CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75733

BIOEQUIVALENCY REVIEW(S)

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA # : 75-733 SPONSOR : Stiefel Laboratories, Inc

DRUG AND DOSAGE FORM : Clobetasol Propionate Emollient Cream

STRENGTH(S) : 0.05%

TYPES OF STUDIES : Pilot Dose-Response and Pivotal Pharmacodynamic bioequivalence studies.

CLINICAL STUDY SITE(S) :

ANALYTICAL SITE(S) :

STUDY SUMMARY : The two studies demonstrated that Stiefel's Clobetasol Propionate Emollient Cream 0.05%, is bioequivalent to Glaxo Wellcome's Temovate E® Emollient Cream 0.05%.

DISSOLUTION : N/A

DSI INSPECTION STATUS

Inspection needed: NO	Inspection status:	Inspection results:
First Generic _No__ New facility _ For cause _____ other _____	Inspection requested: (date) Inspection completed: (date)	

PRIMARY REVIEWER : Zakaria Z. Wahba, Ph.D. BRANCH : III

INITIAL : ZZW DATE : 8/2/01

TEAM LEADER : Barbara M. Davit, Ph.D. BRANCH : III

INITIAL : BMD DATE : 8/2/01

for DIRECTOR, DIVISION OF BIOEQUIVALENCE : DALE P. CONNER, Pharm. D.

INITIAL : /S/ DATE : 8/16/2001

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 75-733 APPLICANT: Stiefel Laboratories, Inc.

DRUG PRODUCT: Clobetasol Propionate Emollient Cream, 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/

for 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 # 75-733
Reviewer: Z.Z. Wahba
V:\firmsnz\stiefel\ltrs&rev\75733a1.101

Stiefel Laboratories
Coral Gables, FL
Submission Date:
January 30, 2001

REVIEW OF AN AMENDMENT

BACKGROUND

1. The firm previously submitted an application with two studies, one pilot and one pivotal (submission date: 11/12/99, DBE review date 4/11/00). The pivotal study was unacceptable because an unacceptable ED50 value was calculated in the pilot study. The firm's reported ED50 (45 minutes) was much greater than the DBE calculated value (11.25 minutes).

2. The firm was asked to conduct another pivotal bioequivalence study using an ED50 of approximately 11 minutes.

3. In this amendment, the firm submitted a new pivotal bioequivalence study comparing its Clobetasol Propionate Emollient Cream 0.05%, with the reference listed drug (RLD), Glaxo Wellcome's Temovate E® Cream 0.05%.

4. Clobetasol is a topical, synthetic fluorinated corticosteroid with anti-inflammatory, antipruritic, and vasoconstrictive properties. It is used to relieve the inflammatory and pruritic manifestations of moderate to severe corticosteroid-responsive dermatoses and psoriasis. Clobetasol is the most potent topical corticosteroid, and is for short-term therapy only.

Pivotal Study: Bioequivalence of Clobetasole Propionate Gel 0.05% Protocol #0005, Study #932).

A. **Objective**:
To demonstrate *in vivo* bioequivalence between Stiefel's Clobetasol Propoionate Emollient Cream, 0.05%, and the reference listed product, Glaxo Wellcome's Temovate E® Cream, 0.05%.

B. **Study Information**:

Sponsor:	Stiefel Laboratories, Inc.
Clinical Site:	University of Utah School of Medicine

Department of Dermatology,
Salt Lake City, UT

Principal Investigator: Lynn K. Pershing, Ph.D.
Study Date: 8/22/00 to 12/06/00

C. **Subjects**:
Sixty-nine (69) healthy subjects (46 females and 23 males) were enrolled and completed this pivotal study. Subjects were selected on acceptable medical history.

