

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**21-152**

**CHEMISTRY REVIEW(S)**

**NDA 21-152**

**CUTIVATE®**  
**fluticasone propionate lotion**  
**0.05%**

**GlaxoSmithKline**

**Allan Fenselau, Ph.D.**  
**Division of Dermatologic and Dental Drug Products**  
**(HFD-540)**

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# Chemistry Review Data Sheet

1. **NDA 21-152**
2. **REVIEW: # 2**
3. **REVIEW DATE: 21-MAR-2005**
4. **REVIEWER: Allan Fenselau**
5. **PREVIOUS DOCUMENTS:**  
**SUBMISSIONS REVIEWED PREVIOUSLY IN REVIEW #1**

<b>Submission(s) Reviewed</b>	<b>Document Date</b>
Original	13-DEC-1999
Withdrawn	25-MAY-2000
Resubmission	11-MAR-2004
Amendment (BZ)	13-MAY-2004
Amendment (BC)	19-JUL-2004
Amendment (BZ)	23-JUL-2004
Amendment (BL)	03-AUG-2004
Amendment (BC)	01-NOV-2004
Amendment (BC)	19-NOV-2004
Amendment (BC)	09-DEC-2004

6. **SUBMISSION(S) BEING REVIEWED:**

<b>Submission(s) Reviewed</b>	<b>Document Date</b>
Original	13-DEC-1999
Resubmission	11-MAR-2004
Amendment (AZ)	31-JAN-2005
Amendment (BC)	17-MAR-2005
Amendment (BL)	24-MAR-2005
Amendment (BC)	25-MAR-2005
Amendment (BL)	29-MAR-2005
[received as an e-mail]	

7. **NAME & ADDRESS OF APPLICANT:**

<b>Name:</b>	GlaxoSmithKline
<b>Address:</b>	1500 Littleton Road Parsippany, NJ 07054-3884
<b>Representative:</b>	Anthony Amitrano
<b>Telephone:</b>	973-889-2566

**8. DRUG PRODUCT NAME/CODE/TYPE:**

- a) Proprietary Name: **CUTIVATE® Lotion**
- b) Non-Proprietary Name (USAN): **Fluticasone propionate**
- c) Code Name/# (ONDC only):
- d) Chem. Type/Submission Priority: **3/S**

**9. LEGAL BASIS FOR SUBMISSION: Not Applicable**

**10. PHARMACOLOGICAL CATEGORY: Anti-inflammatory**

**11. DOSAGE FORM: Lotion**

**12. STRENGTH/POTENCY: 0.05% w/w**

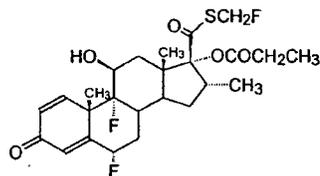
**13. ROUTE OF ADMINISTRATION: Topical**

**14. R<sub>x</sub>/OTC DISPENSED:  X  R<sub>x</sub>      OTC**

**15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):**

SPOTS product – Form Completed  
 X  Not a SPOTS product

**16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:**



**FLUTICASONE PROPIONATE**

$C_{25}H_{31}F_3O_5S$

M.W.: 500.58

CAS-80474-14-2

*S*-(Fluoromethyl) 6 $\alpha$ ,9-difluoro-11 $\beta$ ,17-dihydroxy-16 $\alpha$ -methyl-3-oxoandrosta-1,4-diene-17 $\beta$ -carbothioate, 17-propionate

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# EXECUTIVE SUMMARY

## Chemistry Review for NDA 21-152

### I. Recommendations

#### A. Recommendation and Conclusion on Approvability

The recommendation of the initial chemistry, manufacturing and controls [CMC] review for NDA 21-152, CUTIVATE (fluticasone propionate) Lotion, 0.05%, was that the submission was APPROVABLE. Resolution of the following CMC issues was required for approval: 1) no regulatory testing of the particle size of the [redacted] drug substance, 2) no testing of [redacted] of the bulk product, 3) no regulatory testing of product viscosity, including a validated analytical method and satisfactory acceptance criteria, 4) an unapproved drug product specification, 5) no stability studies performed with the recently-specified 60mL bottle, 6) CMC-related labeling issues (e.g., statement of storage conditions and number of commercial sizes), and 7) an unapproved product tradename [redacted]. The amendments dated 31-JAN-2005, 17-MAR-2005, and 25-MAR-2005 have addressed these issues.

