duration-Response Study
2. Pivotal Study

-Available Guidance in the DBE/OGD/CDER: TOPICAL DERMATOLOGIC CORTICOSTEROIDS: IN VIVO BIOEQUIVALENCE (Issue Date: June 2, 1995).

II. BACKGROUND:

TEMOVATE E Emollient Cream contains 0.5 mg/g (0.05%) Clobetasol Propionate for topical dermatologic use. It is a super-high potency corticosteriod formulation. Clobetasol Propionate, a synthetic corticosteroid has anti-inflammatory, antipruritic, and vasoconstrictive properties.

Topical corticosteroids can be absorbed from normal intact skin. The percutaneous absorption may increase when inflammation and/or other diseases are present in the skin. Many factors, including the vehicle and the integrity of the epidermal barrier determine the extent of percutaneous absorption of topical corticosteroids (PDR, 1998).

III. PILOT DOSE DURATION-RESPONSE STUDY:

Objective:

To determine the duration of application of clobetasol 0.05% cream to be used in the pivotal study.

Design:

-One phase, open label
-Fifteen (15) subjects were enrolled (13 were evaluated)
-Multiple dose duration-response study
-Staggered application, synchronized removal
-Dose durations: 5, 10, 15, 20, 30, 60, 90, and 120 minutes
-Response: Predose (0.0), 0.25, 2, 4, 6, 8, 10, 19, and 24 hours after drug removal

Study Information:

-Study Number:	163-04-11188
-Protocol Number:	11188
-Sponsor:	Altana, Inc., Melville, NY
-Clinical Facility:	Inc.,
-Principal Investigator:	, Inc.
-Clinical Study Dates:	Group 1: May 15-16, 1997 Group 2: May 27-28, 1997

Product Tested:

-Temovate E (Clobetasol Propionate, 0.05% Cream)
-Manufacturer: Glaxo Wellcome
-Lot #6L222, Expiration Date: November 1998
-Temovate E, 0.05% (NDA 20340 001, June 17, 1994) is the RLD in the Orange Book, 1998. It is coded as BX.

Housing:

From approximately 2 hours before the drug administration until 10 hours after the drug removal.

Meal Restrictions:

Meals were not permitted within one hour of any skin blanching assessment.

Subjects:

-Fifteen (15) healthy volunteers (6 males and 9 females) of light complexion were enrolled in two groups:

Group 1:
Subjects #1-10. The data obtained from two of the volunteers (#7 and #9) from this group were incomplete. Two additional subjects were enrolled with the second group of three subjects.

Group 2:
Subjects #11-15

-Total of thirteen (13) subjects were evaluated.

-Age range: 19-51 years

-Smoking Status:
Subjects #1, 8, 10, 11, and 14 were smokers. However, the subjects were not allowed to smoke throughout the study.

Subject Eligibility was based on the following:
-medical history,
-physical examination including vital signs,
-demographic data,
-signed informed consent prior to screening for vasoconstriction to topical corticosteriods and study initiation,
-negative serum pregnancy test for all female subjects during the eligibility screening process,
-negative urine pregnancy test for all female subjects prior to study dosing, and
-vasoconstriction response to topical corticosteriods. The Assessment of Vasoconstriction Response was determined as follows:

μl of cream was applied to a test site diameter on the ventral side of the upper arm). The subjects were instructed to remove the cream after six hours. The subjects returned to the facility at approximately 10 ± 2 hours for the visual assessment of skin blanching.

Fifteen (15) subjects who were identified with a skin blanching effect of 1 or greater were enrolled into the pilot study. The

visual Skin Blanching Scales were as follows:

0 = normal skin
1 = slight, diffuse blanching with an indistinct outline
2 = more intense blanching with half of the drug-treated site perimeter Outlined
3 = marked blanching with a distinct outline of the drug-treated skin site
4 = extreme skin blanching with a distinct outline of the drug-treated skin site

Method of the Pilot Study:

Test Sites:

Twelve (12) test sites were marked with a dermatological pencil on each subject ventral forearms (6 on each arm). The sites, which were approximately in diameter, were no closer than m from center-to-center. The sites were located at least from the antecubital fossa and from the wrist.