Demographic Data	• 69 subjects used for statistical analysis. • Gender: 23 males, 46 females • Race: 19 Caucasians, 3 Asian, 1 Hispanic • Age: Average 32.7 years (19-65 years) Zero subjects < 18 years 57 subjects between 18-40 years 11 subjects between 41-64 years 1 subjects between 65-75 years zero subjects between > 75 years • Height (in): Average 66.5 (59-73 in) • Weight (lb): 147.4 (96-250 lb)

E. **Inclusion/Exclusion Criteria**:
Information listed in vol. A3.1, pages 19-20.

F. **Study design**:
The pivotal study was conducted as a one-period per group study with randomized applications of the test and reference formulations (pages 10-11, and 28, volume A3.1). For each subject, eight 1.2 cm diameter circular skin sites were marked on each ventral forearm. Baseline chromameter readings were taken at all sites before the study drug products were applied. Thereafter, 5 mg of Temovate E® cream was applied for 8 (D1=1/2*ED50), 15 (ED50), or 30 (D2=2*ED50) minutes to the assigned sites on both arms. The test product (5 mg) was also applied at two sites on each arm for 15 (ED50) minutes. Two sites on each arm were left untreated. Application of drug products was in a staggered application design. The sites were protected with nonoccluding tape guards. At the end of the treatment duration (time zero) all sites were wiped with three independent nonsterile cotton applicators to remove residual drug. Chromameter readings (skin blanching assessments)

were then taken at all sites at zero time and again at 2, 4, 6, 20 and 24 hours after drug removal.

Note: The firm's pilot dose-response study was previously reviewed by the Agency. The firm was advised to conduct a pivotal study using an ED50 of approximately 11 minutes. The firm used an estimated ED50 of 15 minutes based on the Agency's June 2, 1995 Guidance, *Topical Dermatologic Corticosteroids: In Vivo Bioequivalence*. The ED50 of 15 minutes used by the firm is within the range of ED50 values for clobetasol propionate 0.05% topical cream products previously accepted by DBE.

The following treatments were administered in this study:

Test product:	Stiefel's Clobetasol Propionate Emollient Cream 0.05%, lot #H0611, lot size [redacted] Kg, expiration Date: 6/02
Reference product:	Glaxo Wellcome's Temovate E® Cream 0.05%, lot #9M321, expiration Date: 1/02
D1:	Glaxo Wellcome's Temovate E® Cream 0.05%, lot #9M321, expiration Date: 1/02, applied for dose duration of 8 minutes.
D2:	Glaxo Wellcome's Temovate E® cream 0.05%, lot #9M321, expiration Date: 1/02, applied for dose duration of 30 minutes.

Study Dates:

Group I (n=13):	August 22-23, 2000
Group II (n=14):	August 29-30, 2000
Group III (n=9):	September 5-6, 2000
Group IV (n=12):	October 17-18, 2000
Group V (n=13):	October 24-25, 2000
Group VI (n=8):	December 5-6, 2000

Total n=69 subjects

Pharmacodynamic Data Analysis

Of the 69 subjects completing the study, 32 subjects met the ratio D2/D1 $\geq$ 1.25 criterion and were determined "detectors" for statistical analysis (page 38, volume A3.1).

Average AUEC $_{(0-24)}$ of the 32 detector subjects for the test and reference products are shown below:

Table 1.
Mean AUEC $_{(0-24)}$ for the test and reference products (n=32)

Subject #	Test	Ref	T/R
3	-16.1	-15.11	1.07
4	-19.86	-17.98	1.10
7	-21.41	-23.1	0.93
8	-30.93	-33.87	0.91
9	-30.62	-28.14	1.09
11	-23.16	-17.26	1.34
15	-23.16	-24.51	0.94
17	-26.44	-35.94	0.74
22	-19	-21.32	0.89
23	-26.21	-21.63	1.21
24	-12.97	-14.5	0.89
25	-35.27	-38.88	0.91
26	-19.67	-11.91	1.65
27	-26.23	-28.85	0.91
28	-25.81	-21.45	1.20
29	-28.22	-22.74	1.24
33	-21.58	-29.54	0.73
34	-33.38	-43.32	0.77
35	-18.33	-27.38	0.67
36	-27.07	-25	1.08
37	-34.53	-26.45	1.31
42	-18.03	-12.08	1.49
46	-27.9	-23.55	1.18
48	-2.88	-14.56	0.20
52	-19.48	-17.17	1.13
55	-2.7	-13.54	0.20
59	-22.55	-21.39	1.05
62	-33.07	-9.58	3.45
63	-12.62	-14.82	0.85
64	-19.86	-4.1	4.84
65	-4.6	-13.25	0.35
67	-13.98	-14.3	0.98

Locke's method for calculating confidence intervals was applied to the chromameter data from the qualifying subjects.