#### B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

Not Applicable

### II. Summary of Chemistry Assessments

#### A. Response to Approvability Issues

Details of the complete CMC review of drug substance and drug product may be found in Chemistry Review #1 for NDA 21-152. The following summarizes the review of the sponsor's responses to the ten approvability issues forwarded to them in the 12-JAN-2005 Approvability Letter. Acceptable testing of [redacted] of the bulk product has been incorporated into manufacturing operations. The requested regulatory testing of the particle size of the drug substance and viscosity of the drug product has now been included. The corresponding specifications have been revised appropriately and are now acceptable. The first batch of product in the new 60mL bottle will be subjected to an acceptable stability test protocol employing storage conditions that comply with ICH Guideline Q1A(R2). These stability study results will be submitted in subsequent annual reports. All of the CMC-related labeling issues, such as the statement of storage conditions and number of commercial sizes, have been satisfactorily resolved. Finally, the product tradename will now employ "lotion" [redacted] permitting approval of the product name.

#### B. Intended Use of the Drug Product

CUTIVATE (fluticasone propionate) Lotion, 0.05% is intended to serve as an alternative mode of treatment for corticosteroid-responsive dermatoses, such as psoriasis and eczematous dermatitis. This lotion product extends the line of CUTIVATE products that includes CUTIVATE Ointment, 0.005% (NDA 19-957 approved 14-DEC-1990) and CUTIVATE Cream 0.05% (NDA 19-958 approved 18-DEC-1990).

#### C. Basis for Recommendation

Based on the CMC information provided in the amendments submitted in response to specific items contained in the Approvable Letter dated 12-JAN-2005, this New Drug Application can now be approved.

**III. Administrative**

**A. Reviewer's Signature**

**B. Endorsement Block**

A.FENSELAU/22-MAR-2005: Same date as draft review

R.SOOD/22-MAR-2005:

M.WRIGHT/22-MAR-2005:

**C. CC Block**

HFD-830

C.-w.CHEN/:

N.SCHMUFF/:

8 Page(s) Withheld

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/s/

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Allan Fenselau  
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Ramesh Sood  
3/29/05 03:50:39 PM  
CHEMIST

CHEMISTRY REVIEW

CDER

CDER

*Cme  
review  
for VI2/05 A&B*

**NDA 21-152**

**CUTIVATE®  
fluticasone propionate lotion  
0.05%**

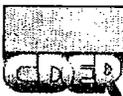
**GlaxoSmithKline**

**Allan Fenselau, Ph.D.  
Division of Dermatologic and Dental Drug Products  
(HFD-540)**



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# Chemistry Review Data Sheet

1. **NDA 21-152**
2. **REVIEW: # 1**
3. **REVIEW DATE: 12-JAN-2005**
4. **REVIEWER: Allan Fenselau**
5. **PREVIOUS DOCUMENTS: None**
6. **SUBMISSION(S) BEING REVIEWED:**

Submission(s) Reviewed	Document Date
Original	13-DEC-1999
Withdrawn	25-MAY-2000
Resubmission	11-MAR-2004
Amendment (BZ)	13-MAY-2004
Amendment (BC)	19-JUL-2004
Amendment (BZ)	23-JUL-2004
Amendment (BL)	03-AUG-2004
Amendment (BC)	01-NOV-2004
Amendment (BC)	19-NOV-2004
Amendment (BC)	09-DEC-2004

**7. NAME & ADDRESS OF APPLICANT:**

<b>Name:</b>	GlaxoSmithKline
<b>Address:</b>	1500 Littleton Road Parsippany, NJ 07054-3884
<b>Representative:</b>	Anthony Amitrano
<b>Telephone:</b>	973-889-2566

**8. DRUG PRODUCT NAME/CODE/TYPE:**

- a) **Proprietary Name:** CUTIVATE® Lotion
- b) **Non-Proprietary Name (USAN):** Fluticasone propionate
- c) **Code Name/# (ONDC only):**
- d) **Chem. Type/Submission Priority:** 3/S

**9. LEGAL BASIS FOR SUBMISSION: Not Applicable**



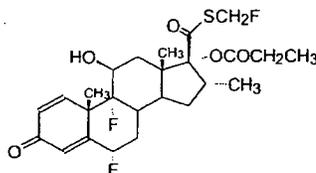
# CHEMISTRY REVIEW



10. PHARMACOLOGICAL CATEGORY: Anti-inflammatory
11. DOSAGE FORM: Lotion
12. STRENGTH/POTENCY: 0.05% w/w
13. ROUTE OF ADMINISTRATION: Topical
14. R<sub>x</sub>/OTC DISPENSED:  X  R<sub>x</sub>    \_\_\_ OTC
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

\_\_\_ SPOTS product – Form Completed  
 X  Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:



**FLUTICASONE PROPIONATE**

C<sub>26</sub>H<sub>31</sub>F<sub>3</sub>O<sub>5</sub>S

M.W.: 500.58

CAS-80474-14-2

S-(Fluoromethyl) 6 $\alpha$ ,9-difluoro-11 $\beta$ ,17-dihydroxy-16 $\alpha$ -methyl-3-oxoandrosta-1,4-diene-17 $\beta$ -carbothioate, 17-propionate

or

( $\pm$ )-*cis*-1-Acetyl-4-[p-[[2-(2,4-dichlorophenyl)-2-(imidazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]piperazine

**LISTING of MANUFACTURING and TESTING SITES USED in the MANUFACTURE of the DRUG PRODUCT, CUTIVATE LOTION**

DMF NO./TYPE	CFN	HOLDER	DESCRIPTION	LOA	Insp. Ready	Insp. Status	ADDRESS
<b>FLUTICASONE PROPIONATE</b>							
NDA 19-957	NI	GlaxoSmithKline	DS manuf. /testing (release & stability)	----	NI	NI	NI
<b>CUTIVATE Lotion</b>							
----	NI	Glaxo Wellcome Inc.	DP manuf./ testing/ (release & stability) DP microb.limit testing DP filling/pckging.	----	NI	NI	7333 Mississauga Rd.North Mississauga, Ontario L5N5L4 Canada

Abbreviations used: DS, Drug Substance; DP, Drug Product; NI, No information. (See Review p. 48)

**CHEMISTRY REVIEW**

**SUPPORTING DOCUMENTS:**

DMF No.	TYPE	HOLDER	ITEM REFERENCED	LOA <sup>1</sup> DATE	DATE of LAST REVIEW
NDA 19-957	---	GlaxoSmithKline	Fluticasone propionate	NA <sup>2</sup>	NA <sup>2</sup>
	III			Y 27-OCT-1999 <sup>3</sup>	Adequate info. provided in NDA
	III			Y 10-NOV-1999 <sup>3</sup>	Adequate info. provided in NDA
	III			Y 14-OCT-1999 <sup>3</sup>	Adequate info. provided in NDA
	III			Y 13-OCT-1999 <sup>3</sup>	Adequate info. provided in NDA
				01-NOV-1999	

- 1 LOA = Letter of Authorization; Included Yes/No [Y/N]; LOA Date
- 2 NA = Not Applicable
- 3 Letter is not dated within 1 year of the submission date. (See Review p. 30.)

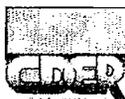
**17. RELATED/SUPPORTING DOCUMENTS:**

Documents	Document Date
INDs: 63,153	Filed 03-OCT-2002
NDA's: 19-957 19-958	Approved 14-DEC-1990 Approved 18-DEC-1990
Patents: None listed	-----

**18. STATUS: ONDC**

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	NA	---	---
EES	Acceptable	29-MAR-2004	S.Adams
Pharm/Tox	NA	---	---
Biopharm	NA	---	---
LNC	Unresolved	---	G.Poochikian
Methods Validation	To be submitted to FDA labs.	---	---
DMETS/OPDRA	Acceptable	09-NOV-2004	S.Dallas
EA	Acceptable	12-JAN-2005	A.Fenselau
Microbiology	NA	---	---

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# EXECUTIVE SUMMARY

## Chemistry Review for NDA 21-152

### I. Recommendations

#### A. Recommendation and Conclusion on Approvability

The recommendation for NDA 21-152, CUTIVATE (fluticasone propionate lotion) 0.05%, is APPROVABLE. Satisfactory resolution of the following chemistry, manufacturing and controls [CMC] issues is required: 1) no regulatory testing of the particle size of the [redacted] drug substance, 2) no testing of [redacted] of the bulk product, 3) no regulatory testing of product viscosity, including a validated analytical method and satisfactory acceptance criteria, 4) an unapproved drug product specification, 5) no stability studies performed with the recently-specified 60mL bottle, 6) CMC-related labeling issues (e.g., statement of storage conditions and number of commercial sizes), and 7) an unapproved product tradename [redacted].

#### B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Applicable

Not Applicable

### II. Summary of Chemistry Assessments

#### A. Description of the Drug Substance(s) and Drug Product(s)

Drug Substance: Fluticasone propionate is synthesized according to the procedure described in the NDA 19-957 for Cutivate Ointment and is supplied by Glaxochem, Ltd. (Montrose, UK) or Glaxo Wellcome (Jurong, Singapore). The drug substance specification (as contained in either NDA 19-957 or NDA 19-958 for Cutivate Cream) is generally acceptable; however, it lacks testing for particle size that would be expected for a drug substance indicated to be [redacted]. To justify the absence of particle size testing in the drug product, the drug substance specification for fluticasone propionate [redacted] will need to be revised to include particle size testing, employing acceptance criteria that are consistent with those applied to the batch of drug substance used to manufacture drug product stability batches.