Untreated sites: Randomly assigned to 2 sites on one arm and to the corresponding 2 sites on the other arm.

Treated sites: The different treatment durations were randomly assigned to the 8 sites (4 on each arm).

Drug Administration and Removal:

μl of cream was applied to the center of each site, and evenly spread around. The sites were covered with a non-occlusive dressing and protective guard to prevent smearing or premature removal of the cream. **The cream was removed by wiping with dry cotton swabs at 5, 10, 15, 20, 30, 60, 90, and 120 minutes after application.**

Skin Blanching Assessment:

Skin blanching was assessed with a Model . The system of representing perceived color and color difference was used, where represents the lightness factor, and are the red-green and yellow-blue chromacity coordinates, respectively. The scale was used to

monitor the extent of skin blanching.

The skin blanching was monitored at 0.0 hour (predose), and at 0.25, 2, 4, 6, 8, 10, 19, and 24 hours after cream removal. The 6.0, 8.0, and 10.0 hour assessments were obtained between 5 p.m. and 12 a.m. Baseline readings were determined within one hour before dosing.

Validation Study for Use of the Chroma Meter to Measure Skin Blanching (Protocol # 10962):

Objective: To determine precision of repeated measurement of skin color with a [illegible].

Design: Two instruments were used to measure the skin color of 8 forearm test sites 4 times within 1 hour.

Number of Subjects: Six (6) healthy male and female subjects who satisfied the eligibility criteria according to the protocol (page 1350).

Method: Eight (8) test sites were marked with a dermatological pencil on each subject's arms (4 on each ventral forearm). The sites were approximately in diameter. The sites were located at least from the antecubital fossa and from the wrist. Assessment of baseline skin color was obtained at approximately evenly spaced time interval within 1 hour.

The CV of the Chroma Meter readings for skin color measured on each arm (16 observations) and on both arms combined (32 observations) for each subject and for each instrument was calculated.

Result: The range of LSMEANS from readings of sites (L1, L2, L3, L4, R1, R2, R3, and R4) for Instrument 1 was 8.315 - 8.831 and for Instrument 2 was 8.232 - 8.957.

The CV% range (6 subjects) from readings of each arm (16 observations) were as follows:

Instrument	Left Arm	Right Arm
1	5.90 - 9.30	2.90 - 9.17
2	4.84 - 9.79	4.48 - 10.28

The CV% range (6 subjects) from readings of both arms (32 observations) were as follows:

Instrument	
1	6.07 - 11.19
2	6.15 - 13.28

Conclusion: The variabilities of the observations were similar for the two instruments.

Data Analysis:

The population Emax and ED50 were estimated using the software package

The AUEC0-24 data from the 13 individual subjects for each treatment duration were fitted simultaneously to the following equation:

$$E = Emax*D/(ED50+D)$$

where E = effect, the AUEC for a given dose
Emax = maximum observed effect
D = dose, the duration of application of cream
ED50 = the dose that causes a half-maximal effect

Results:

-Data obtained from subjects #7 and #9 were incomplete. Therefore, results from 13 subjects were analyzed.

-The population ED50 was determined to be 18.76 minutes. The corresponding Emax was -48.63 in AUEC units.

-The population Emax and ED50 were also estimated by Dr. Gur Jai Pal Singh (Division of Bioequivalence) using the software package It was concluded that "An ED50 estimate of approx. 18 min is independent of the initial parameter values in the range of 5 - 22 min (Constant variance model and normal distribution). The use of log-normal distribution for ED50, and homoscadestic variance did not significantly affect the goodness of fit, based on a variety of graphics."

-Nine of the thirteen evaluable subjects showed individual ED50 estimates greater than 5 minutes, which was the minimum drug

application duration in this study.

-Adverse Events: No adverse event was reported.