Table 2.

Mean $AUEC_{(0-24)}$ results of Stiefel's test product vs. the RLD and 90% confidence interval determined using Locke's Method, are shown below.

		Mean Area Under the Effect Curve		Ratio	Confidence Interval	
Assessment Method	N	Test	Reference	T/R	Low	High
Chromameter	32	-21.80	-21.48	1.02	91.31	113.01

Results: The 90% confidence intervals comparing these products were within the acceptable limit of 80-125%. The study is acceptable.

Note: The reviewer's calculation agrees with the firm's submitted calculation (page 98, volume A3.1). See the Attachment.

Adverse Events

No treatment-related adverse events were reported.

FORMULATION COMPARISON (NOT TO BE RELEASED UNDER FOI):

Stiefel's formulation for its test product, Clobetasol Propionate Emollient Cream, 0.05%, and the formulation of the RLD Glaxo Wellcome's Temovate E® Cream, 0.05%, are given below:

Ingredient	[a]Stiefel's clobetasol propionate emollient cream, 0.05% (W/W%)	[b]Glaxo Wellcome's Temovate E® cream, 0.05% (W/W%)
Clobetasol Propionate, USP		
Ceteth-20		
Cetostearyl Acohol,NF		
Citric Acid USP (Monohydrate)		
Dimethicone NF		
Isopropyl Myristate NF		
Methylparaben NF		
Propylene		

Glycol USP		
Propylparaben NF		
Purified Water USP		
Sodium Citrate USP (Anhydrous)		

[a]The formulation was from the ANDA #75-733, reported on page 913, volume A1.4.
[b]From COMIS and also reported in the ANDA #75-430 report review (review date 11/28/99, reviewed by C. Kim, Pharm.D.)

All inactive ingredients used in the test products are within the IIG range for topical dermatologic route of administration.

Comments

1. The firm conducted a pilot dose-response study on the RLD Temovate E® Cream 0.05%, based on the Agency's June 2, 1995 Guidance, *Topical Dermatologic Corticosteroids: In Vivo Bioequivalence*. Based on a population fitting technique of the chromameter dose-response data, an ED_{50} of 11.25 minutes was calculated. For the pivotal bioequivalence study, the firm used estimated D1, ED_{50} and D2 values of 8, 15 and 30 minutes, respectively. The selection of these values are appropriate, based on the recommendations in the guidance, and data on clobetasol propionate emollient cream 0.05% products reviewed within the Division of Bioequivalence.

2. Sixty-nine (69) subjects were dosed for the pivotal bioequivalence study and all the subjects completed the study. Bioequivalence evaluation was performed on the chromameter dose response data of the 32 subjects whose D2/D1 ratio was $\geq$ 1.25.

3. Based on the Chromameter evaluation of skin blanching, the $AUEC_{0-24}$ was 2% higher than the reference product. The 90% confidence intervals comparing these products were within the acceptable limit of 80-125%. The study is acceptable.

4. The sponsor did not perform visual assessment of skin blanching. The Agency guidance on topical dermatologic corticosteroids does not require documentation of bioequivalence based on both chromameter and visual

assessment of vasoconstriction. Therefore, the evidence for bioequivalence of test and reference products based on chromameter data is sufficient.

5. The sponsor did not submit *in vitro* release data. Based on the aforementioned Agency guidance such data are not required for demonstration of bioequivalence of multisource dermatologic corticosteroid formulations.

Recommendation:

The *in vivo* pharmacodynamic study conducted by Stiefel Laboratories, Inc., comparing its Clobetasol Propionate Emollient Cream 0.05% (lot #H0611) to the reference product, Temovate E® Emollient Cream 0.05% (lot #9M321) has been found to be acceptable to the Division of Bioequivalence. The results of this vasoconstrictor study demonstrate that Stiefel's Clobetasol Propionate Emollient Cream 0.05%, is bioequivalent to the reference product, Glaxo Wellcome's Temovate E® Cream 0.05%.

The firm should be informed of the above recommendation.

/S/

Zakaria Z. Wahba, Ph.D.
Division of Bioequivalence
Review Branch III

RD INITIALLED BDAVIT BZW 8/2/01
FT INITIALLED BDAVIT /S/ 8/2/01

Concur: /S/ Date: 8/16/2001
for Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence

SEP 18 2000

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 75-733 APPLICANT: Stiefel Laboratories, Inc.