Drug Product: The composition of the proposed new product Cutivate Lotion is similar to that for the approved product Cutivate Cream. Many of the components are shared by the two formulations, providing reassurance on the compatibility of the materials in the new lotion drug product. The lotion formulation, however, does include two [redacted] (methylparaben and propylparaben) in addition to imidurea, the [redacted] dimethicone, and [redacted] cetomacrogol 1000. All of these components, except cetomacrogol 1000, are USP/NF compendial grade. Cetomacrogol 1000 is described in the British Pharmacopeia, whose specification is employed in testing for this excipient. UV-visible absorption spectra of the components of Cutivate Lotion, 0.05% from [redacted] have been provided [as requested by the Agency at the pre-NDA meeting] and are satisfactory. The product contains no novel excipients or excipients of human or animal origin.

The manufacturing, packaging, and testing operations are performed at the same facility: Glaxo Wellcome Inc. (Mississauga, Canada). The manufacturing process has been adequately summarized. Details of a batch manufacturing record have been provided for a primary NDA stability batch (8J257) of Cutivate Lotion, 0.05%, manufactured at Mississauga, Canada. Process controls are generally acceptable, except that no discussion of [redacted] has been provided. Any batch of Cutivate Lotion, 0.05% that fails to meet the release specifications will not be reprocessed, but will be fully accounted for and properly destroyed.

The product specification includes testing for Appearance, Identification (by HPLC and TLC), pH (of 10% aqueous solution), Viscosity, Fluticasone Propionate Content (by HPLC), Drug-Related Impurities [redacted] Individual Unspecified, and Total] (by HPLC), [redacted] [Imidurea (by colorimetry) and Methylparaben and Propylparaben (by HPLC)], and Microbial Limits. The product does not make a sterile claim; however, it does contain preservatives in adequate amounts to ensure compliance with



## CHEMISTRY REVIEW



antimicrobial preservative efficacy requirements. Except for determining product viscosity, the listed testing and acceptance criteria are acceptable. Also, where required, method validation appears adequate; the method validation package will be submitted to the FDA laboratories following NDA approval. The viscosity method, which underwent significant change after stability studies with the registration batch had passed the 18-month test station, has not been described. Acceptance criteria for product viscosity have not been proposed, which will impede efforts at unequivocally differentiating the approved cream product from the proposed lotion product (see later comment on product viscosity). The absence of viscosity testing precludes approval of the product specification.

The original submission stated that Cutivate Lotion, 0.05% would be packed in 60mL [redacted] round, white [redacted] bottles with white [redacted] flip-top closures for commercial use [redacted].

[redacted] Subsequently, the sponsor learned that the mold for the original commercial size bottles had been discontinued by the supplier. [redacted]

[redacted] In their 29-NOV-2004 amendment, the sponsor notified the Agency that they intend to employ a 60mL (or 2 ounce) [redacted] Round bottle as the only commercial-sized container. The information comparing the two 60mL bottles supports the conclusion that the new 60mL bottle is equivalent to the original 60mL bottle and that its use in the product manufacture can be approved.

Stability studies have been performed on three [redacted] production-scale batches of CUTIVATE (fluticasone propionate lotion) 0.05%. These batches were manufactured at GSK Mississauga, Canada, using drug substance manufactured at GSK Operations, Montrose, UK (Batches 8C283 and 8B310) and GSK Operations, Singapore (Batch 8J257). Each batch was stored in the [redacted] 60mL, [redacted] bottles with [redacted] flip-top closures. Details on the manufacture and packaging of these batches have been submitted and verify that at release all batches complied with the product specification. No studies with the proposed replacement 60mL bottle have been carried out.

[redacted] The samples of the 60mL [redacted] bottles were stored at 30°C/60% RH in various orientations. Batches 8B310 and 8C283 were tested through 24 months, while batch 8J257 was tested over 30 months. [redacted] bottle sizes were also stored at 40°C/75% RH in only the horizontal orientation and tested through 6 months.