Comments:

1. The population ED50 was determined to be 18.76 minutes. The firm decided to use 20 minutes in the pivotal bioequivalence study.

A D1 duration of 10 minutes and a D2 duration of 40 minutes were used to test the 'detector' subjects in the pivotal in vivo bioequivalence study.

2. The cream was applied 5 minutes early for subject 11 at 90 minutes and 1 minute late for subject 15 at 20 minutes.

3. The readings for subject #9 at 19-hour were 12 minutes late due to the late arrival of the subject.

Deficiency of the Pilot Study:

The firm was requested by phone call from the Division of Bioequivalence on January 29, 1999 to submit results of the clinical screening for the subjects who participated in the pilot study. The firm was given 10 days to respond.

The firm responded on February 08, 1999, and submitted screening information for 10 subjects as follows:

Subject New No.	Subject Old No.	Subject Initials
1	(15)	;
2	(17)	;
3	(16)	;
3	(04)	;
4	(14) (01)	;
5	(13)	;
6	(02)	
7	(04)	
8	(14)	
9	(12)	
10	(05)	

However, the information submitted on February 08, 1999 is incomplete and confusing. The firm should clarify the following deficiencies:

1. The firm has provided the screening information for 10 subjects. The screening information should also be submitted for the subjects #11-15.

2. The firm should explain about the information submitted for the subject #03. The number for this subject was changed from 16 to 03 for Vital Signs, Medical History, and Physical Examination data (pages 16-18). Then, the number was changed from 04 to 03 for the Vital Signs and Inclusion/Exclusion Criteria data (pages 19-21).

3. It is not clear why each subject's number was changed.

IV. PIVOTAL STUDY:

Objective:

To demonstrate the bioequivalency of the test and reference products.

Design:

-Randomized, open label, one period
-Staggered drug application and synchronized removal
-Dose Duration for the test and reference products: 20 minutes
-Dose duration for "detector" evaluation: 10 and 40 minutes for the reference formulation
-Detectors: Subjects who had a ratio of 1.25 fold or greater blanching response after 40 and 10 minutes dose duration
-The blanching response from the test and reference products were compared for only the detector subjects.

Study Information:

Study Number: 163-08-11189
Protocol Number: 11189
Sponsor: Altana, Inc., Melville, NY
Clinical Facility:

Principal Investigator:

Clinical Study Dates:

Group	Subjects	Dates Studied
1	1-15	April 29-30, 1998
2	16-30	May 1-2, 1998
3	31-45	May 4-5, 1998
4	46-58	May 8-9, 1998
5	59-66	May 11-12, 1998
6	67-73	May 14-15, 1998
7	74-78	May 19-20, 1998

Products Tested:

Test Product:

-Clobetasol Propionate, 0.05% Emollient Cream
-Lot #: B156
-Batch Size:
-Assay: 98.5%
-Manufacturer: Altana, Inc.
-Manufacturing date: December 1997

Reference Product:

-Temovate E (Clobetasol Propionate, 0.05% Emollient Cream)
-Lot #: 7J370
-Assay: 97.9%
-Manufacturer: Glaxo Dermatology, Division of Glaxo Wellcome Inc.
-Expiration Date: September 1999

Subjects:

-Seventy-eight (78) healthy male (10) and female (68) subjects Of light complexion were enrolled in the study after being screened from the general population.

-Age range: 18-58 years

-Seventy-five (75) subjects had complete data.

-Forty (40) subjects considered detectors.

-Smoking Status:
Subject #20 was a smoker. However, the subjects were not allowed to smoke throughout the study.

Subject Eligibility was based on:
-medical history,
-physical examination including vital signs determination,
-demographic data,
-signed informed consent prior to screening for vasoconstriction to topical corticosteriods and study initiation. The subjects signed an informed consent which incorrectly stated that during

the screening process the cream would be removed 2 hours after application instead of 6 hours,
-negative serum pregnancy test for all female subjects during the eligibility screening process,
-negative urine pregnancy test for all female subjects prior to drug application, and
-vasoconstriction response to topical corticosteriods. The vasoconstriction response to topical corticosteriods was assessed the same as in the Pilot Study.

