CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75733

CHEMISTRY REVIEW(S)

APPROVAL PACAGE SUMMARY FOR 75-733

ANDA: 75-733

FIRM: Stiefel Laboratories, Inc.

DRUG: Clobetasol Propionate

DOSAGE: Emollient Cream

STRENGTH: 0.05%

CGMP STATEMENT/EIR UPDATE STATUS: EER is acceptable 1/7/00

BIO STUDY/BIOEQUIVALENCE: Bio is satisfactory 8/16/01

METHOD VALIDATION: Method validation is satisfactory 8/15/01

STABILITY: The firm has provided satisfactory six months accelerated stability data at 40°C/75%RH, 30°C/60%RH and 24 months room temperature at 25°±2°C/60%±5%RH. The stability samples stored horizontal and will be assayed at top, middle, and bottom for all the packaging sizes. The firm has provided cycle study data.

LABELING REVIEW STATUS: Labeling is satisfactory 5/11/01

STERILIZATION VALIDATION: N/A

BATCH SIZES: The firm has provided blank batch record for largest intended commercial production (1094.8) kg. Also submitted a copy of the exhibit batch lot #D0673 of (182.0) Kg. The firm will be using the same drug substance manufacture, same equipment and same process.

COMMENTS: The application is approvable.

REVIEWER: /S/ Nashed E. Nashed, Ph.D. DATE: 8/20/01 8/17/01

SUPERVISOR: Paul Schwartz, Ph.D. for RKS 8/17/01

1. CHEMISTRY REVIEW NO. 1

2. ANDA # 75-733

3. NAME AND ADDRESS OF APPLICANT

Stiefel Laboratories, Inc.
Route 145
Oak Hill, NY 12460

4. LEGAL BASIS FOR SUBMISSION

The firm certifies that to the best of their knowledge patent # 3,721,687 expired on 3/20/1992. The exclusivity expired May 3, 1999.

5. SUPPLEMENT(s)

Original 11/8/99

6. PROPRIETARY NAME

N/A

7. NONPROPRIETARY NAME

Clobetasol Propionate

8. SUPPLEMENT(s) PROVIDE(s) FOR:

N/A

9. AMENDMENTS AND OTHER DATES:

Amendment 12/10/99

10. PHARMACOLOGICAL CATEGORY

Anti-inflammatory

11. Rx or OTC

Rx

12. RELATED IND/NDA/DMF(s)

13. DOSAGE FORM

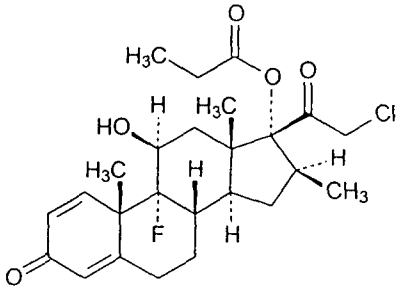
Emollient Cream

14. POTENCY

0.05%

15. CHEMICAL NAME AND STRUCTURE

Clobetasol Propionate. Pregna-1,4-diene-3,20-dione, 21-chloro-9-fluoro-11-hydroxy-16-methyl-17-(1-oxopropoxy)-, (11β,16β)-. $C_{25}H_{32}ClFO_5$. 466.99. 25122-46-7. Anti-inflammatory.



16. RECORDS AND REPORTS

17. COMMENTS

The firm will be asked to justify the reason for having (3)% overage.

The firm will be asked to provide integrity test for the liner.

The firm will be asked to explain the difference between certificates of analysis p. 1202 and p. 1225 regarding the individual and total related substances. In addition revise your limits based on your data.

The firm will be asked to revise their specifications for bulk and finished drug product to include limits and specifications for specific gravity and viscosity.

The firm will be asked to revise their stability specifications to include limits and specifications for specific gravity and viscosity.

The firm will be asked to revise their stability specifications for individual and total related substances based on their data.

The firm will be asked to explain the reason for having 3 tests for related substances for the drug substance.

The firm will be asked to revise their organic volatile impurities for the drug substance according to current USP 24.

The firm will be asked to define the objectionable microorganisms.