Only 12 months of data were submitted in the 2004 NDA, requiring the sponsor, upon request, to provide updates through the termination of the original studies (indicated to be no later than February 2001). Results of all testing with the 60mL [redacted] bottles complied with the product specification. Evident in the results for selected quantitative tests (contents of fluticasone propionate, total degradants, and methylparaben) is the satisfactory stability of the product during 24 months of storage at 30°C and 6 months at 40°C. These findings support a 24 month expiry period for the [redacted] "commercial" sizes. [redacted]

[redacted] The proposed post-approval stability protocol and stability commitment are standard statements and are acceptable.

When the product was stored at 30°C and 40°C, viscosity remained stable with a tendency to decrease over time. However, during 12 months of storage at lower temperatures from 2°-8°C, viscosity irreversibly increased from an initial value of approximately [redacted]. Similar but smaller in magnitude were the viscosity increases when the product was subjected to heat/cool (2°C/40°C) cycling. No explanation for these findings was presented. When placebo samples with viscosity values at these limits were obtained from the sponsor, it was found that a [redacted] sample was a pourable liquid (consistent with a lotion), whereas a [redacted] sample was a non-pourable semi-solid (consistent with a cream). These findings reveal that, unless it is stored properly, the product—claimed to be a lotion—can become a cream, bringing into doubt any advantage that this temperature-modified Cutivate Lotion would have over the approved product, Cutivate Cream. The results also justify the need to perform viscosity testing using satisfactory acceptance criteria as part of the product specification.

Three labeling issues have been identified: 1) storage statements to be made on the container label and in the Package Insert, 2) the "How Supplied" statement, and 3) the product name (primarily regarding the [redacted]). The issue with the label storage conditions will be resolved by revising the label to read: "Store between 15°C and 30°C (59°F and 86°F). Do not refrigerate. Keep container tightly closed." Another revision requires that the statement regarding the availability of the product in [redacted] fill sizes (60mL [redacted]) be corrected to read only a 60mL size will be available.

The major issue still to be resolved is whether the product name [redacted] "Lotion" (Agency recommendation). Although the product name of Cutivate Lotion given in the original 1999 NDA submission has been changed to Cutivate [redacted] in the 2004 submission now under review, no justification for this name change has ever been provided. The term [redacted] is not acceptable to the Agency in that the term creates and prolongs unnecessary confusion by its general use in [redacted]. Presently the Agency is in the process of re-examining the existing classification of dosage forms for topical drugs to ensure that definitions for different dosage forms are based on consistent principles and that dosage forms can be distinguished from one another. In this context of re-evaluating the classification of topical dosage forms, the term "lotion" is defined as a "liquid emulsion," which is consistent with the present product. The more cogent arguments presented by the sponsor to support approval of their preferred name are the existence of approved products whose names include the use of [redacted] and the need to clinically differentiate topical products that contain or lack [redacted]. The Agency recognizes that mislabeling of topical drug products exists and that this will be corrected with adoption of a new classification system. At this time, however, there is no justification for continuing to approve mislabeled products. [redacted]

[redacted] The sponsor's definition of an emulsion would only add more confusion to an already-confused situation. The recommendation is that the product name of "CUTIVATE (fluticasone propionate lotion) 0.05%" be employed. If, after all other deficiencies have been satisfactorily addressed, the sponsor cannot agree with this product name, they will be informed that the product may not be marketed until issues surrounding the designation of the dosage form have been fully resolved.

The proposed action is subject to the categorical exclusion listed in 21 CFR Part 25.31(b). All manufacturing and testing sites for drug substance and drug product have been recommended for Approval by the Office of Compliance [OC].

**B. Intended Use of the Drug Product**

CUTIVATE (fluticasone propionate) Lotion 0.05% is intended to serve as an alternative mode of treatment for corticosteroid-responsive dermatoses, such as psoriasis and eczematous dermatitis. This lotion product extends the line of CUTIVATE products that includes CUTIVATE Ointment, 0.005% (NDA 19-957 approved 14-DEC-1990) and CUTIVATE Cream 0.05% (NDA 19-958 approved 18-DEC-1990).

**C. Basis for Approvability or Not-Approval Recommendation**

*See opening comment.*

**III. Administrative**

**A. Reviewer's Signature**

**B. Endorsement Block**

A.FENSELAU/12-JAN-2005: Same date as draft review

R.SOOD/12-JAN-2005:

M.WRIGHT/12-JAN-2005:

**C. CC Block**

HFD-830

C.-w.CHEN/:

N.SCHMUFF/:

43 Page(s) Withheld

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/s/  
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Allan Fenselau  
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CHEMIST

I included under "Submission Information" the original submission 13-DEC-19  
and its withdrawal date 25-MAY-2000. This may not  
be correct. I did not include a BC  
in 2000 because I never looked at it.

Ramesh Sood  
1/12/05 10:50:16 AM  
CHEMIST