DRUG PRODUCT: Clobetasol Propionate Emollient Cream, 0.05%

The Division of Bioequivalence has completed its review of your submission(s) acknowledged on the cover sheet. The following comments are provided for your consideration:

1. Your proposal to manufacture a pilot batch of kg for your test drug product Clobetasol Propionate Emollient Cream, 0.05% to perform pivotal bioequivalence study is acceptable.

2. Your proposal to fill the manufactured pilot batch in two sizes of tubes (30 mg and 45 mg), is acceptable.

3. As mentioned in our previous correspondence, based on the analysis of your pilot study data the Division calculated an ED_{50} value of 11.25 minutes. Please use an ED_{50} not exceeding that value in designing your pivotal bioequivalence study.

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 # **75-733**
Reviewer: Z.Z. Wahba

Stiefel Laboratories
Coral Gables, FL
Submission Date:
June 20, 2000

REVIEW OF A STUDY AMENDMENT
(RESPONSE TO THE FIRM)

I. BACKGROUND

The firm is proposing to conduct the following:

1. Manufacture of a pilot batch of kg of its drug product Clobetasol Propionate Emollient Cream, 0.05% to perform a new pivotal bioequivalence study. The firm mentioned that it plans to use an ED_{50} of 15 minutes in the new study Note: The firm previously submitted a pivotal bioequivalence study which was found unacceptable (review date 4/11/200).

2. To fill the manufactured pilot batch in approximately seven hundred (700) - 30 g tubes which are identical to those submitted in the firm's ANDA. The remainder of the pilot batch will be filled in size tubes. The number of units filled is limited by available inventory of subject tubes. The firm plans to utilize the tubes to support a post approval change following anticipated approval of the ANDA.

II. COMMENTS (It should not be released under FOI)

1. With regard to the manufacturing of the pilot batch of kg and filled it in 30 g and g tubes: The CDER-Guidance "SUPAC-SS: Nonsterile Semisolid Dosage Forms; Scale-Up and Post-Approval Changes: Chemistry, Manufacturing and Controls; In Vitro Release Testing and In Vivo Bioeqivalence Documentation, issued 5/1997 and posted 6/16/1997" asks for at least 100 kg or 10% of a production batch, which is greater. Therefore, the firm's proposed batch size meets the Agency requirements.

   The issue of filling the manufactured pilot batch in two sizes of tubes (30 g and g), is more related to Chemistry than Bioequivalence. The Division of Chemistry I (Dr. Paul Schwartz, Team Leader) was consulted, and it was concluded that the firm's proposed plan is acceptable from the Division of Chemistry's point of view.

2. The firm mentioned that its goal is to achieve an acceptable pivotal bioequivalence study by utilizing an ED_{50} value of 15 minutes to comply with FDA's bioequivalence deficiency letter (dated 4/14/200).

Historical background: In the analysis of the firm's pilot study data (submission date 11/12/99), the Division of Bioequivalence calculated an ED_{50} of 11.25 minutes. This was one fourth of the ED_{50} value which the firm reported (review date 4/11/200). According to the Agency's research, sensitivity of the vasoconstrictor assay to detect potential difference in bioavaliability of test and reference products is markedly reduced at dose durations greater than the population ED_{50}. In house data, ANDAs #75-325, 75-633, 75-430 and a published article 1999 by Sing et al. in *Clin Pharmacol Ther* 1999;66:346-357, reported ED_{50} values of 6.9, 5.1, 6.3, and 10 minutes, respectively, for clobetasol propionate cream product.
Based on the available data, the acceptable value of an ED_{50} of a pilot study should not exceed 11 minutes.

III. RECOMMENDATIONS

1. The firm's proposal to manufacture a pilot batch of kg of its drug product Clobetasol Propionate Emollient Cream, 0.05% to perform pivotal bioequivalence study is acceptable.