The firm will be asked to provide in-process bulk uniformity Test and specification including RSD limits.

18. CONCLUSIONS AND RECOMMENDATIONS

The application is not approvable.

19. REVIEWER: DATE COMPLETED:

Nashed E. Nashed, Ph.D 2/24/00

Supervisor: Paul Schwartz, Ph.D. 4/3/00

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Chem Review #1

38. Chemistry Comments to be Provided to the Applicant.

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

DRUG PRODUCT: Clobetasol Propionate Emollient Cream, 0.05%

The deficiencies presented below represent MAJOR deficiencies.

A. Deficiencies:

1. Please justify the reason for having a % overage of the drug substance in your formulation.

2. Please provide integrity testing for the tube liner.

3. Please explain the difference between certificates of analysis on page 1202 and page 1225 regarding the individual and total related substances. In addition, revise your limits based on your data.

4. Please revise your specifications for bulk and finished drug product to include limits and specifications for specific gravity and viscosity.

5. Please revise your stability specifications to include limits and specifications for specific gravity and viscosity.

6. Please revise your stability specifications for individual and total related substances based on your data.

7. Please explain the reason for having three tests for related substances for the drug substance.

8. Please revise your organic volatile impurities for the drug substance according to the current USP 24.

9. Please define the objectionable microorganisms.

10. Please provide an in-process bulk uniformity test and specification including RSD limits.

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

1. The firms referenced in your application regarding the manufacturing and testing of the drug product should be in compliance with CGMP's at the time of the approval.

2. The methods validation for the drug product has been submitted to an FDA District Laboratory for validation.

3. Your bioequivalence section is under review.

Sincerely yours,

/S/

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

1. CHEMISTRY REVIEW NO. 2

2. ANDA # 75-733

3. NAME AND ADDRESS OF APPLICANT

Stiefel Laboratories, Inc.
Route 145
Oak Hill, NY 12460

4. LEGAL BASIS FOR SUBMISSION

The firm certifies that to the best of their knowledge patent # 3,721,687 expired on 3/20/1992. The exclusivity expired May 3, 1999.

5. SUPPLEMENT(s)

Original 11/8/99

6. PROPRIETARY NAME

N/A

7. NONPROPRIETARY NAME

Clobetasol Propionate

8. SUPPLEMENT(s) PROVIDE(s) FOR:

N/A

9. AMENDMENTS AND OTHER DATES:

Amendment 11/14/00
Amendment 1/30/01 - Bio

10. PHARMACOLOGICAL CATEGORY

Anti-inflammatory

11. Rx or OTC

Rx

12. RELATED IND/NDA/DMF(s)

13. DOSAGE FORM

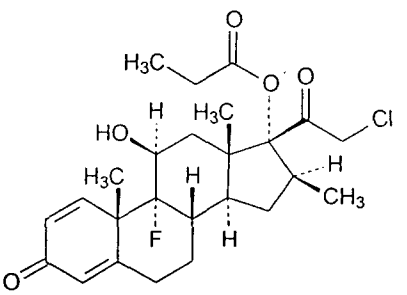
Emollient Cream

14. POTENCY

0.05%

15. CHEMICAL NAME AND STRUCTURE

Clobetasol Propionate. Pregna-1,4-diene-3,20-dione, 21-chloro-9-fluoro-11-hydroxy-16-methyl-17-(1-oxopropoxy)-, (11β,16β)-.$C_{25}H_{32}ClFO_5$. 466.99. 25122-46-7. Anti-inflammatory.



16. RECORDS AND REPORTS

17. COMMENTS

The firm will be asked to propose limits for viscosity and specific gravity based on the available data for bulk, finished drug product and stability.

18. CONCLUSIONS AND RECOMMENDATIONS

The application is not approvable-minor

19. REVIEWER: DATE COMPLETED:

Nashed E. Nashed, Ph.D 6/7/01

Supervisor: Paul Schwartz, Ph.D. 6/8/01

cc: ANDA 75-733
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Endorsements:
HFD-623/NNashed/
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F/T by: DJ 6/15/01

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Chem Review #2

38. Chemistry Comments to be Provided to the Applicant.

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

DRUG PRODUCT: Clobetasol Propionate Emollient Cream, 0.05%

The deficiencies presented below represent MINOR deficiencies.