Housing:

From approximately 2 hours before the drug administration until at least 11 hours after the drug removal.

Meal and Food Restrictions:

Meals were not permitted within one hour of any skin blanching assessment.

Method of the Pivotal Study:

Test Sites:

Sixteen (16) sites were marked on each subject arms (8 on each ventral forearm). The sites, which were approximately in diameter, were no closer than from center-to-center. The sites were located at least from the antecubital fossa and the wrist.

Drug Administration and Removal:

of cream was applied to the center of each site, and was evenly spread around.

Application Method: Staggered
Removal Method: Synchronized

Treatment Duration:

T: test product for 20 minutes, 2 on each arm
R: reference product for 20 minutes, 2 on each arm
D1: reference product for 10 minutes, 1 on each arm
D2: reference product for 40 minutes, 1 on each arm
U: untreated site, 2 on each arm

Monitoring of Skin Blanching:

Skin blanching was assessed with a
one hour before dosing (duplicate), and at 0.25, 3, 5, 7, 9, 11, 20, and 24 hours after removal of the cream. At least one reading was scheduled between 5:00 p.m. and midnight.

The average AUEC(0.25-24) after 10 and 40 minutes treatments were used when they both were negative.

The average of AUEC(0.25-24) for the test and reference products were compared after 20 minutes application from the subjects who were detectors.

Statistical Analysis:

Subjects with complete data sets were considered for statistical analysis. The 90% CI was calculated for the ratio of the average AUEC(0.25-24) response due to the test product to the average of AUEC(0.25-24) response due to the reference product using Locke's method, which provides an exact confidence interval from untransformed data (J Pharmacokinet Biopharm 1984; 12:649-55).

Results:

-Number of subjects completed the study and were evaluable: 75

-Withdrawn from the study: Subject #22, because of a dosing error.

-Incomplete Data Set: Subject #7 for the 9 hour readings
Subject #50 for the 3 hour readings
The data from these subjects were considered unevaluable.

-Number of subjects determined as detectors: 40

-The AUEC(0.25-24) calculated for the test and reference products are compared in Table 1. The mean AUEC(0.25-24) values for the test (-25.51) and the reference (-25.15) products are very similar.

-Locke's exact 90% confidence interval: 88.5% - 116.4% for AUEC(0.25-24) using 20 minutes treatment duration. The ratio of the mean test to the mean reference AUEC(0.25-24) was 1.01.

-Adverse Events: None was reported.

Comments:

1. There were some deviations from the scheduled readings times (from 1 to 37 minutes late) for some of the subjects. The AUEC(0.25-24) was calculated using the scheduled times.

Since the ratios of D2/D1 for subjects #75 and #76 were at border line, the reviewer calculated the AUEC(0.25-24) for D1 and D2 (both arms) using the actual times for these subjects. The reported ratio of D2/D1 by the firm and those calculated by the reviewer are compared as follows:

	Subject 75	Subject 76
Reported D2/D1 (Scheduled times)	1.210	1.262
Reviewer D2/D1 (actual times)	1.202	1.257

Using the actual times in calculation of the AUEC, the ratio of D2/D1 is still less than 1.25 for subject #75 and meets the requirement for subject #76.

The reviewer also calculated the AUEC using the actual times for D1(L) for subjects #66 who had a 37 minutes late reading at 20 hours, and for subject #16 who had a 23 minutes late reading at 5 hours. The AUEC using the scheduled and actual times were very similar: -4.89 and respectively for subject #66
-35.123 and respectively for subject #16.

Therefore recalculations of all the AUEC using the actual times may not be necessary for this study. However, the firm should be advised to use actual times of the observations for future studies.

2. The AUEC was calculated from 0.25 to 24 hours, since the readings of the sites were started at 0.25 hour after removal of the treatments.