2. The firm's proposal to fill its manufactured pilot batch in two sizes of tubes (30 g and 45 g), is acceptable.

3. An ED_{50} value not exceeding 11.25 minutes should be used for an acceptable pivotal bioequivalence study.

/S/
Zakaria Z. Wahba, Ph.D.
Division of Bioequivalence
Review Branch III

RD INITIALLED BDAVIT 8/14/00
FT INITIALLED BDAVIT /S/ 8/14/00

Concur: /S/ Date: 8/18/00
Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence

APR 14 200

BIOEQUIVALENCY DEFICIENCIES

ANDA: 75-733 APPLICANT: Stiefel Laboratories, Inc.

DRUG PRODUCT: Clobetasol Propionate Emollient Cream, 0.05%

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

From analysis of the pilot study data, the Division of Bioequivalence calculated an ED_{50} value of 11.25 minutes, which is one fourth of the ED_{50} value which you reported. Based on your ED_{50} value, you have used a dose duration of 45 minutes to compare the test and reference products in the pivotal bioequivalence study.

Based on the Agency research, sensitivity of the vasoconstrictor assay to detect potential difference in bioavaliability of test and reference products is markedly reduced at dose durations greater than the population ED_{50} (Singh et al, *Clin Pharmacol Ther* 1999;66:346-357).

Comparison of the test and reference products at dose durations greater than the population ED_{50} is not appropriate. Therefore, the pivotal bioequivalence study is not acceptable, due to the lack of sensitivity to detect potential differences between test and reference products.

You should conduct another pivotal bioequivalence study based on ED_{50} of approximately 11 minutes.

Sincerely yours,

/S/

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

CC: ANDA #75-733
ANDA DUPLICATE
DIVISION FILE
FIELD COPY
HFD-651/ Bio Secretary - Bio Drug File
HFD-658/ Reviewer (Z. Wahba)
HFD-658/ Team Leader (B. Davit)

Endorsements:
HFD-658/ Z. Wahba Z.W. 3/27/00
HFD-658/ B. Davit BDD 3/27/00
HFD-655/ G. Singh GDS 3/28/00
HFD-650/ D. Conner DJC 4/11/00

BIOEQUIVALENCY-DEFICIENCY Submission Date: November 12, 1999

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

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

Outcome Decisions:
UN *- Unacceptable*

WinBio Comments

Clobetasol Propionate
Emollient Cream, 0.05%
ANDA # **75-733**
Reviewer: Z.Z. Wahba

Stiefel Laboratories
Coral Gables, FL
Submission Date:
November 12, 1999

Review of a pilot dose response study and a pharmacodynamic bioequivalence study

I. BACKGROUND

Clobetasol propionate is a synthetic corticosteroid and an analog of prednisolone. It has a high degree of glucocorticoid activity and a slight degree of mineralocorticoid activity. It has anti-inflammatory, antipruritic, and vasoconstrictive properties.

The reference listed product is Glaxo Wellcome's Temovate E® cream, 0.05%

The firm has submitted two vasoconstrictor studies, a pilot dose-response study on the reference listed drug, Glaxo Wellcome's Temovate E® cream, 0.05%, and a pivotal bioequivalence study on its clobetasol propionate emollient cream, 0.05%, comparing it with Glaxo Wellcome's Temovate E® cream, 0.05%. The studies were conducted following the Agency's June 2, 1995 Guidance on Topical Dermatologic Corticosteroides.

II. Pilot Study #913 (Protocol #9608):

The pilot study was performed with the reference drug product, Glaxo Wellcome's Temovate E® cream, 0.05%.

A. Objective:

To estimate the population ED_{50} of the vasoconstrictive dose-response relationship for topical clobetasol propionate (Temovate E® cream, 0.05%).

B. Study Information:

Sponsor:	Stiefel Laboratories, Inc.
Clinical Site:	University of Utah School of Medicine Department of Dermatology, Salt Lake City, UT
Principal Investigator:	Lynn K. Pershing, Ph.D.
Medical Consultant:	Tena Rallis, M.D.
Study Date:	12/02/96 to 12/03/96

C. Study design:

One period, randomized, dose response of Temovate E® cream,

0.05%.

D. **Treatment information:**

Drug Treatment:	Temovate E® cream, 0.05%
Manufacturer:	Glaxo Wellcome
Lot No.:	#6J216
Expiration Date:	September 98

E. **Subjects**:

Twelve healthy subjects (11 female and 1 male), between ages of 19 to 65 were enrolled in the pilot study and all 12 subjects completed the study. Subjects were selected on acceptable medical history.