A. Deficiencies:

1.) Please propose limits for viscosity and specific gravity based on the available data for bulk, finished drug product and stability.

2.) In addition to responding to the deficiencies presented above, please note and respond to the FDA district laboratory comments regarding your methods validation:

a.) For the related substances test, response factor was not used in the calculation. The absorptivity of the related substances may not be the same as that of clobetasol propionate at nm.

b.) The sample preparation for the assay analysis was also used for the related substances determination, however, an internal standard was used for the assay analysis. The presence of an internal standard in the solution used for related substance determination rendered the determination inaccurate. In this case, the internal standard,) contains some impurities with retention times that are very similar to the retention times of the related substances of clobetasol propionate. If the sample preparation is to be used for the assay and related substances determination, an internal standard should not be used.

c.) Page 5 of the method states "consult your supervisor if peaks appear after the internal standard peak". Review of the company's worksheet found that peaks eluted after the internal standard peak were not calculated. If these peaks are to be excluded in the calculation of the related substances, the method should state so clearly.

d.) The method calls for the preparation of the limit of detection preparation only for the analysis of the placebo. In addition, the procedure of the preparation only states to prepare an appropriate dilution of "standard A". The limit of detection

test is mandatory for every related substances determination.

e.) The specifications used were from page 1377 of the submission. These specifications were approved in August, 1999. The specifications indicated on the firm's worksheet were slightly different (% for assay as compare to the limits of % % that used). The district laboratory could not determine which are the current specifications.

B. In addition to the above deficiencies, please note and acknowledge the following:

1.) Your bioequivalence amendment of Jan 30, 2001 is under review.

2.) Please provide any additional long-term stability data.

Sincerely yours,

/S/

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

1. CHEMISTRY REVIEW NO. 3

2. ANDA # 75-733

3. NAME AND ADDRESS OF APPLICANT

Stiefel Laboratories, Inc.
Route 145
Oak Hill, NY 12460

4. LEGAL BASIS FOR SUBMISSION

The firm certifies that to the best of their knowledge patent # 3,721,687 expired on 3/20/1992. The exclusivity expired May 3, 1999.

5. SUPPLEMENT(s)

Original 11/8/99

6. PROPRIETARY NAME

N/A

7. NONPROPRIETARY NAME

Clobetasol Propionate

8. SUPPLEMENT(s) PROVIDE(s) FOR:

N/A

9. AMENDMENTS AND OTHER DATES:

Amendment 11/14/00
Amendment 1/30/01 - Bio
Amendment 8/7/01

10. PHARMACOLOGICAL CATEGORY

Anti-inflammatory

11. Rx or OTC

Rx

12. RELATED IND/NDA/DMF(s)

13. DOSAGE FORM

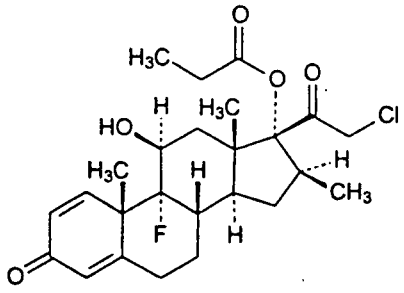
Emollient Cream

14. POTENCY

0.05%

15. CHEMICAL NAME AND STRUCTURE

Clobetasol Propionate. Pregna-1,4-diene-3,20-dione, 21-chloro-9-fluoro-11-hydroxy-16-methyl-17-(1-oxopropoxy)-, (11β,16β)-. $C_{25}H_{32}ClFO_5$. 466.99. 25122-46-7. Anti-inflammatory.



16. RECORDS AND REPORTS

17. COMMENTS

18. CONCLUSIONS AND RECOMMENDATIONS

The application is approvable.

19. REVIEWER: DATE COMPLETED:

Nashed E. Nashed, Ph.D 8/17/01

Supervisor: Ramesh Sood, Actg. TL 8/17/01

cc: ANDA 75-733
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Endorsements:

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Chem Review #3