CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75276

BIOEQUIVALENCY REVIEW(S)

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE
SIGN-OFF FORM

ANDA: 75-276 SPONSOR : Altana Inc.
DRUG & DOSAGE FORM : Betamethasone Dipropionate Gel 0.05%

TYPE OF STUDY: PILOT PD STUDY
STUDY: XAcceptable ☐Not Applicable
TYPE OF STUDY: PIVOTAL PD STUDY
STUDY: XAcceptable ☐Not Applicable

DISSOLUTION : ☐Acceptable XNot Applicable

WAIVER: ☐Acceptable XNot Applicable

REVIEWER: Hoainhon Nguyen BRANCH: I
INITIAL: HNN DATE : 6/16/98

BRANCH CHIEF : Yih-Chain Huang, Ph.D. BRANCH : I
INITIAL : YCH DATE : 6/16/98

DIRECTOR: Dale Conner, Pharm.D. DIVISION OF BIOEQUIVALENCE
INITIAL : DWC DATE : 6/23/98

1-1 P. Schwartz

BIOEQUIVALENCY COMMENTS

ANDA: 75-276 APPLICANT: Altana Inc.

DRUG PRODUCT: Betamethasone Dipropionate Gel, 0.05%

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

CC:ANDA 75-276
ANDA DUPLICATE
DIVISION FILE
FIELD COPY
HFD-652/ Bio Secretary - Bio Drug File
HFD-652/ HNguyen
HFD-652/ YHuang

Endorsements: (Final with Dates)
HFD-652/ HNguyen
HFD-652/ YHuang 6/16/98
HFD-617/ L. Sanchez or N.Chamberlin
HFD-650/ D. Conner 6/23/98

Printed in final on / /

BIOEQUIVALENCY - ACCEPTABLE Submission date: 1-29-98

1. PILOT STUDY
   Clinical:
   Analytical
   Strengths: 0.05%
   Outcome: **AC**

2. PIVOTAL STUDY
   Clinical:
   Analytical
   Strengths: 0.05%
   Outcome: **AC**

OUTCOME DECISIONS: **IC** - Incomplete **UN** - Unacceptable (fatal flaw)
AC - Acceptable

WINBIO COMMENTS:

Betamethasone Dipropionate Gel 0.05%
ANDA # 75-276
Reviewer: Hoainhon Nguyen
WP # 75276s.198

Altana Inc.
Melville, NY
Submission Date:
January 29, 1998
June 11, 1998 (Telephone Amendment)

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

I. Background:

Betamethasone dipropionate is a synthetic fluorinated corticosteroid with anti-inflammatory, anti-pruritic, and vasoconstrictive properties, indicated for topical relief of manifestations of corticosteroid-responsive dermatoses. The extent of percutaneous absorption of topical corticosteroids is determined by many factors including the vehicle and the integrity of the epidermal barrier. Occlusive dressings with hydrocortisone for up to 24 hours have not been demonstrated to increase penetration; however, occlusion of hydrocortisone for 96 hours markedly enhances penetration. Topical corticosteroids can be absorbed from normal intact skin. In addition, inflammation and/or other disease processes in the skin may increase percutaneous absorption.

Frequent adverse reactions of betamethasone dipropionate include stinging or burning, dry skin and pruritus.

The RLD product for betamethasone dipriopionate gel, 0.05%, is Diprolene® Gel 0.05% manufactured by Schering.

The firm has submitted a pilot dose duration-response study and a pivotal vasoconstrictor bioequivalence study comparing its Betamethasone Dipropionate Gel, 0.05%, to the RLD product, Diprolene® Topical Gel, 0.05%.

II. *In Vivo* Studies:

A. Pilot Dose Duration-Response Study: (Protocol No. 9728209D)

Study Objective:

The purpose of this study was to determine the ED_{50} of the vasoconstrictive dose-response relationship for betamethasone dipropionate 0.05% topical gel (Diprolene®).

Study Investigators and Facilities:

The study was conducted at [redacted] between March 8 and 9, 1997. The principal investigator was [redacted] Methods of measurement of vasoconstrictive effect were by visual assessment (identication of evaluator not given) and by a chromameter (operators identified [redacted] The effect evaluation and data collection were completed within 48 hours post-application.

Demographics:

Fifteen normal, healthy, non-tobacco using, caucasian female volunteers between 19-40 years of age, and within 15% of their ideal weight according to the Metropolitan Life Insurance Company Bulletin, 1983, participated in a one treatment, one-period, randomized study. The subjects were selected on the basis of their acceptable medical history, physical examination and clinical laboratory tests. The subjects' weight and height ranged 106 - 158 lbs and 61 - 70 in., respectively.