Inclusion/Exclusion Criteria:
Information listed in vol. 1.2, pages 152-154

IRB Approved: Information listed in vol. 1.2, pages 187-189

F. **Drug Application**:

Six 1.2 cm diameter circular skin sites were marked on both ventral forearms of each subject. Each skin site was assigned to a number (I-XII) on each subject, the right arm containing site numbers I-VI and left arm containing site number VII-XII (see schematic diagram on page 160, vol. C1.2). Each skin site was randomly assigned between two ventral forearms of each subject to dose durations of 0.25, 0.50, 0.75, 1, 1.5, 2, 4, and 6 hours. Two skin sites on each ventral forearm remained untreated and were used as control. The method of application used in this study was the "*Staggered application and synchronized removal*" method. All marked skin sites were measured for skin blanching of skin color at baseline by chromameter one hour prior to the 6-hour dose drug application. All designated sites were treated with a single dose of 5 µl (5 mg) of the drug formulation over the 1.13 cm^2 skin surface area using the conical end of a 1.5 mL polypropylene microcentrifuge tube. Skin blanching was evaluated visually as well using a chromameter at 0, 2, 4, 6, 8, 19 and 24 hours after drug removal (see schematic diagram on page 165, vol. C1.2).

G. **Adverse Events**: none

H. **Method of Validation**:

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pages of trade

secret and/or

confidential

commercial

information

method Validation

III. Pivotal Study #914 (Protocol #9609): Bioequivalence of Clobetasol Propionate Emollient Cream 0.05%

A. Objective:

To demonstrate *in vivo* bioequivalence between Stiefel's Clobetasol Propoionate Emollient Cream, 0.05%, and the reference listed product, Glaxo Wellcome's Temovate E® Cream, 0.05%.

B. Study Information:

Sponsor:	Stiefel Laboratories, Inc.
Clinical Site:	University of Utah School of Medicine Department of Dermatology, Salt Lake City, UT
Principal Investigator:	Lynn K. Pershing, Ph.D.
Medical Consultant:	Tena Rallis, M.D.
Study Date:	1/19/99 to 4/21/99

C. Subjects:

Seventy (70) healthy subjects (49 female and 21 male), between ages of 19 to 65 were enrolled and completed this pivotal study. Subjects were selected on acceptable medical history.

E. Inclusion/Exclusion Criteria:

Information listed in vol. 1.2, pages 280-281

F. Study design:

The pivotal study was conducted as a one-period/group study involving randomized applications of the test and reference formulations (page 289, volume C1.2). For each subject, eight 1.2 cm diameter circular skin sites were marked on each ventral forearm. Baseline chromameter readings were taken at all sites before the study drug products were applied. Thereafter, 5 mg of Temovate E® cream was applied for 22 (D1=1/2*ED50), 45 (ED50), or 90 (D2=2*ED50) minutes to the assigned sites on both arms. The test product (5 mg) was also applied at two sites on each arm for 45 (ED50) minutes. Two sites on each arm were left untreated. Application of drug products was in a staggered application design. The sites were protected with nonoccluding tape guards. At the end of the treatment duration (time zero) all sites were wiped with three independent nonsterile cotton applicators to remove residual drug. Chromameter readings (skin blanching assessments) were then taken at all sites at zero time and again at 2, 4, 6, 20 and 24 hours after drug removal.

The following treatments were administered in this study:

Test product: Stiefel's Clobetasol propionate emollient cream 0.05%, lot #D0739, expiration Date: 7/2000

Reference product: Galaxo Wellcome's Temovate E® cream 0.05%, lot #8H306, expiration Date: 9/2000

D1: Galaxo Wellcome's Temovate E® cream 0.05%, lot #8H306, expiration Date: 9/2000, applied for dose duration of 22 minutes.

D2: Galaxo Wellcome's Temovate E® cream 0.05%, lot #8H306, expiration Date: 9/2000, applied for dose duration of 90 minutes.