3. The Locke's exact 90% confidence interval was 88.5% - 116.4% for AUEC(0.25-24) using 20 minutes treatment duration. The ratio of the mean test to the mean reference AUEC(0.25-24) was 1.01.

4. The formulations of the test and reference products are qualitatively identical and quantitatively very similar (Table 2).

Cetomacrogol 1000) in the test product is) and in the reference product is . . Ceteth-20 is present in topical products of emulsion and cream in a range of (IIG, 1996).

Propylene Glycol in the test product is w/w) and in the reference product is). Propylene Glycol is present in topical products of emulsion and cream in a range of 1996).

Isopropyl Myristate in the test product is (w/w) and in the reference product is % (w/w). Isopropyl Myristate is present in topical products of emulsion and cream in a range of (IIG, 1996).

Deficiency of the Pivotal Study: None.

V. DEFICIENCIES OF THE PILOT STUDY AMENDMENT SUBMITTED ON FEBRUARY 08, 1999:

A. The firm should clarify the following deficiencies:

1. The firm has provided the screening information for 10 subjects. The screening information should also be submitted for the subjects #11-15.

2. The firm should explain about the information submitted for the subject #03. The number for this subject was changed from 16 to 03 for Vital Signs, Medical History, and Physical Examination data (pages 16-18). Then, the number was changed from 04 to 03 for the Vital Signs and Inclusion/Exclusion Criteria data (pages 19-21).

3. It is not clear why each subject's number was changed.

B. Reviewer's Comments:

The reviewer was requested by Dr. Conner and Dr. Davit on February 24, 1999 to explain in her review reasons for requesting from the firm to respond to the above deficiencies. The reviewer had earlier suggested to Dr. Davit and Dr. Conner that the firm be informed by a phone call from the DBE.

The reviewer believes that the firm should respond to the deficiencies of the pilot study for the following reasons:

a. The firm submitted incomplete and confusing information to the agency on February 08, 1999. The firm should document accurate and complete information.

b. The reliability of the pilot and pivotal studies depend on submission of the complete and accurate data for the clinical screening of the subjects who participated in the pilot study.

c. The firm should be discouraged from sending incomplete or confusing data to the agency for future.

VI. RECOMMENDATIONS:

1. The in vivo pharmacodynamic study conducted by Altana, Inc. on its Clobetasol Propionate Emollient Cream, 0.05% (lot #B156) comparing it to the reference product, Temovate E (lot #7J370) manufactured by Glaxo Wellcome Inc. has been found acceptable by the Division of Bioequivalence **provided the firm clarifies the deficiencies of the pilot study regarding the clinical subject screening summarized under section V.A.: DEFICIENCIES OF THE PILOT STUDY AMENDMENT SUBMITTED ON FEBRUARY 08, 1999.**

2. The firm should be advised for future studies that actual times of observations should be used for calculations of the AUEC.

/26/1999

Farahnaz Nouravarsani, Ph.D.
Division of Bioequivalence
Review Branch III

BMD 2/22/99

Table 1: AVERAGE AUEC(0.25-24)

Subject	Test	Reference
1		
4		
8		
9		
12		
14		
15		
21		
23		
24		
26		
28		
29		
30		
31		
36		
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47		
51		
52		
53		
54		
56		
57		
59		
63		
66		
68		
73		
74		
76		
77		
78	-14..	
Mean	-25.51	-25.15
Variance	140.40	148.39
Covariance	60.85	
N	40	40
Test/Ref.	1.01	

Table 2: COMPARISON BETWEEN THE TEST AND THE REFERENCE PRODUCTS

Component	Test, W/W%	Ref., W/W% (PDR & COMIS)
Clobetasol Propionate		
Cetostearyl Alcohol		
Isopropyl Myristate		
Propylene Glycol		10.
Cetomacrogol 1000(1)		
Dimethicone 360		
Citric Acid		
Sodium Citrate		
Purified Water		
Imidurea		

(1) Polyethylene Glycol 1000 Monocetyl Ether; Ceteth-20