Inclusion criteria:

The subjects demonstrated a blanching response to Diprolene® gel. In addition, subjects especially did not have any history of: allergy to any corticosteroids including betamethasone dipropionate, or to any creams, lotions, gels, ointments, cotton, or cosmetics; any skin condition, excess hair, or coloration which would interfere with assessment of skin blanching; chronic infectious disease, system disorder or organ dysfunction; drug or alcohol addiction requiring treatment in past 12 months; or use of any dermatological drug therapy on the flexor surface of the forearms within 30 days of dosing. All subjects were tested negative for the urine pregnancy test and drug screen.

Restrictions:

They were free of all prescription medications at least 7 days, and all over-the-counter medications at least 72 hours prior to each study period and allowed no concomitant medications during the study sessions. No alcohol and no xanthine-containing products were allowed within 48 hours of dosing. No use of any creams, emollients or similar products on the forearms with 24 hours of dosing. Meals were served at traditional mealtimes. Duration of confinement was approximately 19 hours pre-dose to approximately 27 hours post-dose (application).

Treatments and Sampling:

The treatment consisted of a single 10μL application/each site of the reference product, Diprolene® 0.05% gel (Schering Corp., Lot #6RFH503).

There were 8 sites on each arm for 5-, 10-, 15-, 20-, 30-, 60- and 120-minute duration sites and one untreated site per each arm. The treated area was not occluded and the dosing followed the staggered application with synchronized removal method. In the pilot study, the degree of blanching response was assessed at each site prior to treatment application (baseline) and at 0, 2, 4, 6, 8, 10, 12, 20 and 24 hours after removal.

Bioassay Methodology Validation:

Pharmacodynamic Results:

The areas under the effect curve (AUEC) were calculated using the trapezoidal rule. For visual assessments, raw data were used for calculation of AUEC. For chromameter assessments, the data were adjusted for the average value of the duplicate pre-dose (baseline) readings, and then for the untreated site on each arm (to compensate for skin tone changes that occur over time) before used for calculation of AUEC.

NOTE: The chromameter areas were multiplied by -1 to conform the conventional formal for area under the curve (EMAX values become positive).

Statistical Analyses:

The dose-response relationships were evaluated from all individual observations of all individual subjects simultaneously. SAS version 6.2 PROC NLIN was used for fitting an EMAX model to the pooled areas: $E=[(EMAX^{*}C)/(EC_{50}+C)]$ with E being the response value at C, the duration of application, and EC_{50} being $ED_{50,}$ the duration at which half-maximal response occurs.

Plots of the mean area and the predicted area from the fitted EMAX model for each duration of application were prepared to graphically assess the dose-response relationship.

Results:

Fourteen of 15 enrolled volunteers completed the clinical portion of the study. Subject # 14 withdrew from the study participation after dosing due to adverse events of emesis (3 times) and headache. The statistical analysis was performed using 14 data sets. The results are summarized below.

Table I
Mean Results and EMAX Model Parameter Estimates
n=14
Pilot Dose Response Study

Duration(min)	Visual AUEC(CV%)	ChromaMeter AUEC(CV%)
5	24.2(55)	16.0(109)
10	30.8(34)	28.3(46)
15	33.6(35)	31.6(49)
20	36.5(27)	32.6(36)
30	41.0(18)	33.0(27)
60	41.8(21)	36.7(36)
120	49.6(9.7)	41.9(31)
EMAX*	48.79	42.62
Standard Error*	2.23	3.10
CV%*	4.57	7.27
ED_{50}(min)*	5.94	6.45
Standard Error*	1.19	1.98
CV%*	20.03	30.70

*Based on EMAX modeling (nonlinear estimate of EMAX)

NOTE: Based on the results of the pilot study, ED_{50} = 6 minutes was chosen as the testing duration for the pivotal bioequivalence study, along with a lower duration D1 = 3 minutes and a longer duration D2 = 12 minutes.

Adverse Effects:

In addition to Subject #14's adverse events mentioned above (headache and emesis x3), Subjects #3 and 6 also reported mild redness on 1 and 2 different skin sites, respectively.

B. Pivotal Bioequivalence Study: (Protocol No. 9728210D)

Study Objective:

The purpose of this study was to compare the relative vasoconstrictive effects of test and reference topical betamethasone diproprionate gels in asymptomatic subjects.

Study Investigators and Facilities:

The study was conducted at . between April 26 and July 12, 1997. The principal investigator was .. Methods of measurement of vasoconstrictive effect were by visual assessment (identication of evaluator not given) and by a chromameter (operators identified as . The effect evaluation and data collection were completed within 48 hours post-application.