Study Dates:

Group I (n=21):	January 19-20, 1999
Group II (n=18):	February 9-10, 1999
Group III (n=8):	February 16-17, 1999
Group IV (n=8):	March 2-3, 1999
Group IV (n=15):	April 20-21, 1999

Total n=70 subjects

Study Protocol and Informed Consent:
The protocol used (Protocol #9609, study #914) and Informed Consent were approved by the (see page 308, vol. C1.1).

G. COMMENTS ON THE PIVOTAL BIOEQIVALENCE STUDY

The sponsor performed a pilot dose response study on the reference listed drug, Glaxo Wellcome's Temovate E® cream, 0.05%, based on the OGD guidance. The sponsor applied the population-based pharmacokinetic-dynamic modeling program (P-Pharm™, version 1.3c, SIMED, France) to determine the ED_{50}. An ED_{50} of 45 minutes was reported. For the pivotal bioequivalence study the sponsor used D_1, ED_{50} and D_2 values of 22, 45 and 90 minutes, respectively.

The dose duration (45 min) used for comparison of the test and reference products in the pivotal bioequivalence study is at least 4 times the ED_{50} calculated by the Division of Bioequivalence. Based on the Division analyses of the pilot study data, the use of the 45 minutes dose duration for comparing the test and reference products is not acceptable.

According to the Agency research, sensitivity of the vasoconstrictor assay to detect potential differences in bioavailability of test and reference products is markedly

reduced at dose durations greater than the population ED_{50} (Singh et al, *Clin Pharmacol Ther* 1999;66:346-357).

Therefore, the results from the pivotal study will not be reviewed since the ED_{50} value calculated by the firm is located on the portion of the dose response curve that is least sensitive to the differences in bioavailability of test and reference products, if any.

IV. FORMULATION COMPARISON (NOT TO BE RELEASED UNDER FOI):

Stiefel formulation for its test product, clobetasol propionate emollient cream, 0.05%, and the reference listed drug Glaxo Wellcome's Temovate E® cream, 0.05%, are given below:

Ingredient	[a]Stiefel's clobetasol propionate emollient cream, 0.05% (W/W%)	[b]Glaxo Wellcome's Temovate E® cream, 0.05% (W/W%)
Clobetasol Propionate, USP		
Ceteth-20		
Cetostearyl Acohol,NF		
Citric Acid USP (Monohydrate)		
Dimethicone NF		
Isopropyl Myristate NF		
Methylparaben NF		
Propylene Glycol USP		
Propylparaben NF		
Purified Water USP		
Sodium Citrate USP (Anhydrous)		

[a]The formulation was from the ANDA #75-733, reported on page 913, volume A1.4.
[b]From COMIS and also reported in the ANDA #75-430 report review (review date 11/28/99, reviewed by C. Kim, Pharm.D.)

V. **DEFICIENCY:**

Based on the analysis of the pilot study data, the Division of Bioequivalence calculated an ED_{50} value of 11.25 minutes, which is one fourth of the ED_{50} value reported by the firm. Based on its ED_{50} value, the firm used a dose duration of 45 minutes to compare the test and reference products in the pivotal bioequivalence study.

According to the Agency research, sensitivity of the vasoconstrictor assay to detect potential difference in bioavaliability of test and reference products is markedly reduced at dose durations greater than the population ED_{50} (Singh et al, *Clin Pharmacol Ther* 1999;66:346-357).

Comparison of test and reference at dose durations greater than the population ED_{50} is not appropriate. Therefore, the pivotal bioequivalence study is not acceptable, due to the lack of sensitivity to detect potential differences between test and reference products.

The sponsor should conduct another pivotal bioequivalence study based on ED_{50} of approximately 11 minutes.

VI. **RECOMMENDATIONS:**

The pivotal bioequivalence study conducted by Stiefel Laboratories comparing its clobetasol propionate emollient cream, 0.05%, lot #D0739 to the reference listed drug, Glaxo Wellcome's Temovate E® cream 0.05%, lot #8H306 has been found unacceptable to the Division of Bioequivalence due to the deficiency cited above.

/S/

Zakaria Z. Wahba, Ph.D.
Review Branch III
Division of Bioequivalence

3/24/00

RD INITIALLED BDAVIT
FT INITIALLED BDAVIT /S/ 3/27/00

Concur: /S/ Date 4/11/00
Dale P. Conner, Pharm. D.
Director
Division of Bioequivalence