Demographics:

Eighty normal, healthy, non-tobacco using, asymptomatic female volunteers between 18-47 years of age, and within 15% of their ideal weight according to the Metropolitan Life Insurance Company Bulletin, 1983, participated in a one-period, randomized study. The subjects were selected on the basis of their acceptable medical history, physical examination and clinical laboratory tests. The subjects' weight and height ranged 97 - 182 lbs and 59 - 70 in., respectively.

Inclusion criteria and Restrictions:

Same as in the Pilot Study protocol above.

Treatments and Sampling:

The treatment consisted of a single 10μL application/each site of either the reference or test product:

Test Product: Augmented Betamethasone Diproprionate topical gel 0.05%, Altana,

(Lot#9753, Potency of 111.1% (per telephone amendment dated June 11, 1998))

Reference Product: Diprolene® 0.05% gel (Augmented Betamethasone Diproprionate), Schering Corp., (Lot #6RFH503, Potency of 108.4%).

There were 8 sites on each arm: For single 3- and 12-minute (D1 and D2, respectively) duration sites for Reference product applications only, for duplicate 6-minute duration sites for both Test and Reference product applications, and for duplicate untreated sites per arm. The treated area was not occluded and the dosing followed the staggered application with synchronized removal method.

In the pivotal study, the degree of blanching response was assessed at each site prior to treatment application (baseline) and at 0, 2, 4, 6, 8, 10, 12, 21 and 24 hours after removal.

The subjects were divided into 6 dosing groups (Group 1(Subjects#1-18) dosed on 4/26/97, Group 2(#19-41) on 5/3/97, Group 3(#42-54) on 5/10/97, Group 4(#55, 57-65) on 5/23/97, Group 5(56, 66-78) on 6/28/97 and Group 6(79-80) on 7/12/97). Washout time of at least 7 days between the confinement time was used to evaluate the reference data (D1 and D2 durations).

Bioassay Methodology Validation:

See under the Pilot Study summary report.

Only subjects whose D1/D2 ratio was at least 1.25 were considered qualified for inclusion in the statistical analyses. A subject whose mean D1 value indicated non-blanching but whose D2 showed blanching could also qualify for inclusion if the ratio of the subject's D2 to ED_{50} response for the reference was at least 1.25.

Pharmacodynamic Results:

The areas under the effect curve (AUEC) from 0 to 24 hours were calculated using the trapezoidal rule. For visual assessments, raw data were used for calculation of AUEC. For chromameter assessments, the data were adjusted for the average value of the

duplicate pre-dose (baseline) readings, and then for the untreated site on each arm (to compensate for skin tone changes that occur over time) before used for calculation of AUEC.

Statistical Analyses:

Locke's method for calculating confidence intervals was applied to the visual scoring and chromameter results of the qualifying detectors.

Results:

The data from 36 subjects qualified for inclusion in the visual analyses by the D2/D1 criteria; an additional 2 subjects qualified by the D1/ED_{50} criteria. Therefore, the data from a total of 38 of the 80 subjects were included in the visual evaluation for bioequivalence of the test and reference products.

In the analyses of the chromameter data, 28 subjects qualified for inclusion by the D2/D1 criteria, and 5 additional subjects qualified by the D2/ED_{50} criteria, for a total of 33 subjects.

The results of from the analyses of both data are summarized below.

Table II
Mean Results for Visual and Chromameter Evaluation
of Altana's Product(Test) and Diprolene® Gel(Reference)
Using Locke's Method for Calculating Confidence Intervals

	N	Means		Ratio	90% C.I.
		Test	Reference	(%)	
Visual	38	25.86	24.67	104.8	[0.99;1.11]
Chroma.	33	18.17	18.54	98.0	[0.85;1.11]

Adverse Effects:
There was one adverse event reported during the study: a mild headache by Subject # 79. The event was judged remotely related to the study drug by the investigator.

III. *In Vitro* Testing: Not required.

IV. Comments and Recommendations:

The pilot dose duration-response study and the pivotal vasoconstrictor bioequivalence study conducted by Altana Inc. on the test product, Augmented Betamethasone Dipropionate Topical Gel, 0.05%, lot # 9753, comparing it with the reference product, Diprolene^{R} Topical Gel, 0.05%, lot # 6RFH503, demonstrate that the test product is equivalent to the reference product in their extent of absorption as measured by AUEC of bethamethasone dipropionate using the update of the vasoconstrictor bioassay.

The test product, Altana's Augmented Betamethasone Dipropionate Topical Gel, 0.05%, is deemed bioequivalent to the RLD product, Diprolene® Topical Gel, 0.05%, manufactured by Schering.

/S/

Hoainhon Nguyen
Division of Bioequivalence
Review Branch I

RD INITIALED YHUANG
FT INITIALED YHUANG /S/ 6/16/98

Concur: /S/ Date: 6/23/98
Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence