

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-152

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS

Department of Health and Human Services
Food and Drug Administration

Form Approved: OMB No. 0910-0513
Expiration Date: 7/31/06
See OMB Statement on Page 3.

**PATENT INFORMATION SUBMITTED WITH THE
FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT**
*For Each Patent That Claims a Drug Substance
(Active Ingredient), Drug Product (Formulation and
Composition) and/or Method of Use*

NDA NUMBER
21-152

NAME OF APPLICANT / NDA HOLDER
GlaxoSmithKline Consumer Healthcare

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME)

Cutivate®

ACTIVE INGREDIENT(S)
fluticasone propionate

STRENGTH(S)
0.05%

DOSAGE FORM
Topical emulsion

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4). Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the *only* information relied upon by FDA for listing a patent in the Orange Book.

For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

FDA will not list patent information if you submit an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number

b. Issue Date of Patent

c. Expiration Date of Patent

d. Name of Patent Owner

Address (of Patent Owner)

City/State

ZIP Code

FAX Number (if available)

Telephone Number

E-Mail Address (if available)

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)

Address (of agent or representative named in 1.e.)

City/State

ZIP Code

FAX Number (if available)

Telephone Number

E-Mail Address (if available)

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above?

Yes

No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?

Yes

No

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

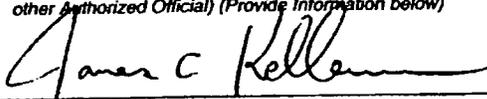
2. Drug Substance (Active Ingredient)	
2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?	<input type="checkbox"/> Yes <input type="checkbox"/> No
2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?	<input type="checkbox"/> Yes <input type="checkbox"/> No
2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).	<input type="checkbox"/> Yes <input type="checkbox"/> No
2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.	
2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)	
<input type="checkbox"/> Yes <input type="checkbox"/> No	
2.6 Does the patent claim only an intermediate?	
<input type="checkbox"/> Yes <input type="checkbox"/> No	
2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	
<input type="checkbox"/> Yes <input type="checkbox"/> No	
3. Drug Product (Composition/Formulation)	
3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?	
<input type="checkbox"/> Yes <input type="checkbox"/> No	
3.2 Does the patent claim only an intermediate?	
<input type="checkbox"/> Yes <input type="checkbox"/> No	
3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	
<input type="checkbox"/> Yes <input type="checkbox"/> No	
4. Method of Use	
<i>Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:</i>	
4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	
<input type="checkbox"/> Yes <input type="checkbox"/> No	
4.2 Claim Number (as listed in the patent)	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?
	<input type="checkbox"/> Yes <input type="checkbox"/> No
4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: (Submit indication or method of use information as identified specifically in the proposed labeling.)
5. No Relevant Patents	
For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product.	
<input checked="" type="checkbox"/> Yes	

6. Declaration Certification

6.1 *The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.*

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide Information below)



Date Signed

03/11/2004

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

<input type="checkbox"/> NDA Applicant/Holder	<input type="checkbox"/> NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
<input type="checkbox"/> Patent Owner	<input checked="" type="checkbox"/> Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name

James C. Kelleman

Address

709 Swedeland Rd.

City/State

King of Prussia, PA

ZIP Code

19406

Telephone Number

(610) 270-5929

FAX Number (if available)

(610) 270-5090

E-Mail Address (if available)

james.c.kelleman@gsk.com

The public reporting burden for this collection of information has been estimated to average 9 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Food and Drug Administration
CDER (HFD-007)
5600 Fishers Lane
Rockville, MD 20857

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

EXCLUSIVITY SUMMARY

NDA # 21-152

SUPPL #

HFD # 540

Trade Name Cutivate Lotion, 0.05%

Generic Name fluticasone propionate

Applicant Name GlaxoSmithKline

Approval Date, If Known

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3, SE4, SE5, SE6, SE7, SE8

505(b)(1)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES NO

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES NO

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

3 years

e) Has pediatric exclusivity been granted for this Active Moiety?

YES NO

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

Yes, but additional studies were also done with other formulations. Please note this NDA was WD because Sponsor didn't want to pursue marketing at that time.

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES NO

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 19-957 Cutivate (fluticasone propionate) Ointment, 0.005%

NDA# 19-958 Cutivate (fluticasone propionate) Cream, 0.05%

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary

for that investigation.

YES NO

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES NO

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES NO

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES NO

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES NO

If yes, explain:

- (c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

1. FPL30003
2. FPL30004

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES NO

Investigation #2 YES NO

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES NO

Investigation #2 YES NO

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Jonathan Wilkin
3/31/05 03:46:39 PM

New Drug Application

NDA 21-152; CUTIVATE®
(fluticasone propionate) 0.05%

DEBARMENT CERTIFICATION

Glaxo Wellcome hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug and Cosmetic Act in connection with this application.



Charles E. Mueller
Head, Clinical Compliance
World Wide Compliance

19 NOV 1999

Date

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA #: 21-152 Supplement Type (e.g. SE5): _____ Supplement Number: _____

Stamp Date: February 1, 2005 (AZ for AE ltr) Action Date: April 1, 2005

HFD-540 Trade and generic names/dosage form: Cutivate (fluticasone propionate) Lotion, 0.05%

Applicant: GlaxoSmithKline Therapeutic Class: 3S

Indication(s) previously approved: NDA 19-957/Cutivate Ointment, 0.005%--tx of corticosteroid-responsive dermatoses in adult patients. NDA 1919-958 --958/Cutivate Cream, 0.05%--tx of corticosteroid-responsive dermatoses;

Cutivate Cream may be used with caution in pediatric patients as young as 3 months

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): 1

Indication #1: Tx of atopic dermatitis in patients as young as 1 year

Is there a full waiver for this indication (check one)?

Yes: Please proceed to Section A.

X No: Please check all that apply: Partial Waiver x Deferred x Completed

NOTE: More than one may apply

Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Other: _____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Reason(s) for partial waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: _____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____ kg _____ mo. 0 yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. 1 Tanner Stage _____

Reason(s) for deferral:

Products in this class for this indication have been studied/labeled for pediatric population

Disease/condition does not exist in children

Too few children with disease to study

There are safety concerns

Adult studies ready for approval

Formulation needed

Other: Post-marketing commitment to study 3 months to 1 year.

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____ kg _____ mo. _____ yr. 1 Tanner Stage _____
Max _____ kg _____ mo. _____ yr. 18 Tanner Stage _____

Comments:

Completed studies do not provide an adequate assessment of safety in the 3 month to 1 year population, especially when used to treat _____ atopic dermatitis.

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

cc: NDA 21-152
HFD-960/ Grace Carmouze

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337.

(revised 12-22-03)

Attachment A

(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: N/A

Is there a full waiver for this indication (check one)?

- Yes: Please proceed to Section A.
- No: Please check all that apply: Partial Waiver Deferred Completed
NOTE: More than one may apply
Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Other: _____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Reason(s) for partial waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: _____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Reason(s) for deferral:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: _____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Comments:

If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

cc: NDA ##-####
HFD-960/ Grace Carmouze

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337.

(revised 10-14-03)

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Markham Luke
3/23/05 11:30:09 AM

Jonathan Wilkin
3/30/05 06:29:17 PM

(17)

ORIGINAL



GlaxoSmithKline

GlaxoSmithKline
1500 Litvinton Road
Parsippany, NJ
07054-3884

Tel: 973 889 2100
Fax: 973 888 2390
www.gsk.com

March 30, 2005

NDA 21-152

Jonathan K. Wilkin, M.D., Director
Division of Dermatologic and Dental Drug Products
Center for Drug Evaluation and Research
Document Control Room
Office of Drug Evaluation V
Food and Drug Administration
HFD-540
9201 Corporate Boulevard, Bldg. 2
Rockville, MD 20850

ORIG AMENDMENT
N-000(BL)

RECEIVED
MAR 30 2005
MEGA / CDER

Attention: Ms. Millie Wright, Project Manager

**Re: NDA 21-152
CUTIVATE® (fluticasone propionate) Lotion, 0.05%
Amendment to Pending Application: Revised Draft Labeling**

Dear Dr. Wilkin:

GlaxoSmithKline Consumer Healthcare (GSKCH) hereby submits, in duplicate, an amendment to pending NDA 21-152 for CUTIVATE® (fluticasone propionate) Lotion, 0.05% consisting of the revised draft labeling for the [redacted] as requested by the FDA in a telephone call on March 29, 2005. This submission consists of the following draft labeling components:

[redacted]

If there are any questions concerning this submission, please contact me at 973-889-2566.

Sincerely,



Anthony Amitrano

Director, US Regulatory Affairs

GlaxoSmithKline Consumer Healthcare, L.P.

1 Page(s) Withheld

 Trade Secret / Confidential

 ✓ Draft Labeling

 Deliberative Process

Withheld Track Number: Administrative- 1

16

ORIGINAL



GlaxoSmithKline

GlaxoSmithKline
1500 Littleton Road
Raritan, NJ
07054-3884

Tel: 973 889 2100
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www.gsk.com

March 30, 2005

NDA 21-152

Jonathan K. Wilkin, M.D., Director
Division of Dermatologic and Dental Drug Products
Center for Drug Evaluation and Research
Document Control Room
Office of Drug Evaluation V
Food and Drug Administration
HFD-540
9201 Corporate Boulevard, Bldg. 2
Rockville, MD 20850

RECEIVED

MAR 30 2005

MEGA / CDER

NEW CORRESP

N-000(c)

Attention: Ms. Millie Wright, Project Manager

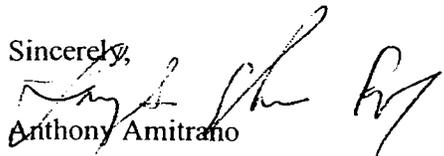
**Re: NDA 21-152
CUTIVATE® (fluticasone propionate) Lotion, 0.05%
Amendment to Pending Application: Acceptance of Draft Package
Insert**

Dear Dr. Wilkin:

GlaxoSmithKline Consumer Healthcare (GSKCH) hereby submits, in duplicate, an amendment to pending NDA 21-152 for CUTIVATE® (fluticasone propionate) Lotion, 0.05% concerning the draft package insert. GSKCH hereby informs the agency of its acceptance of the draft package insert that was provided to GSKCH in an e-mail on March 29, 2005. It is understood that this version of the package insert will be included in the approval letter for this drug product.

If there are any questions concerning this submission, please contact me at 973-889-2566.

Sincerely,

A handwritten signature in black ink, appearing to read 'Anthony Amitrano', written over the printed name.

Anthony Amitrano

Director, US Regulatory Affairs

GlaxoSmithKline Consumer Healthcare, L.P.

15



GlaxoSmithKline

GlaxoSmithKline
1500 Littleton Road
Parsippany, NJ
07054-3884

Tel: 973 888 2100
Fax: 973 889 2390
www.gsk.com

March 29, 2005

NDA 21-152

Jonathan K. Wilkin, M.D., Director
Division of Dermatologic and Dental Drug Products
Center for Drug Evaluation and Research
Document Control Room
Office of Drug Evaluation V
Food and Drug Administration
HFD-540
9201 Corporate Boulevard, Bldg. 2
Rockville, MD 20850

N-000(4S)
ORIG AMENDMENT

RECEIVED

MAR 30 2005

MEGA / CDER

Attention: Ms. Millie Wright, Project Manager

**Re: NDA 21-152
CUTIVATE® (fluticasone propionate) Lotion, 0.05%
Amendment to Pending Application: Phase IV Commitment
Timelines (Clinical & Pharmacology/Toxicology)**

Dear Dr. Wilkin:

GlaxoSmithKline Consumer Healthcare (GSKCH) hereby submits, in duplicate, an amendment to pending NDA 21-152 for CUTIVATE® (fluticasone propionate) Lotion, 0.05% consisting of the revised tentative timelines for the Clinical and Pharmacology/Toxicology Phase IV Commitments that were previously provided to the agency in an amendment on March 28, 2005. The timelines have been revised as requested by the FDA in a fax that was received on March 29, 2005. This submission consists of the following information:

- Attachment I - Revised timeline for the Phase IV Commitment requiring the conduct of a photoco-carcinogenic study.
- Attachment II - Revised timeline for the Phase IV Commitment requiring the conduct of a safety and efficacy study in pediatric patients aged 3months to 12 months.

ORIGINAL

If there are any questions concerning this submission, please contact me at 973-889-2566.

Sincerely,



Anthony Amitrano

Director, US Regulatory Affairs

GlaxoSmithKline Consumer Healthcare, L.P.

submission
every tomorrow 3/30

Wright, Mildred

From: Larry.S.Alphas@gsk.com
Sent: Tuesday, March 29, 2005 4:18 PM
To: WrightM@cder.fda.gov
Cc: Anthony.G.Amitrano@gsk.com; Joseph.A.Zuccarini@gsk.com
Subject: Revised [REDACTED] (NDA 21-152)

Hello Millie:

Per your telephone conversation with Anthony Amitrano today, attached below is the revised draft label for the [REDACTED]. The statement [REDACTED] has been removed.

Also, attached is the cover letter for the submission that will be sent out today to the FDA concerning this revision.

I reviewed the draft package insert that was e mailed to Anthony Amitrano today. My comments concerning editorial corrections to the Clinical Studies section (lines 81 and 82) were discussed with you. As you stated, the approval letter will contain the revised package insert with corrections incorporated.

If you have any questions, please call me at 973-889-2577.

Thank you.

Sincerely,

Larry S. Alphas

3/29/2005

*Submission
arriving tomorrow 3/30/05*

Wright, Mildred

From: Larry.S.Alphas@gsk.com
Sent: Tuesday, March 29, 2005 2:49 PM
To: WrightM@cder.fda.gov
Cc: Anthony.G.Amitrano@gsk.com; Joseph.A.Zuccarini@gsk.com
Subject: *One* [REDACTED] Timelines for Phase IV Commitments (NDA 21-152)

Hello Millie:

GSK agrees to the revised timelines for the Phase IV Commitments as indicated in FDA's 2 faxes received today, March 29, 2005. Attached below are the revised timelines.

An official submission will be sent out today.

If you have any questions, please call me at 973-889-2577.

Thank you.

Sincerely,

Larry S. Alphas

Attachment I

Phase IV Commitment: Photoco-Carcinogenicity

Study Timeline

The following tentative timeline is being submitted by GlaxoSmithKline Consumer Healthcare for the conduct of a study to determine the photoco-carcinogenic potential of CUTIVATE® (fluticasone propionate) Lotion, 0.05%:

MILESTONE	COMPLETION DATE (Tentative)
Dose range finding study start date	By October 1, 2005
Study protocol submission	By August 1, 2006
Definitive study start date	By February 1, 2007
Final report submission	By August 1, 2009

The study protocols and final reports will be submitted to NDA 21-152. Additionally, as stated under 21 CFR 314.8 1(b)(2)(vii) and 314.8 1(b)(2)(viii), a status summary of these studies will be submitted in the annual report to this NDA. The summary will include the status of ongoing work and findings to date, and a summary of action completion and final report submission dates. The summary will also include any changes in plans since the previous annual report. All submissions, including supplements, relating to this postmarketing commitment will be prominently labeled "Postmarketing Study Protocol", "Postmarketing Study Final Report", or "Postmarketing Study Correspondence."

ATTACHMENT II

Phase IV Commitment: Pediatric Safety and Efficacy

Study Timeline

The following tentative timeline is being submitted by GlaxoSmithKline Consumer Healthcare for the conduct of a study to determine the safety and efficacy of CUTIVATE® (fluticasone propionate) Lotion, 0.05% in children aged 3-12 months:

MILESTONE	COMPLETION DATE (Tentative)
Submission of study protocols to FDA	By November 15, 2005
Initiation of definitive study	By May 15, 2006
Submission of study final report	By May 15, 2008

The study protocols and final reports will be submitted to NDA 21-152. Additionally, as stated under 21 CFR 314.8 1(b)(2)(vii) and 314.8 1(b)(2)(viii), a status summary of these studies will be submitted in the annual report to this NDA. The summary will include the status of ongoing work and findings to date, and a summary of action completion and final report submission dates. The summary will also include any changes in plans since the previous annual report. All submissions, including supplements, relating to this postmarketing commitment will be prominently labeled "Postmarketing Study Protocol", "Postmarketing Study Final Report", or "Postmarketing Study Correspondence."



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation V

FACSIMILE TRANSMITTAL SHEET

Date: March 29, 2005
To: GlaxoSmithKline
Attn: Tony Amitrano
Director, US Regulatory Affairs
Phone: (973) 889-2566
Fax: (973) 889-2501
From: Millie Wright, Project Manager
Phone: (301) 827-2020
Fax: (301) 827-2091

This transmission includes 3 pages (including this page)

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this page is the manifestation of the electronic signature.**

/s/

Mildred Wright
3/29/05 12:25:21 PM
CSO

14

ORIGINAL



GlaxoSmithKline

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www.gsk.com

March 28 2005

NDA 21-152

Jonathan K. Wilkin, M.D., Director
Division of Dermatologic and Dental Drug Products
Center for Drug Evaluation and Research
Document Control Room
Office of Drug Evaluation V
Food and Drug Administration
HFD-540
9201 Corporate Boulevard, Bldg. 2
Rockville, MD 20850

ORIG AMENDMENT
N-000-45

RECEIVED

MAR 29 2005

MEGA / CDER

Attention: Ms. Millie Wright, Project Manager

Re: NDA 21-152
CUTIVATE® (fluticasone propionate) Lotion, 0.05%
Amendment to Pending Application: Phase IV Commitment
Timelines (Clinical & Pharmacology/Toxicology)

Dear Dr. Wilkin:

GlaxoSmithKline Consumer Healthcare (GSKCH) hereby submits, in duplicate, an amendment to pending NDA 21-152 for CUTIVATE® (fluticasone propionate) Lotion, 0.05% consisting of the tentative timelines for the Clinical and Pharmacology/Toxicology Phase IV Commitments. These timelines for the Phase IV Commitments were requested by the FDA in the teleconference that was held on March 21, 2005.

This submission consists of the following information:

- Attachment I: Tentative timeline for the Phase IV Commitment requiring the conduct of a photoco-carcinogenic study.
- Attachment II - Tentative timeline for the Phase IV Commitment requiring the conduct of a safety and efficacy study in pediatric patients aged 3

months to 12 months. This study is intended to obtain additional safety information in the pediatric population and to obtain pediatric exclusivity upon the study's completion.

Although GSKCH did not agree with the requirement to conduct the above two studies, we did understand the agency's position and consented to provide the tentative timelines for the initiation and completion of these studies as Phase IV Commitments.

If there are any questions concerning this submission, please contact me at 973-889-2566.

Sincerely,

Anthony Amitrano
Anthony Amitrano

Director, US Regulatory Affairs

GlaxoSmithKline Consumer Healthcare, L.P.

Wright, Mildred

From: Larry.S.Alphas@gsk.com
Sent: Monday, March 28, 2005 11:54 AM
To: WrightM@cder.fda.gov
Cc: Anthony.G.Amitrano@gsk.com; Joseph.A.Zuccarini@gsk.com
Subject: Timelines for Two Phase IV Commitments - NDA 21-152 (CUTIVATE Lotion)

Hello Millie:

As requested I am providing the timelines for the two Phase IV Commitments:

The official submission will go out today. You should receive it tomorrow.

If you have any questions, please call mde at 973-889-2677.

Thank you.

Larry S. Alphas

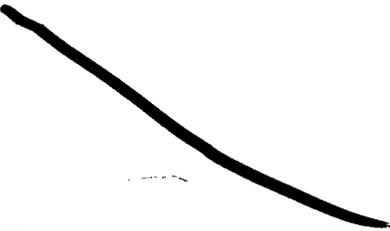
3/28/2005

Attachment I

Phase IV Commitment: Photoco-Carcinogenicity

Study Timeline

The following tentative timeline is being submitted by GlaxoSmithKline Consumer Healthcare for the conduct of a study to determine the photoco-carcinogenic potential of CUTIVATE® (fluticasone propionate) Lotion, 0.05%:

MILESTONE	COMPLETION DATE (Tentative)
Submission of study protocols to FDA	
Initiation of pilot study	
Initiation of definitive study	
Submission of study final report	

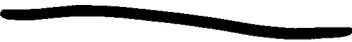
The study protocols and final reports will be submitted to NDA 21-152. Additionally, as stated under 21 CFR 314.8 1(b)(2)(vii) and 314.8 1(b)(2)(viii), a status summary of these studies will be submitted in the annual report to this NDA. The summary will include the status of ongoing work and findings to date, and a summary of action completion and final report submission dates. The summary will also include any changes in plans since the previous annual report. All submissions, including supplements, relating to this postmarketing commitment will be prominently labeled "Postmarketing Study Protocol", "Postmarketing Study Final Report", or "Postmarketing Study Correspondence."

ATTACHMENT II

Phase IV Commitment: Pediatric Safety and Efficacy

Study Timeline

The following tentative timeline is being submitted by GlaxoSmithKline Consumer Healthcare for the conduct of a study to determine the safety and efficacy of CUTIVATE® (fluticasone propionate) Lotion, 0.05% in children aged 3-12 months:

MILESTONE	COMPLETION DATE (Tentative)
Submission of study protocols to FDA	By November 15, 2005
Initiation of definitive study	By May 15, 2006
Submission of study final report	

The study protocols and final reports will be submitted to NDA 21-152. Additionally, as stated under 21 CFR 314.8 1(b)(2)(vii) and 314.8 1(b)(2)(viii), a status summary of these studies will be submitted in the annual report to this NDA. The summary will include the status of ongoing work and findings to date, and a summary of action completion and final report submission dates. The summary will also include any changes in plans since the previous annual report. All submissions, including supplements, relating to this postmarketing commitment will be prominently labeled "Postmarketing Study Protocol", "Postmarketing Study Final Report", or "Postmarketing Study Correspondence."

Wright, Mildred

From: Larry.S.Alphas@gsk.com
Sent: Friday, March 25, 2005 1:43 PM
To: WrightM@cder.fda.gov
Cc: Anthony.G.Amitrano@gsk.com; Joseph.A.Zuccarini@gsk.com
Subject: Additional Revision to Post-Approval Commitment - Cutivate Lotion (NDA 21-152)

Hello Millie:

Per FDA request received on 3-25-05, attached is the revised post-approval stability commitment. The document has been changed to reflect the following changes:

- One batch of the 60mL [REDACTED] bottle will be placed on stability annually.
- Microbial Limit Test will be performed at [REDACTED]

I have attached the revised post-approval commitment below. This revision supersedes the version that was sent to you on 3-24-05.

Thank you.

Sincerely,

Larr S. Alphas

1 Page(s) Withheld

Trade Secret / Confidential

Draft Labeling

Deliberative Process

Withheld Track Number: Administrative-2

Wright, Mildred

From: Larry.S.Alphas@gsk.com
Sent: Friday, March 25, 2005 12:45 PM
To: WrightM@cder.fda.gov
Cc: Anthony.G.Amitrano@gsk.com; Joseph.A.Zuccarini@gsk.com
Subject: Final Labeling - Package Insert

*Submission
arriving tomorrow
(for to submit
acceptance
elt)* 3/25/05

Hello Millie:

GSK accepts the final revision to the Cutivate Lotion package insert that was provided via e-mail on 3/25/05.

Please note: As per our telephone conversation, the immediately to the right of the GSK Logo has been removed.

_____ that was located

If you have any questions, please call me at 973-889-2577.

Thank you.

Larry S. Alphas

ORIGINAL



GlaxoSmithKline

GlaxoSmithKline
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March 25, 2005

N-000(80)
ORIG AMENDMENT

NDA 21-152

Jonathan K. Wilkin, M.D., Director
Division of Dermatologic and Dental Drug Products
Center for Drug Evaluation and Research
Document Control Room
Office of Drug Evaluation V
Food and Drug Administration
HFD-540
9201 Corporate Boulevard, Bldg. 2
Rockville, MD 20850

RECEIVED
MAR 28 2005
MEGA / CDER

Attention: Ms. Millie Wright, Project Manager

**Re: NDA 21-152
CUTIVATE® (fluticasone propionate) Lotion, 0.05%
Amendment to Pending Application: Chemistry**

Dear Dr. Wilkin:

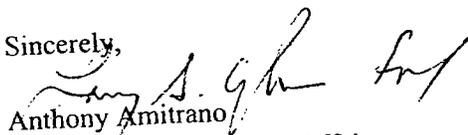
GlaxoSmithKline Consumer Healthcare (GSKCH) hereby submits, in duplicate, an amendment to pending NDA 21-152 for CUTIVATE® (fluticasone propionate) Lotion, 0.05% consisting of Chemistry, Manufacturing and Controls information that was previously provided to Ms. Millie Wright, Project Manager, via e-mail on March 25, 2005. This submission consists of the revised post-approval stability commitment; section F6.2. Per FDA's request, the following revisions were made to the commitment:

- The first sentence was revised to state that one batch of CUTIVATE® Lotion packaged in 60mL [redacted] bottles will be placed on stability annually.
- Revised Table F4 to indicate that the microbial limit test will be performed at [redacted]

Note: The post-approval commitment document was previously provided as Attachment IX in an amendment to NDA 21-152 on January 31, 2005.

If there are any questions concerning this submission, please contact me at 973-889-2566.

Sincerely,



Anthony Amitrano
Director, US Regulatory Affairs
GlaxoSmithKline Consumer Healthcare, L.P.

12

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MAR 25 2005
MEGA / CDER



GlaxoSmithKline

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Fax: 973 898 2280
www.gsk.com

March 24, 2005

NDA 21-152

Jonathan K. Wilkin, M.D., Director
Division of Dermatologic and Dental Drug Products
Center for Drug Evaluation and Research
Document Control Room
Office of Drug Evaluation V
Food and Drug Administration
HFD-540
9201 Corporate Boulevard, Bldg. 2
Rockville, MD 20850

ORIG AMENDMENT
N-000 (BL)

Attention: Ms. Millie Wright, Project Manager

**Re: NDA 21-152
CUTIVATE® (fluticasone propionate) Lotion, 0.05%
Amendment to Pending Application: Draft Labeling**

Dear Dr. Wilkin:

GlaxoSmithKline Consumer Healthcare (GSKCH) hereby submits, in duplicate, an amendment to pending NDA 21-152 for CUTIVATE® (fluticasone propionate) Lotion, 0.05% consisting of the draft labeling that was previously provided via e-mail on March 23, 2005. This submission consists of the following draft labeling components:

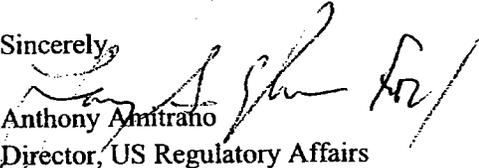
- Attachment I consisting of the draft package insert in word format incorporating the revisions requested by the agency during the teleconference that was held on March 21, 2005. Please note: To facilitate the review of the package insert, the following color codes have been used:
 - Blue type represents the agreed to text that was underlined in the draft labeling that was faxed to GSK on March 18, 2005.

- Black type represents the agreed to text in the draft labeling that was faxed to GSK on March 18, 2005.
 - Brown type represents revised text proposed by GSK.
 - Track changes represents additional revisions requested by the FDA subsequent to the draft labeling that was faxed to GSK on March 18, 2005.
-
- Attachment II consists of the draft [redacted] bottle label in pdf format.
 - Attachment III consists of the draft [redacted] in pdf format.
 - Attachment IV consists of the draft 60mL bottle label in pdf format..
 - Attachment V consists of the draft 60mL carton in pdf format.

The above attachments are also being provided on CD.

If there are any questions concerning this submission, please contact me at 973-889-2566.

Sincerely,


Anthony Amirano
Director, US Regulatory Affairs
GlaxoSmithKline Consumer Healthcare, L.P.

5 Page(s) Withheld

 Trade Secret / Confidential

✓ Draft Labeling

 Deliberative Process

Wright, Mildred

From: Larry.S.Alphas@gsk.com
Sent: Thursday, March 24, 2005 3:18 PM
To: WrightM@cder.fda.gov
Cc: Anthony.G.Amitrano@gsk.com; Joseph.A.Zuccarini@gsk.com
Subject: Revised Post-Approval Stability Commitment

Dear Millie:

As requested, attached is the revised post-approval stability commitment. The document has been changed to reflect that one batch of the 60mL  bottle will be placed on stability annually.

If you have any questions, please let me know.

Thank you.

Sincerely,

Lary S. Alphas

3/30/2005

1 Page(s) Withheld

Trade Secret / Confidential

Draft Labeling

Deliberative Process

Withheld Track Number: Administrative-

 4

Wright, Mildred

From: Joseph.A.Zuccarini@gsk.com
Sent: Wednesday, March 23, 2005 4:50 PM
To: WrightM@cder.fda.gov
Cc: Anthony.G.Amitrano@gsk.com; Larry.S.Alphas@gsk.com
Subject: NDA 21-152 Cutivate Draft Label - Draft Carton Labels

Millie:

As we discussed, attached find the Cutivate Lotion carton and container Draft labeling.

Joseph

MEMORANDUM OF TELECON

DATE: 3/10/05, 9:00 A.M.

APPLICATION NUMBER: NDA 21-152
DRUG PRODUCT: Cutivate Lotion, 0.05%

BETWEEN:

Name: Anthony Amitrano, Director, US Regulatory Affairs
Joseph Zuccarini, Associate Director, US Regulatory Affairs
Larry Alphas, Manager, US Regulatory Affairs
Randy Koslo, Ph.D., Director, Medical Affairs, North America
Simon Gliburt, R & D Team Leader
Phone: (973) 889-2501
Representing: GlaxoSmithKline

AND

Name: Chi-Wan Chen, Ph.D., Director, ONDC/DNDCIII, HFD-830
Norman Schmuff, Ph.D./Acting Deputy Division Director,
ONDC/DNDCIII, HFD-830
Ramesh Sood, Ph.D., Chemistry Team Leader, ONDC/DNDCIII, HFD-830
Allan Fenselau, Ph.D., Chemistry Reviewer, ONDC/DNDCIII, HFD-830
Melinda Harris-Bauerlien, M.S., Regulatory Project Manager, DDDDP,
HFD-540

SUBJECT: NDA 21-152

The teleconference was requested by the Agency to request specific information from the sponsor concerning the submitted NDA.

1. The Agency stated that the sponsor has requested the name Cutivate [REDACTED] The Agency has recommended that [REDACTED] be changed to "Lotion." [REDACTED]

Although the term [REDACTED] has been used in the names of a handful of topical drug products, the Agency has not approved the use of this term recently. Efforts at establishing a scientific nomenclature system for topical dosage forms, including lotion, are in progress. Evidence to these efforts can be found in a paper from the Agency recently accepted for publication by the International Journal of Pharmaceutics and in the transcripts of two Advisory Committee for Pharmaceutical Science (ACPS) meetings held on this topic.

[Copies of the transcripts from the 3/12/03 and 10/22/03 ACPS meetings will be forwarded to the sponsor.] Eventually the Agency will address the issue of correcting the names of those products in which the term [REDACTED] is used.

The Agency asked the sponsor why they changed from Lotion [REDACTED] when they resubmitted the NDA.

The sponsor responded that they went back and decided to change it to [REDACTED] after consulting their experts. They stated that the last product to use [REDACTED] as dosage form was in 1997.

The Agency stated that we would recommend the use of a more specific term, lotion, from both the chemist's and the clinician's point of view.

The Sponsor agreed to change [REDACTED] Lotion.

2. The Agency stated they would like the letters [REDACTED] removed after Cutivate. The Agency stated it is the general policy to not place letters after the drug's name.

The sponsor agreed to remove the [REDACTED] after Cutivate.

The conversation ended amicably.

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/s/

Melinda Harris-Bauerlien
3/23/05 03:08:34 PM
CSO

Chi Wan Chen
3/25/05 04:21:48 PM
CHEMIST

11

ORIGINAL



GlaxoSmithKline

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N-000(BC)
ORIG AMENDMENT

March 17, 2005

NDA 21-152

Jonathan K. Wilkin, M.D., Director
Division of Dermatologic and Dental Drug Products
Center for Drug Evaluation and Research
Document Control Room
Office of Drug Evaluation V
Food and Drug Administration
HFD-540
9201 Corporate Boulevard, Bldg. 2
Rockville, MD 20850

RECEIVED

MAR 21 2005

MEGA / CDER

Attention: Ms. Millie Wright, Project Manager

**Re: NDA 21-152
CUTIVATE® Lotion (fluticasone propionate, 0.05%)
Amendment to Pending Application: Chemistry**

Dear Dr. Wilkin:

GlaxoSmithKline Consumer Healthcare (GSKCH) hereby submits, in duplicate, an amendment to pending NDA 21-152 for CUTIVATE® Lotion (fluticasone propionate, 0.05%) consisting of Chemistry, Manufacturing and Controls information. This submission constitutes GSKCH's response to the March 15, 2005 FDA fax requesting the submission of information based on FDA's review of this application. In order to facilitate the review process, the original FDA questions/comments are provided and are immediately followed by GSKCH's response.

3 Page(s) Withheld

Trade Secret / Confidential

Draft Labeling

Deliberative Process

Withheld Track Number: Administrative-

5



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation V

FACSIMILE TRANSMITTAL SHEET

DATE: March 15, 2005

To: Anthony Armitrano	From: Melinda Harris-Bauerlien, M.S. Project Manager for Millie Wright
Company: GlaxoSmithKline	Division of Dermatologic & Dental Drug Products
Fax number: (973) 889-2501	Fax number: (301) 827-2091 or 2075
Phone number: (973) 889-2566	Phone number: (301) 827-2020
Subject: NDA 21-152	

Total no. of pages including cover: 3

Comments: CMC request for Information

Document to be mailed: YES NO

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this page is the manifestation of the electronic signature.**

/s/

Melinda Harris-Bauerlien
3/15/05 11:07:46 AM
CSO



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation V

FACSIMILE TRANSMITTAL SHEET

DATE: 3/14/05

For Millie Wright

To: Anthony Armitrano	From: Mary Jean Kozma-Fornaro Supervisor, Project Management Staff
Company: GlaxoSmithKline Consumer Healthcare, L.P.	Division of Dermatologic & Dental Drug Products
Fax number: 973 889-2501	Fax number: (301) 827-2091
Phone number: 973 889-2566	Phone number: (301) 827-2020
Subject: NDA 21-152 Cutivate Lotion: Pharmacology Toxicology Comments to 2/1/05 submission receipt	

Total no. of pages including cover:

Comments: See Attached

Document to be mailed: YES NO

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If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at (301) 827-2020. Thank you.

1) The Sponsor's proposal to calculate the multiples of human exposure values for the Cutivate lotion label assuming 3% percutaneous absorption of Cutivate lotion is not acceptable. In the absence of AUC data, the Division's policy is to calculate the multiples of human exposure values for topical drug product labels assuming 100% percutaneous absorption. Therefore, the Division recommends that the Sponsor accept the Division's original wording for the nonclinical portions of the Cutivate label relayed to them in the NDA Approvable Letter sent on January 12, 2005.

2) The Division notes that the Sponsor did not submit any new data in this submission to support their request for a waiver for conduct of a study to determine the photocarcinogenic potential of Cutivate lotion. Therefore, the Sponsor is relying on the data that was included in the original NDA 21-152 submission (date of submission – March 12, 2004). The Division previously relayed to the sponsor in the NDA Approvable Letter for NDA 21-152 (dated January 12, 2005) that the Division has determined that the data submitted to NDA 21-152 to support a waiver for a study to determine the photocarcinogenic potential of Cutivate lotion is not adequate. This determination has not changed since no new data has been submitted to the Division. There are a number of reasons why the data was determined not to be adequate to grant the waiver. A few of these reasons are provided below.

a) The lack of photoreactivity of Cutivate lotion (does not demonstrate any appreciable absorption in the [redacted] range), is not an acceptable reason to grant a waiver for the study because there are other mechanisms besides direct photoreactivity that can contribute to an enhanced photoco-carcinogenic risk (i.e., enhanced UV exposure, thinning of the skin, etc).

b) In the original NDA submission, the sponsor included a few literature references to support their belief that published data indicate that corticosteroids in general elicit a photoprotective effect by inhibiting the induction of UV-induced skin tumors. It was determined that the published data submitted to support the Sponsor's viewpoint was not adequate. Only a few corticosteroids were tested in the studies referenced in the submitted literature. It is not possible to designate a class effect based on the limited data set. Not much information was provided about the UV lamps and filters used in the studies described in the submitted literature references. The lamps used in these

10 studies may have been sunlamps that had UVC present (with inadequate filtering). A drug that absorbs UVC might appear to be protective in these studies versus UVC exposure. In addition, an important question that is not addressed in these studies is whether any "protective" effect (which all anti-inflammatory drugs may possess) could be outweighed by optical effects. One literature reference study was conducted with hydrocortisone dissolved in propylene glycol, which does not mimic the composition of the Cutivate lotion vehicle. The composition of the emollient vehicle used in another reference study is not clear. Results from photoco-carcinogenesis studies conducted in hairless mice to support the safety of other topical drug products

have demonstrated that the optical properties of the vehicle (i.e., enhance the UV exposure to the skin) frequently is the predominant effect for enhancement of photocarcinogenesis. Therefore, it would be important to determine the photocarcinogenic potential of Cutivate lotion.

c) The Sponsor claims that the clinical data submitted in the original NDA demonstrate that the potential degree of skin thinning resulting from topical application of fluticasone propionate is not significant and is comparable or less than that of hydrocortisone. The skin thinning assessed in the clinical studies after administration of fluticasone propionate 0.5% cream may not be an appropriate marker for assessing the photocarcinogenic potential of Cutivate lotion. The thinning of the skin measured in the referenced clinical studies measured the thickness of collagen, but not of the stratum corneum. The "Photosafety testing" guidance document refers to measurement of thinning of the "protective" layers of the skin (e.g., the stratum corneum). Therefore, measurement of thinning of the skin by measurement of collagen thickness is not an appropriate marker for photocarcinogenic potential.

3) In summary, the data submitted to NDA 21-152 to support a waiver for a study to determine the photocarcinogenic potential of Cutivate lotion is not adequate. It is requested that the Sponsor submit their plan for conduct of a study to determine the photocarcinogenic potential of Cutivate lotion. The applicant is referred to the guidance document titled "Guidance for Industry – Photosafety Testing" published in May, 2003 for assistance in determining an appropriate study design.

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Mary Jean Kozma Fornaro
3/14/05 02:41:55 PM
CSO



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-152

GlaxoSmithKline Consumer Healthcare, L.P.
Attention: Anthony Amitrano
Director, US Regulatory Affairs
1500 Littleton Road
Parsippany, NJ 07054-3884

Dear Mr. Amitrano:

We acknowledge receipt on February 1, 2005 of your January 31, 2005 resubmission to your new drug application for Cutivate (fluticasone propionate) Lotion, 0.05%.

We consider this a complete, class I response to our January 12, 2005 action letter. Therefore, the user fee goal date is April 1, 2005.

If you have any questions, call Millie Wright, Regulatory Project Manager, at (301) 827-2020.

Sincerely,

{See appended electronic signature page}

Mary Jean Kozma-Fornaro
Supervisor, Project Management Staff
Division of Dermatologic & Dental Drugs
Office of Drug Evaluation V
Center for Drug Evaluation and Research

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Mary Jean Kozma Fornaro
2/17/05 09:48:04 AM

217

ORIGINAL



GlaxoSmithKline

GlaxoSmithKline
2355 North 17th Ave
P.O. Box 100
Kenilworth, NJ 07033
USA
Tel: 201 261 6000
Fax: 201 261 6001
www.gsk.com

RECEIVED
FEB 01 2005
MEGA / CDER

January 31, 2005

NDA 21-152

Jonathan K. Wilkin, M.D., Director
Division of Dermatologic and Dental Drug Products
Center for Drug Evaluation and Research
Document Control Room
Office of Drug Evaluation V
Food and Drug Administration
HFD-540
9201 Corporate Boulevard, Bldg. 2
Rockville, MD 20850

ORIG AMENDMENT
N-000(BZ)

Attention: Ms. Millie Wright, Project Manager

Re: NDA 21-152
CUTIVATE[®] (fluticasone propionate) 0.05%
Amendment to Pending Application: Response to NDA Approvable
Letter (Chemistry, Pharmacology/Toxicology, Clinical)

Dear Dr. Wilkin:

GlaxoSmithKline Consumer Healthcare (GSKCH) hereby submits, in duplicate, an amendment to pending NDA 21-152 for CUTIVATE[®] (fluticasone propionate) 0.05% consisting of the following information: responses to questions from the Chemistry Reviewer, Pharmacology/Toxicology Reviewer and Clinical Reviewer. This submission constitutes GSKCH's response to the FDA correspondences that were received on December 16, 2004, December 23, 2004 and January 12, 2005 requesting the submission of information based on FDA's completion of their review of this application. In order to facilitate the review process, the original FDA questions/comments from the latest fax that was received on January 12, 2005 (approvable letter) are provided and are immediately followed by GSKCH's response.

FDA Comment

1. Initiate labeling discussions with the division to address the outstanding labeling issues, identified in the attached draft labeling. The Division acknowledges your January 6, 2005, correspondence in which you state your commitment to further labeling negotiations with the Division.

GSKCH Response

1. In order to facilitate labeling negotiations with the Division, GSKCH has provided the following documents as attachments:
 - Original draft labeling (in track changes format) provided by the agency in their fax dated December 16, 2004 (Attachment I).
 - Revised draft labeling (in track changes format) indicating those changes that were accepted in black color type and those changes identified for further discussion as brown color type (Attachment II).

Note: Both the original draft labeling and the revised draft labeling located in the two attachments above are provided electronically in both word and pdf format on the enclosed disk.

- A detailed line-by-line listing of the changes indicated in Attachment II in tabular format intended as a guide for the agency reviewers (Attachment III).
- Supporting information for GSKCH's proposed text changes to the Carcinogenesis, Mutagenesis, and Impairment of Fertility and Pregnancy: Teratogenic Effects sections of the package insert (Attachment IV).
- Supporting information for GSKCH's proposed text changes to the CLINICAL PHARMACOLOGY, CLINICAL STUDIES and PRECAUTIONS sections of the package insert (Attachment V).

Please note that GSKCH's proposed text changes to the package insert presented in Attachment II described above include retaining the use of the CUTIVATE ██████████ drug name. While we recognize that this is contrary to the agency's suggestion, we are committed to discussing this

difference, as well as the other proposed changes, via a teleconference with the appropriate reviewers. It is hoped that through this discussion, a mutually agreeable decision can be reached.

FDA Comment

2. Present your plans to evaluate the safety (both local and systemic, to include laboratory tests) and systemic availability of this product for the treatment of [REDACTED] atopic dermatitis in patients ages 3 months to 1 year.

GSKCH Response

2. GSKCH recognizes that, although there were patients less than 12 months of age included in both the pivotal and safety studies performed in support of the application, the number of patients were relatively low. Therefore, GSKCH accepts the agency's revision to the age range to 12 months and older. Presently, there are no plans to further evaluate the safety of CUTIVATE [REDACTED] in children under the age of 12 months.

FDA Comment

3. Present your plans to evaluate the long term safety of your product when used in humans as per ICH E1A.

GSKCH Response

3. GSKCH has reviewed the above-mentioned guidance titled, "The Extent of Population Exposure to Assess Clinical Safety: For Drugs Intended for Long-Term Treatment of Non-Life-Threatening Conditions" published in March 1995. After considering this guidance, GSKCH has determined that there is no concern that this drug would cause late developing adverse drug events or cause adverse drug events that increase in severity or frequency over time. Therefore, the ongoing safety of CUTIVATE [REDACTED] [REDACTED] will be monitored through the GSKCH safety reporting process where adverse event reports (from spontaneous, clinical studies, literature sources, etc.) are collected and submitted to the FDA in accordance with 21 CFR 314.80 and 21 CFR 314.81. The safety of CUTIVATE

(fluticasone propionate) has been established through the work submitted in the pending NDA [REDACTED] and the approved NDAs for Cream (NDA 19-958) and Ointment (NDA 19-957), supplemented by millions of exposures ([REDACTED] packs sold in the US alone) since launch of the approved products in 1990.

FDA Comment

4. The Division has determined that the data submitted to NDA 21-152 to support a waiver for a study to determine the photo-carcinogenic potential of Cutivate Lotion is not adequate. It is requested that the Sponsor submit their plan for conduct of a study to determine the photo-carcinogenic potential of Cutivate Lotion. The applicant is referred to the guidance document titled "Guidance for Industry - Photosafety Testing" published in May 2003 for assistance in determining an appropriate study design.

GSKCH Response

4. Based on the guidance document entitled "Guidance for Industry - Photosafety Testing" published in May 2003, the sponsor considers the data submitted to NDA 21-152 to be sufficient to appropriately evaluate the photoco-carcinogenic potential of CUTIVATE [REDACTED] 0.05% and as such, considers photocarcinogenicity testing to be unnecessary. In consideration of the guidance document, the package insert text proposed by FDA, which states "No studies were conducted to determine the photoco-carcinogenic potential of CUTIVATE Lotion", is considered appropriate. This position is based on the following rationale:

As stated in the guidance document, "long-term photosafety testing is generally conducted only when it can provide useful information. Long-term photosafety studies should be avoided when sufficient information has already been collected for a drug or a class of drugs to appropriately inform potential users regarding photoreactivity". Data submitted to NDA 21-152 clearly demonstrated that CUTIVATE [REDACTED] 0.05% would not enhance UV-induced skin carcinogenesis by a photoreactive mechanism. The composite formulation exhibited no appreciable

absorption in the [REDACTED] range of the UV spectrum and would therefore not become photoactivated or biologically photoreactive in the presence of sun light. Studies in guinea pigs and humans demonstrated that fluticasone propionate, in ointment and cream formulations, was neither a photoirritant nor a photosensitizer. Data submitted to NDA 21-152 also demonstrated that corticosteroids as a class of drugs do not enhance UV-induced skin carcinogenesis by non-photoreactive mechanisms. The published data indicate that corticosteroids in general elicit a photoprotective effect by inhibiting the induction of UV-induced skin tumors and by down-regulating mediators of inflammation and tumor promotion. The submitted clinical data demonstrated that the potential degree of skin thinning resulting from topical application of fluticasone propionate is not significant and is comparable or less than that of hydrocortisone.

Furthermore, the guidance document indicates that even in the absence of information about the risks associated with potentially silent enhancers of UV-induced skin carcinogenesis, most nonphotoreactive drugs would not be tested for their potential to enhance UV-induced skin carcinogenesis, even if they were administered chronically, assuming they were tested for carcinogenicity in the traditional bioassays. Some secondary mechanisms of enhancement of UV-induced carcinogenicity, such as immunosuppression or inhibition of DNA repair, would be detected by use of traditional carcinogenicity studies. Two 18-month studies in mice that evaluated the carcinogenic potential of fluticasone propionate when administered topically and orally were submitted to NDA 21-152. No evidence of carcinogenicity was found in either study.

In consideration of the guidance document, the body of data submitted to NDA 21-152 provides sufficient information to appropriately evaluate the photoco-carcinogenic potential of CUTIVATE [REDACTED] 0.05% and long-term photosafety testing is not necessary. As this position differs from that of the Agency, the sponsor requests a teleconference to discuss the necessity of the photoco-carcinogenicity study in light of the available data.

FDA Comment

5. Respond to the following Chemistry, Manufacturing and Control Information requests:

- a. Revise the drug substance specification for fluticasone propionate [redacted] to include particle size testing. Employ acceptance criteria that are consistent with those applied to the batch of drug substance (No. WC116005RB) used to manufacture drug product stability batch 8J257 (see Certificate of Analysis submitted on p. 342 in the original NDA). Provide a copy of the revised drug substance specification.

GSKCH Response

- a. The drug substance specification will be immediately amended to include the following specification:

Particle size: [redacted]
[redacted]

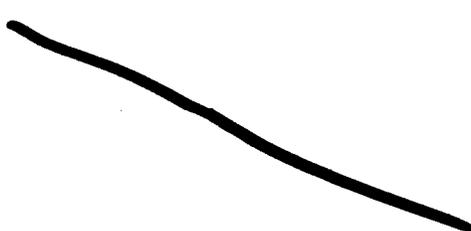
The revised drug substance specification is provided as Attachment VI.

FDA Comment

- b. Provide a discussion of [redacted] of the bulk product, including a description of tests that monitor this property

GSKCH Response

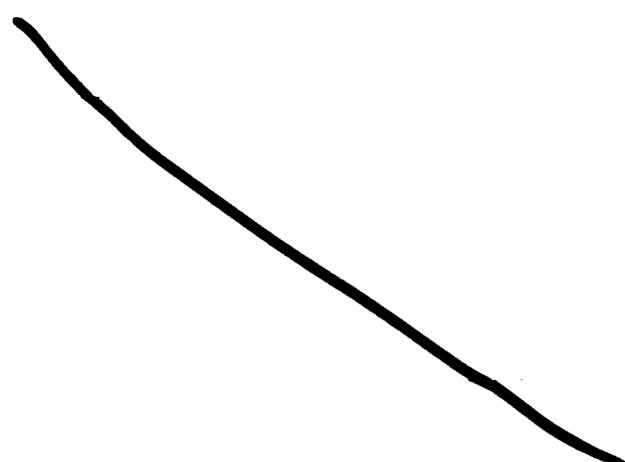
- b. [redacted]
[redacted]



FDA Comment

- c. Revise the Appearance criterion in the product specification to read: 

GSKCH Response

- c. 

1 Page(s) Withheld

Trade Secret / Confidential

Draft Labeling

Deliberative Process

FDA Comment

- e. Explain the decrease in viscosity that is evident generally at 24 months in the stability studies (submitted in the amendment dated 23-JUL-2004) and appears to be attributable to the use of the new method for determining viscosity.

GSKCH Response

- e. It was noted that the original assay method demonstrated poor repeatability of replicate viscosity readings during CUTIVATE® stability testing. Increasing the shear rate on the sample improved the repeatability of the viscosity results. Therefore, a new method was developed that employed an increased shear rate due to the [REDACTED]. As shear rate is increased, viscosity is decreased, explaining the difference in the viscosity measured by the two methods. Measurement of viscosity is being employed as a comparative test to track the relative viscosities of samples between batches, or as one batch ages. Thus, the noted decreases in measured viscosities for the pivotal stability batches are attributable to the method change and not in changes to the product itself.

FDA Comment

- f. Identify the method used to determine the viscosities of the vehicle samples submitted to the Agency in November 2004.

GSKCH Response

- f. The method used to determine the viscosities of the vehicle samples submitted to the agency in November 2004 is the method used at the final time point. The conditions are repeated here for convenience.

Apparatus: _____ with
Small Sample Adapter
Sample size: _____
Spindle: _____
Rotation Speed: _____
Sample Temperature: 25C

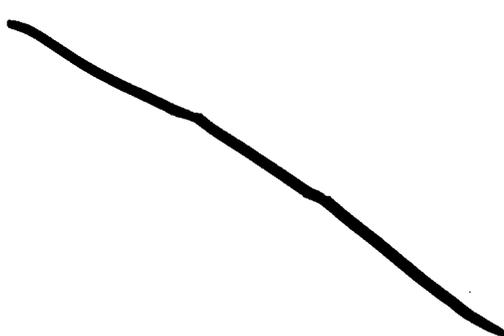
Single reading taken at _____ minutes.

FDA Comment

- g. Determine the viscosity at which the drug product is no longer pourable. Use this viscosity value to determine the upper limit for the acceptance criterion for viscosity in the product specification. [Based on the results from the reported stability studies, an _____ with a viscosity value below _____ is expected to remain pourable.] Until definitive data are obtained on the relation between viscosity and pourability, employ an acceptance criterion for Viscosity of NMI _____

GSKCH Response

- g. As explained in response to question c, the "pourability" of the product can be ambiguous. However, to ensure that Cutivate[®] _____ would readily be expressed from the commercial 60mL bottle, _____ placebo samples with viscosities of approximately _____ were examined. Samples flowed from the bottom of the bottle to the aperture via inversion, though some



FDA Comment

- h. Provide a copy of the product specification that includes the revisions for Appearance and Viscosity tests.

GSKCH Response

- h. The viscosity specification has been revised to read “Not more than _____ A copy of the revised specification that includes both revisions to Appearance and Viscosity testing is provided as Attachment VII.

FDA Comment

- i. Confirm that the container closure system that employs the new 60mL bottle will be subjected to the stability test protocol described in Section F7 of your original submission. For the first batch of product in this container closure system, include determination of weight loss along with the listed tests. Submit the results as part of the subsequent annual reports.

GSKCH Response

- i. We confirm that the first batch of product in the new 60mL bottle will be subject to the stability test protocol described in Section F7 (i.e. Table F5), with the addition of the weight loss test. These results will be submitted in subsequent annual reports. For your convenience, an amended Table F5 (Stability Test Protocol for Future Change in Container Closure System of CUTIVATE[®] [REDACTED] is included as Attachment VIII, and includes the weight loss test.

FDA Comment

- j. Revise your commitment for the suitability protocol to indicate that all annual batches placed on stability will include testing initially and at 6, 12, 18 and 24 months (with optional testing at 36 months). [Deletion of testing at 6 and 18 months is not acceptable.]

GSKCH Response

- j. We confirm that all annual batches placed on stability will include testing at initial, 6, 12, 18 and 24 months (with optional testing at 36 months) and there will be no reduction in the number of test points. An amended section F6.2 (Post-Approval Commitment) is included as Attachment IX.

FDA Comment

When you respond to the above deficiencies, please also include a safety update as described at 21CFR 314.50(d)(5)(vi)(b). The safety update should include data from all non-clinical and clinical studies of the drug under consideration regardless of indication, dosage form, or dose level.

Attachment X provides the revision to the 120 Day Safety Update that was submitted to the agency on July 9, 2004. Attachments XI to XVIII provide information on all post-marketing adverse events reported to GSK (as of December 31, 2004) that are associated with CUTIVATE Cream and CUTIVATE Ointment marketed worldwide. Please refer to these attachments for additional information concerning GSKCH's responses to the questions below.

1. Describe in detail any significant changes or findings in the safety profile.

GSKCH Response

1. There are no significant changes to the safety profile from the information submitted in the original NDA.

FDA Comment

2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:
 - Present new safety data from the studies for the proposed indication using the same format as the original NDA.
 - Present tabulations of the new safety data combined with the original NDA data.
 - Include tables that compare frequencies of adverse events in the original NDA with the re-tabulated frequencies described in the bullet above.
 - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

GSKCH Response

2. There is no new safety data to be incorporated into the tables originally submitted with the NDA.

FDA Comment

3. Present a re-tabulation of the reasons for premature study discontinuation by incorporating the dropouts from the newly completed studies. Describe any new trends or patterns identified.

GSKCH Response

3. There are no new studies to report. All information pertaining to the studies were included in the original NDA. Therefore, re-tabulation of discontinuation data is not necessary.

FDA Comment

4. Provide case report forms and narrative summaries for each patient who died during a clinical study or who did not complete a study because of an adverse event. In addition, provide narrative summaries for serious adverse events.

GSKCH Response

- 4 All narrative summaries were submitted with the original NDA. There is no new data to report.

FDA Comment

5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.

GSKCH Response

5. There is no new data to report. Therefore, there are no changes in the incidence of common, but less serious, adverse events between the new data and the original NDA data to report.

FDA Comment

6. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.

GSKCH Response

6. GSKCH is unable to provide information pertaining to the worldwide experience on the safety of this particular formulation since it has not been launched in any of the countries where it has been approved (Finland, Mauritius and India). However, the agency does have this data for the other formulation (cream and ointment), via the periodic ADE reports.

FDA Comment

7. Provide English translations of current approved foreign labeling not previously submitted.

GSKCH Response

7. As indicated in our response to question 6 above, this drug product has not been launched in any country. Therefore, english translations of current approved foreign labeling cannot be provided at this time because the drug has not been launched in those countries listed in the response to question 6 above.

GSKCH is committed to independent discussions with the respective reviewers in order to address any outstanding issues that remain. To this end, GSKCH proposes the use of separate teleconferences with the agency in order to obtain a timely approval of this NDA.

If there are any questions concerning this submission, please contact me at 973-889-2566.

Sincerely,

Joseph Zuccarini for

Anthony Amitrano

Director, US Regulatory Affairs

GlaxoSmithKline Consumer Healthcare, L.P.

DUPLICATE

257



GlaxoSmithKline

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JAN 14 2005

MEGA / CDER

January 13, 2005

NDA 21-152

GlaxoSmithKline
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07054-3884

Tel. 973 889 2100
Fax. 973 889 2390
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N-600(C)
NEW CORRESP

Jonathan K. Wilkin, M.D., Director
Division of Dermatologic and Dental Drug Products
Center for Drug Evaluation and Research
Document Control Room
Office of Drug Evaluation V
Food and Drug Administration
HFD-540
9201 Corporate Boulevard, Bldg. 2
Rockville, MD 20850

Attention: Ms. Millie Wright, Project Manager

Re: NDA 21-152
CUTIVATE® (fluticasone propionate) 0.05%
Amendment to Pending Application: Response to NDA Approvable
Letter

Dear Dr. Wilkin:

GlaxoSmithKline Consumer Healthcare (GSKCH) hereby submits, in duplicate, an amendment to pending NDA 21-152 for CUTIVATE® (fluticasone propionate) 0.05% acknowledging receipt of the NDA approvable letter dated January 12, 2005. In accordance with 21 CFR 314.110(a)(1), GSKCH is informing the agency of its intent to file an amendment addressing the questions that were contained in the approvable letter. In addition, GSKCH will be contacting the agency to request teleconferences with the Chemistry, Pharmacology/Toxicology and Clinical Reviewers to address various areas of concern.

If there are any questions concerning this submission, please contact me at 973-889-2566.

Sincerely,

A handwritten signature in black ink, appearing to read "Anthony Amitrano". The signature is written in a cursive style with a large initial "A" and a long horizontal stroke.

Anthony Amitrano

Director, US Regulatory Affairs

GlaxoSmithKline Consumer Healthcare, L.P.



GlaxoSmithKline

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JAN 10 2005

MEGA / CDER

January 6, 2005

NDA 21-152

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Jonathan K. Wilkin, M.D., Director
Division of Dermatologic and Dental Drug Products
Center for Drug Evaluation and Research
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Office of Drug Evaluation V
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HFD-540
9201 Corporate Boulevard, Bldg. 2
Rockville, MD 20850

Attention: Ms. Millie Wright, Project Manager

**Re: NDA 21-152
CUTIVATE® (fluticasone propionate 0.05%
Amendment to Pending Application: FDA Telephone Call - Response
to FDA Reviewer Comments (Faxes Dated 12/16/04 & 12/23/04)**

Dear Dr. Wilkin:

GlaxoSmithKline Consumer Healthcare (GSKCH) contacted the agency on January 5, 2005 to confirm receipt of the two FDA faxes dated 12/16/04 and 12/23/04 and to inform the agency of our intent to provide a written response to the reviewer's requests that were contained in these faxes. While GSKCH is in agreement with the majority of the revisions to the labeling, there are several areas where further discussion is required. As instructed by Ms. Millie Wright, Project Manager, GSKCH will refrain from submitting any response until after receipt of the approvable letter from the agency. This letter is expected to be issued by the PDUFA date (January 12, 2005). Once this letter is received, GSKCH is committed to providing a timely response to both the CMC Reviewer's questions (FDA fax dated 12/23/04) and the labeling revisions (FDA fax dated 12/16/04). As indicated above, the labeling revisions requested by the FDA will require further negotiation with the agency prior to our commitment to finalize the labeling.

If there are any questions concerning this submission, please contact me at 973-889-2566.

Sincerely,

Anthony Amtrano

Anthony Amtrano

Director, US Regulatory Affairs

GlaxoSmithKline Consumer Healthcare, L.P.



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation V

FACSIMILE TRANSMITTAL SHEET

DATE: December 23, 2004

To: Anthony Armitrano	From: Margo Owens for Millie Wright Project Manager
Company: GlaxoSmithKline	Division of Dermatologic & Dental Drug Products
Fax number: (973) 889-2501	Fax number: (301) 827-2091 or 2075
Phone number: (973) 889-2566	Phone number: (301) 827-2020

Subject: NDA 21-152

Total no. of pages including cover: 4

Comments: CMC request for information

Document to be mailed: • YES NO.

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.
If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at (301) 827-2020. Thank you.

Please respond to the following request for information by 05-JAN-2004. Please let us know if this deadline cannot be met. If you have any questions about specific items in the list or any other points in need of clarification, call the project manager Millie Wright (301-827-2020).

NDA Number: 21-152
Drug Name: CUTIVATE Lotion, 0.05%

Applicant: GlaxoSmithKline
23-DEC-2004

These comments are being provided to you prior to completion of our review of the application to give you preliminary notice of issues that have been identified. Per the user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and are subject to change as the review of your application is finalized. In addition, we may identify other information that must be provided prior to approval of this application. If you choose to respond to the issues raised in this letter during this review cycle, depending on the timing of your response, as per the user fee reauthorization agreements, we may or may not be able to consider your response prior to taking an action on your application during this review cycle.

NOTE: If your response can be found in the contents of your submission, just cite those sections of the submission that are relevant to the issue under consideration. Otherwise, please provide the appropriate information as an amendment to the submission.

Chemist's Concerns

1. In order to validate the justification for the absence of particle size testing in the drug product, revise the drug substance specification for fluticasone propionate [REDACTED] to include particle size testing. Employ acceptance criteria that are consistent with those applied to the batch of drug substance (No. WC116005RB) used to manufacture drug product stability batch 8J257 (see the Certificate of Analysis submitted on p. 341 in the original NDA). Provide a copy of the revised drug substance specification.
2. Provide copies of the methods used at the initial and final time points in determining viscosity of the product batches employed in the submitted stability studies.
3. Explain the decrease in viscosity that is evident in the stability studies (submitted in the amendment dated 23-JUL-2004) and appears to be attributable to the use of the new method for determining viscosity.
4. Identify the method used to determine the viscosities of the vehicle samples submitted to the Agency in November 2004.
5. Determine the viscosity at which the drug product is no longer pourable. Use this viscosity value to determine the upper limit for the acceptance criterion for viscosity in the product specification. [Based on the results from the reported stability studies, an [REDACTED] with a viscosity value below [REDACTED] is expected to remain pourable.] Until definitive data are obtained on the relation between viscosity and pourability, employ an acceptance criterion for Viscosity of NMT [REDACTED]
6. Revise your commitment for the stability protocol to indicate that all annual batches placed on stability will include testing initially and at 6, 12, 18, and 24 months (with optional testing at 36 months). [Deletion of testing at 6 and 18 months is not acceptable.]

NDA 21-152 Cutivate Lotion, 0.05%

7. Confirm that the container closure system that employs the new 60mL bottle will be subjected to the stability test protocol described in Section F7 of your original submission. For the first batch of product in this container closure system, include determination of weight loss along with the listed tests. Submit the results as part of the subsequent annual reports.

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On Original

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Margo Owens
12/23/04 01:46:31 PM
CSO
Faxed 12/23/04 for Millie Wright

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

Form Approved: OMB No. 0910-0338.
Expiration Date: August 31, 2005.
See OMB Statement on page 2.

**APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN
ANTIBIOTIC DRUG FOR HUMAN USE**
(Title 21, Code of Federal Regulations, 314 & 601)

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT

GlaxoSmithKline Consumer Healthcare, L.P.

DATE OF SUBMISSION

12/9/04

TELEPHONE NO. (Include Area Code)

(973) 889-2100

FACSIMILE (FAX) Number (Include Area Code)

(973) 889-2501

APPLICANT ADDRESS (Number, Street, City, State, Country, Zip Code or Mail Code, and U.S. License number if previously issued):

**1500 Littleton Road
Parsippany, NJ 07054-3884**

AUTHORIZED U.S. AGENT NAME & ADDRESS (Number, Street, City, State, Zip Code, telephone & FAX number) IF APPLICABLE

Not Applicable

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (if previously issued)

NDA 21-152

ESTABLISHED NAME (e.g., Proper name, USP/USAN name)

Fluticasone propionate

PROPRIETARY NAME (trade name) IF ANY

CUTIVATE® (fluticasone propionate)

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (if any)

CODE NAME (if any)

DOSAGE FORM:

[REDACTED]

STRENGTHS:

0.05% w/w

ROUTE OF ADMINISTRATION:

Topical

(PROPOSED) INDICATION(S) FOR USE:

Corticosteroid responsive dermatoses

RECEIVED
DEC 10 2004

APPLICATION INFORMATION

APPLICATION TYPE

(check one)

NEW DRUG APPLICATION (21 CFR 314.50)

ABBREVIATED APPLICATION (ANDA, 21 CFR 314.94)

BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE

505 (b) (1)

505 (b) (2)

IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug Holder of Approved Application

TYPE OF SUBMISSION

(check one)

ORIGINAL APPLICATION

AMENDMENT TO A PENDING APPLICATION

RESUBMISSION

PRESUBMISSION

ANNUAL REPORT

ESTABLISHMENT DESCRIPTION SUPPLEMENT

EFFICACY SUPPLEMENT

LABELING SUPPLEMENT

CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT

OTHER

IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION:

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY

CBE

CBE-30

Prior Approval (PA)

REASON FOR SUBMISSION

Response to FDA Reviewer Questions

PROPOSED MARKETING STATUS (check one)

PRESCRIPTION DRUG PRODUCT (Rx)

OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED

1

THIS APPLICATION IS

PAPER

PAPER AND ELECTRONIC

ELECTRONIC

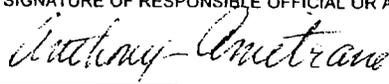
ESTABLISHMENT INFORMATION (Full Establishment information should be provided in the body of the Application)

Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

NDA 19-957, NDA 19-958, IND 54,894

ORIGINAL

This application contains the following items: (Check all that apply)		
<input type="checkbox"/>	1. Index	
<input type="checkbox"/>	2. Labeling (check one) <input type="checkbox"/> Draft Labeling <input type="checkbox"/> Final Printed Labeling	
<input type="checkbox"/>	3. Summary (21 CFR 314.50 (c))	
<input type="checkbox"/>	4. Chemistry section	
<input type="checkbox"/>	A. Chemistry, manufacturing, and controls information (e.g. 21 CFR 314.50(d)(1), 21 CFR 601.2)	
<input type="checkbox"/>	B. Samples (21 CFR 314.50 (e)(1), 21 CFR 601.2 (a)) (Submit only upon FDA's request)	
<input type="checkbox"/>	C. Methods validation package (e.g. 21 CFR 314.50 (e)(2)(i), 21 CFR 601.2)	
<input type="checkbox"/>	5. Nonclinical pharmacology and toxicology section (e.g. 21 CFR 314.50 (d)(2), 21 CFR 601.2)	
<input type="checkbox"/>	6. Human pharmacokinetics and bioavailability section (e.g. 21 CFR 314.50 (d)(3), 21 CFR 601.2)	
<input type="checkbox"/>	7. Clinical Microbiology (e.g. 21 CFR 314.50 (d)(4))	
<input type="checkbox"/>	8. Clinical data section (e.g. 21 CFR 314.50 (d)(5), 21 CFR 601.2)	
<input type="checkbox"/>	9. Safety update report (e.g. 21 CFR 314.50 (d)(5)(vi)(b), 21 CFR 601.2)	
<input type="checkbox"/>	10. Statistical section (e.g. 21 CFR 314.50 (d)(6), 21 CFR 601.2)	
<input type="checkbox"/>	11. Case report tabulations (e.g. 21 CFR 314.50 (f)(1), 21 CFR 601.2)	
<input type="checkbox"/>	12. Case report forms (e.g. 21 CFR 314.50 (f)(2), 21 CFR 601.2)	
<input type="checkbox"/>	13. Patent information on any patent which claims the drug (21 U.S.C. 355 (b) or (c))	
<input type="checkbox"/>	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b)(2) or (j)(2)(A))	
<input type="checkbox"/>	15. Establishment description (21 CFR Part 600, if applicable)	
<input type="checkbox"/>	16. Debarment certification (FD&C Act 306 (k)(1))	
<input type="checkbox"/>	17. Field copy certification (21 CFR 314.50 (k)(3))	
<input type="checkbox"/>	18. User Fee Cover Sheet (Form FDA 3397)	
<input type="checkbox"/>	19. Financial Information (21 CFR Part 54)	
<input checked="" type="checkbox"/>	20. OTHER (Specify)	
CERTIFICATION		
<p>I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:</p> <ol style="list-style-type: none"> 1. Good manufacturing practice regulations in 21 CFR 210 and 211, 606 and/or 820. 2. Biological establishment standards in 21 CFR Part 600. 3. Labeling regulations in 21 CFR 201, 606, 610, 660 and/or 809. 4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR 202. 5. Regulations on making changes in application in FD&C Act Section 506A, 314.71, 314.72, 314.97, 314.99 and 601.12. 6. Regulations on reports in 21 CFR 314.80, 314.81, 600.80 and 600.81. 7. Local, state and Federal environmental impact laws. <p>If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.</p> <p>The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.</p> <p>Warning: a willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.</p>		
SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT 		TYPED NAME AND TITLE Anthony Amitrano Director, US Regulatory Affairs
ADDRESS (Street, City, State, Zip Code) 1500 Littleton Road, Parsippany, NJ, 07054-3884		DATE 12/9/04
Telephone Number (973) 889-2566		
<p>Public reporting burden for this collection of information is estimated to average 24 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:</p> <p>Department of Health and Human Services Food and Drug Administration Food and Drug Administration CDER, HFD-94 CBER, HFM-99 12420 Parklawn Dr., Room 3046 1401 Rockville Pike Rockville, MD 20852 Rockville, MD 20852-1448</p> <p>An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.</p>		
FORM FDA 356h (9/02)		



GlaxoSmithKline

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www.gsk.com

RECEIVED
DEC 10 2004
MEGA/CDER

December 9, 2004

NDA 21-152

Jonathan K. Wilkin, M.D., Director
Division of Dermatologic and Dental Drug Products
Center for Drug Evaluation and Research
Document Control Room
Office of Drug Evaluation V
Food and Drug Administration
HFD-540
9201 Corporate Boulevard, Bldg. 2
Rockville, MD 20850

N. 000(BC)

ORIG AMENDMENT

Attention: Ms. Millie Wright, Project Manager

Re: NDA 21-152
CUTIVATE® (fluticasone propionate) _____
0.05%
Amendment to Pending Application: Chemistry

Dear Dr. Wilkin:

Reference is made to the FDA fax dated June 2, 2004 and GSKCH response dated July 19, 2004. GlaxoSmithKline Consumer Healthcare (GSKCH) hereby submits, in duplicate, an amendment to pending NDA 21-152 for CUTIVATE® (fluticasone propionate) _____ 0.05%. This submission is in response to the November 29, 2004 FDA fax which provides feedback regarding GSKCH's rationale to maintain the current terminology. In the latest fax, the Agency restated its recommendation that this topical product be called a lotion rather than an emulsion.

GSKCH appreciates the Agency's recommendation and we understand the desire to standardize the classification of topical dosage forms. Respectfully, GSKCH would be interested in reviewing any supporting data the Agency has on file concerning the FDA's belief that use of the term _____ permits confusion.

ORIGINAŁ

GSKCH has consulted with Dermatology experts and opinion leaders concerning the use of the terms "lotion [REDACTED]" These discussions revealed that there is a desire to clinically differentiate these products as this would be more beneficial to sufferers of dry skin conditions. The current perception is that some lotions may contain alcohol or other drying agents which can negatively impact the patient, while [REDACTED] do not. GSKCH believes that the use of the term [REDACTED] permits this distinction in the product name. Therefore, retaining the use of the term [REDACTED] is justified until a final compliance guidance has been issued by the Agency. Once a formal classification system has been established, GSKCH will fully cooperate with the Agency in the appropriate re-labeling of our drug product in accordance with the final guidance.

We hope that the Agency understands our position and if there are any questions concerning this submission, please contact me at 973-889-2566.

Sincerely,



Anthony Amitrano

Director, US Regulatory Affairs

GlaxoSmithKline Consumer Healthcare, L.P.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO (Division/Office):

Division of Surveillance, Research and Communication
Support, HFD-410

FROM:

Millie Wright, Project Manager
Division of Dermatologic and Dental Drug Products/HFD-540

DATE: December 2, 2004

IND NO.

NDA NO. 21-152

TYPE OF DOCUMENT

NDA RS

DATE OF DOCUMENT:

March 11, 2004

NAME OF DRUG:

Cutivate (fluticasone propionate)
0.05%

PRIORITY CONSIDERATION

CLASSIFICATION OF DRUG:

3S

DESIRED COMPLETION DATE:

TBD/PDUFA/1/12/05

NAME OF FIRM: GlaxoSmithKline.

REASON FOR REQUEST

I. GENERAL

- | | | |
|--|--|--|
| <input type="checkbox"/> NEW PROTOCOL | <input type="checkbox"/> PRE--NDA MEETING | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER |
| <input type="checkbox"/> PROGRESS REPORT | <input type="checkbox"/> END OF PHASE II MEETING | <input type="checkbox"/> FINAL PRINTED LABELING |
| <input type="checkbox"/> NEW CORRESPONDENCE | <input type="checkbox"/> RESUBMISSION | <input type="checkbox"/> LABELING REVISION |
| <input type="checkbox"/> DRUG ADVERTISING | <input type="checkbox"/> SAFETY/EFFICACY | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE |
| <input type="checkbox"/> ADVERSE REACTION REPORT | <input type="checkbox"/> PAPER NDA | <input type="checkbox"/> FORMULATIVE REVIEW |
| <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION | <input type="checkbox"/> CONTROL SUPPLEMENT | <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> MEETING PLANNED BY | | |

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH

STATISTICAL APPLICATION BRANCH

- | | |
|--|---|
| <input type="checkbox"/> TYPE A OR B NDA REVIEW | <input type="checkbox"/> CHEMISTRY REVIEW |
| <input type="checkbox"/> END OF PHASE II MEETING | <input type="checkbox"/> PHARMACOLOGY |
| <input type="checkbox"/> CONTROLLED STUDIES | <input type="checkbox"/> BIOPHARMACEUTICS |
| <input type="checkbox"/> PROTOCOL REVIEW | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> OTHER (SPECIFY BELOW): | |

III. BIOPHARMACEUTICS

- | | |
|--|---|
| <input type="checkbox"/> DISSOLUTION | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS |
| <input type="checkbox"/> PHASE IV STUDIES | <input type="checkbox"/> IN-VIVO WAIVER REQUEST |

IV. DRUG EXPERIENCE

- | | |
|--|--|
| <input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) | <input type="checkbox"/> POISON RISK ANALYSIS |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP | |

V. SCIENTIFIC INVESTIGATIONS

CLINICAL

PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

The labeling for this NDA can be found in the electronic document room.

PDUFA DATE: January 12, 2005

SIGNATURE OF REQUESTER

METHOD OF DELIVERY (Check one)

MAIL

HAND

SIGNATURE OF RECEIVER

SIGNATURE OF DELIVERER

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/s/

Mildred Wright
12/2/04 12:08:30 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-152

GlaxoSmithKline
Attention: Anthony Amitrano
Director, US Regulatory Affairs
1500 Littleton Road
Parisippany, New Jersey 07054-3884

Dear Mr. Amitrano:

Please refer to your March 11, 2004, new drug application (NDA), received March 12, 2004, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for CUTIVATE® (fluticasone propionate) 0.05% and to your amendment dated July 19, 2004.

You proposed that this topical product be named an [redacted]. The Agency believes that the use of the term [redacted] permits confusion in that it can pertain to any one of the following topical dosage forms: ointments, creams, and lotions. [redacted]

[redacted] Several physicochemical methods can be used to differentiate liquid from semisolid and to classify the different topical dosage forms. These methods include, but are not limited to, composition and rheology (viscosity and shear rate vs. shear stress), which is the most discriminating method based on our experience.

You noted that certain approved topical drugs were designated as [redacted]. We would like to point out that the Orange Book contains considerably more products labeled as "lotions" than those labeled as [redacted]. These few [redacted] may not have been appropriately named when the products were approved. The Agency is in the process of developing a scientifically-based, systematic classification of dosage forms for topical drugs.

[redacted]

NDA 21-152

We hope that you find the above information helpful and that our recommendation is acceptable. We will appreciate your cooperation with our efforts to establish a scientific basis for a systematic, coherent and meaningful classification of dosage forms for topical drugs that will permit more discriminative use of these products by both physicians and patients.

If you have additional comments on these matters for our consideration, please do not hesitate to contact us by calling Millie Wright, Project Manager, at (301) 827-2020.

Sincerely,

{See appended electronic signature page}

David T. Lin, Ph.D.
Acting Division Director
DNDC III, Office of New Drug Chemistry
Center for Drug Evaluation and Research

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/s/

David T. Lin
11/29/04 02:53:01 PM

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November 19, 2004

NDA 21-152

Jonathan K. Wilkin, M.D., Director
Division of Dermatologic and Dental Drug Products
Center for Drug Evaluation and Research
Document Control Room
Office of Drug Evaluation V
Food and Drug Administration
HFD-540
9201 Corporate Boulevard, Bldg. 2
Rockville, MD 20850

N-000(5C)

ORIG AMENDMENT

Attention: Ms. Millie Wright, Project Manager

Re: NDA 21-152
CUTIVATE[®] (fluticasone propionate) 0.05%
Amendment to Pending Application: Chemistry

Dear Dr. Wilkin:

GlaxoSmithKline Consumer Healthcare (GSKCH) hereby submits, in duplicate, an amendment to pending NDA 21-152 for CUTIVATE[®] (fluticasone propionate) 0.05% consisting of updated packaging information. This submission constitutes GSKCH's response to the only remaining outstanding question (Chemistry - 1.b) from the FDA fax that was received on May 24, 2004. In order to facilitate the review process, the original FDA question is provided and is immediately followed by GSKCH's response.

Chemistry

ORIGINAL

FDA Question

1. Please provide the following:
- b. Updated copies of all Letters of Authorization.

GSKCH Response

1. b. There are no DMF letters for the active ingredient and excipients used in the manufacture of CUTIVATE® [REDACTED]. Updated copies of the DMF letters of authorization for the packaging components are provided (see Attachment Ia - Ie). A table has also been provided that lists the following information for the DMFs of the packaging components: DMF numbers, date of the DMF authorization letter and company name (see Attachment II).

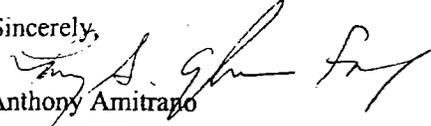
The CMC section of the original NDA that was submitted on March 11, 2004 contained documentation for a [REDACTED] 60mL [REDACTED] package size. Subsequent to this submission, GSKCH was informed that the original molds for the 60mL [REDACTED] bottles were discontinued by the supplier,

[REDACTED]
[REDACTED] In light of this, a decision was made to launch using the [REDACTED] 60mL package sizes only. GSKCH will use a similar 60mL bottle [REDACTED] that is manufactured by the same supplier, [REDACTED]. Provided as Attachment III, are comparison data between the original and proposed 60mL bottles, as well as a stability statement which concludes that the noted differences between the [REDACTED] bottles are minimal and will not affect the stability of the drug product. A revised representative drawing of the proposed 60mL bottle is provided as Attachment IV (note: the original drawing for the 60mL bottle was provided in the NDA submission dated March 11, 2004).

In addition, as per the regulations, GSKCH is committed to performing stability studies on the first three production batches utilizing [REDACTED] the [REDACTED] 60mL bottles. The results of these studies will be provided to the FDA.

If there are any questions concerning this submission, please contact me at 973-889-2566.

Sincerely,


Anthony Amitrano

Director, US Regulatory Affairs

GlaxoSmithKline Consumer Healthcare, L.P.

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications

Predecisional Agency Information

Date: November 8, 2004
From: Sonny Saini, Pharm.D. - DDMAC
To: Mildred Wright
Re: Cutivate  fluticasone propionate  0.05%
N 21-152

Indications and Usage

• 

Precautions

• 

Clinical Studies

- We recommend this section be placed prior to the Indications and Usage section.

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/s/

Sonny Saini
11/8/04 01:44:50 PM
DDMAC REVIEWER

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November 1, 2004

NDA 21-152

Ms Mary Jean Kozma-Fornaro
Division of Dermatologic and Dental Drug Products
Center for Drug Evaluation and Research
Document Control Room
Office of Drug Evaluation V
Food and Drug Administration
HFD-540
9201 Corporate Boulevard, Bldg. 2, Room No. 252
Rockville, MD 20850

Copy To (letter only): Ms. Millie Wright, Project Manager

Re: NDA 21-152
CUTIVATE[®] (fluticasone propionate) 0.05%
AMENDMENT TO PENDING APPLICATION: Chemistry (Request
for Samples), DESK COPY/REVIEW AID

Dear Dr. Wilkin:

Per the November 1, 2004 telephone discussion with Ms. Millie Wright,
GlaxoSmithKline Consumer Healthcare (GSKCH) hereby submits an amendment
to pending NDA 21-152 for CUTIVATE[®] (fluticasone propionate) 0.05%
consisting of ten placebo samples at the following viscosities:
Included with these samples is the quantitative formulation for each
variant manufactured in our pilot plant (Note: the formula is essentially the same
as the Cutivate

This submission constitutes GSKCH's response to the FDA faxes that were
received on August 12, 2004, September 16, 2004 and September 20, 2004.



GlaxoSmithKline

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N.000(BC)

ORIG AMENDMENT

ORIGINAL

If there are any questions concerning this submission, please contact me at 973-889-2566.

Sincerely,

Handwritten signature of Anthony Amitrano in cursive script.

Anthony Amitrano

Director, US Regulatory Affairs

GlaxoSmithKline Consumer Healthcare, L.P.



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation V

FACSIMILE TRANSMITTAL SHEET

Date: September 20, 2004

To: **GlaxoSmithKline**
Attn: Tony Amitrano
Director, US Regulatory Affairs
Phone: (973) 889-2566
Fax: (973) 889-2501

From: Millie Wright, Project Manager
Phone: (301) 827-2020
Fax: (301) 827-2091

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FDA Fax Memorandum

Date: September 20, 2004

Subject: NDA 21-152/Cuticate 0.05%

Hi Tony,

As a follow-up to your phone message, which requested clarification about the Agency's September 16th fax, I spoke with the CMC reviewer. His response is as follows:

[Redacted content]

Again, thanks for your efforts to provide the samples.
Respectfully,
Millie

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/s/

Mildred Wright
9/20/04 01:33:06 PM
CSO



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation V

FACSIMILE TRANSMITTAL SHEET

Date: September 16, 2004

To: **GlaxoSmithKline**
Attn: Tony Amitrano
Director, US Regulatory Affair
Phone: (973) 889-2566
Fax: (973) 889-2501

From: Millie Wright, Project Manager
Phone: (301) 827-2020
Fax: (301) 827-2091

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FDA Fax Memorandum

Date: September 16, 2004

Subject: NDA 21-152/Cutivate 0.05%

Hi Tony,

As a follow-up to our phone conversation about the Cutivate samples, I spoke with the CMC reviewer. His response is as follows:

If possible, provide some specimens of [redacted] lotions with viscosity values of [redacted]. These samples can be the product vehicle [redacted] that is packaged in the proposed container closure system.

Thanks for your efforts to provide the samples.

Respectfully,
Millie

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/s/

Mildred Wright
9/16/04 12:59:43 PM
CSO

210

ORIGINAL



GlaxoSmithKline

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August 18, 2004

NDA 21-152

Jonathan K. Wilkin, M.D., Director
Division of Dermatologic and Dental Drug Products
Center for Drug Evaluation and Research
Document Control Room
Office of Drug Evaluation V
Food and Drug Administration
HFD-540
9201 Corporate Boulevard, Bldg. 2
Rockville, MD 20850

N-001-10
ORIG AMENDMENT

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AUG 19 2004
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Attention: Ms. Millie Wright, Project Manager

**Re: NDA 21-152
CUTIVATE[®] (fluticasone propionate) 0.05%
Amendment to Pending Application: Clinical/Statistical**

Dear Dr. Wilkin:

GlaxoSmithKline Consumer Healthcare (GSKCH) hereby submits an amendment to pending NDA 21-152 for CUTIVATE[®] (fluticasone propionate) 0.05% consisting of clinical and statistical information. This submission is in response to FDA's fax dated July 29, 2004 requesting the following:

Please submit analyses where a treatment success is defined as achieving a score of 0 in all 4 body regions for the signs of erythema, infiltration/papulation, and erosion/oozing/crusting. Include in the analyses only the subset of subjects who meet the following baseline criteria: A minimum score of 2 for any two of the three parameters (i.e., erythema, induration/population, and erosion/crusting/oozing) in at least 1 of the 4 body areas (the scores of 2 may be in different body areas) AND a minimum combined score of 10 of 36.

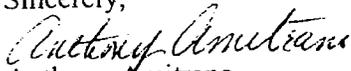
GSKCH is providing the requested analyses as well as additional data sets which reflect the success criterion that was agreed to by the FDA at the time of the original submission and real life clinical practice. This submission consists of the following:

- Summary report of additional analyses performed for studies FPL30003 and FPL30004
- Supporting tables (1a/1b - 4a/4b)

The data presented further support the findings of the original study reports for studies FPL30003 and FPL30004 that were submitted in NDA 21-152. The original data reported in the application showed a clear and consistent advantage in favor of fluticasone propionate over the vehicle control. The current additional analyses support the robustness of the treatment effect even when the sample size is reduced from that originally planned.

If there are any questions concerning this submission, please contact me at 973-889-2566.

Sincerely,


Anthony Amitrano

Director, US Regulatory Affairs
GlaxoSmithKline Consumer Healthcare, L.P.



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation V

FACSIMILE TRANSMITTAL SHEET

Date: August 12, 2004

To: GlaxoSmithKline
Attn: Tony Amitrano
Director, US Regulatory Affair
Phone: (973) 889-2566
Fax: (973) 889-2501

From: Millie Wright, Project Manager
Phone: (301) 827-2020
Fax: (301) 827-2091

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FDA Fax Memorandum

Date: August 12, 2004

Subject: NDA 21-152/Cutivate 0.05%

Hi Tony,

We have the following informational request:

Please provide Cutivate 0.05% product samples for Batch 8C283 that have been stored for a year or more at 2° C and 30° C. Include results from stability testing of these same samples from the initial to the final time station.

Please provide the samples and data by August 26th. If you can not meet the August 26th target date, please give me a call to let me know when you propose to submit the requested samples.

Respectfully,
Millie

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/s/

Mildred Wright
8/12/04 08:37:05 AM
CSO

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GlaxoSmithKline

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www.gsk.com

August 3, 2004

MEGA/CDER

NDA 21-152

Jonathan K. Wilkin, M.D., Director
Division of Dermatologic and Dental Drug Products
Center for Drug Evaluation and Research
Document Control Room
Office of Drug Evaluation V
Food and Drug Administration
HFD-540
9201 Corporate Boulevard, Bldg. 2
Rockville, MD 20850

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AUG 0 4 2004

CDR / CDER

N. 000 (BC)

Attention: Ms. Millie Wright, Project Manager

ORIG AMENDMENT

Re: NDA 21-152

**CUTIVATE[®] (fluticasone propionate) 0.05%
Amendment to Pending Application: Electronic Copies of Labeling**

Dear Dr. Wilkin:

GlaxoSmithKline Consumer Healthcare (GSKCH) hereby submits an amendment to pending NDA 21-152 for CUTIVATE[®] (fluticasone propionate) 0.05% consisting of electronic copies of the revised labeling in both pdf format and as a Word document as requested by the FDA in a fax that was received on July 29, 2004. The revised labeling included in this amendment is identical to that which was provided in the amendment submitted on July 23, 2004.

In summary, the revisions were made to the following sections and are noted in blue type:

- Revisions to Nonclinical portions of the label (Carcinogenesis, Mutagenesis, Impairment of Fertility, Pregnancy subsections under the Precautions Section per Pharm/Tox FDA Question #1 from fax dated 5/21/04).

DUPLICATE

- Revision to the Geriatric Use Subsection under the Precautions Section.
- Revision to the Indication and Usage Section to reflect atopic Dermatitis (per clinical/Statistical FDA Question #8 from fax dated 5/21/04).
- Addition to the Adverse Reactions Section to provide tables depicting the adverse events data for the clinical trials.
- Addition of a Clinical Studies Section (per Clinical/Statistical FDA Question #7 from fax dated 5/21/04).

This submission is being provided in electronic format. The enclosed CD-ROM has been confirmed to virus-free using Symantec Anti Virus Corporate Edition, version 8.00.9374, scan engine 4.1.0.15, updated 8/1/04, rev. 16.

If there are any questions concerning this submission, please contact me at 973-889-2566.

Sincerely,



Anthony Amitrano

Director, US Regulatory Affairs

GlaxoSmithKline Consumer Healthcare, L.P.

DUPLICATE



GlaxoSmithKline

GlaxoSmithKline
1500 Littleton Road
Parsippany, NJ
07054-3884

Tel. 973 889 2100
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August 3, 2004

RECEIVED

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MEGA/CDER

N. 050 (05)
ORIG AMENDMENT

NDA 21-152

RECEIVED

AUG 0 3 2004

CDR / CDER

Jonathan K. Wilkin, M.D., Director
Division of Dermatologic and Dental Drug Products
Center for Drug Evaluation and Research
Document Control Room
Office of Drug Evaluation V
Food and Drug Administration
HFD-540
9201 Corporate Boulevard, Bldg. 2
Rockville, MD 20850

Attention: Ms. Millie Wright, Project Manager

Re: NDA 21-152
CUTIVATE® (fluticasone propionate) 0.05%
Amendment to Pending Application: Biostatistical Package

Dear Dr. Wilkin:

GlaxoSmithKline Consumer Healthcare (GSKCH) hereby submits an amendment to pending NDA 21-152 for CUTIVATE® (fluticasone propionate) 0.05%. In order to facilitate the review of this application, GSKCH is providing the Biostatistical Package for the pivotal clinical studies. The following data are included on CD-ROM:

Studies FPL10005, FPL30003, FPL30004

- Item 11 - Case Report Tabulations: SAS Transport Files for all datasets; Data Definition tables (define.pdf) and Annotated CRFs (blankcrf.pdf)
- Item 12 - Case Report Forms: All CRFs submitted in the original paper NDA have been scanned into PDF format.

This submission is being provided in electronic format. The enclosed CD-ROM has been confirmed to be virus-free using Symantec AntiVirus Corporate Edition, version 8.00.9374, scan engine 4.1.0.15, updated 8/01/04, rev. 16.

If there are any questions concerning this submission, please contact me at 973-889-2566.

Sincerely,

A handwritten signature in cursive script, appearing to read "Anthony Amfrano".

Anthony Amfrano
Director, US Regulatory Affairs
GlaxoSmithKline Consumer Healthcare, L.P.



Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

DATE: August 3, 2004

FROM: Renan A. Bonnel, Pharm.D., M.P.H.
Postmarketing Safety Evaluator
Division of Drug Risk Evaluation, HFD-430

THROUGH: Mark Avigan, M.D., C.M., Director
Division of Drug Risk Evaluation, HFD-430
Office of Drug Safety

TO: Jonathan Wilkin, M.D., Director
Division of Dermatologic and Dental Drug Products, HFD-540

SUBJECT: Office of Drug Safety- Postmarketing Safety Review (PID# D040461)
Drug: Fluticasone propionate cream 0.05% (Cutivate® Cream) and
Fluticasone propionate ointment 0.005% (Cutivate® Ointment) (NDAs –
19-957, 19-958)
Events: All Adverse Drug Reactions

**Confidential: Contains IMS HEALTH data; not to be used outside of the FDA
without clearance.**

INTRODUCTION/EXECUTIVE SUMMARY

In response to a request by the Division of Dermatological and Dental Drug Products (DDDDP), we reviewed adverse event cases in AERS reported in association with fluticasone propionate cream 0.05% and ointment 0.005% (Cutivate®, GlaxoSmithKline). DDDDP is currently reviewing a new drug application for fluticasone propionate lotion 0.05% (Cutivate [REDACTED]). They are particularly interested in postmarketing adverse events related to adrenal suppression, Cushing's syndrome, eczema herpeticum or herpes simplex, and influenza with currently marketed Cutivate products.

We reviewed a total of 35 cases of adverse events with the use of fluticasone propionate (Cutivate®). Sixteen cases were excluded for various reasons and the remaining 19 cases are summarized in this safety review. Thirteen patients received cream, five patients received an ointment and one patient received both formulations. All were domestic cases and most were consumer reports. There were 13 females and 6 males. The ages of the patients ranged from 2 months to 76 years, with a median age of 40 years. The duration of therapy ranged from one week to 2 years in 6 patients. It was unknown in the remaining 13 cases. Three patients required hospitalizations as a result of edema of lower

extremities, severe pustular psoriasis, and immunodeficiency/pneumocystis carinii pneumonia. There were no fatalities.

The reported events were labeled, localized reactions (9 cases), including severe pruritus, periorbital edema, aggravation of skin rash, burning, skin pigmentation, as well as systemic reactions (6 cases), including Cushing's syndrome (labeled), hyperglycemia /glycosuria (labeled), acute urticarial reaction (labeled), generalized body edema /blurred vision (unlabeled), and agitation/fatigue (unlabeled), immunosuppression /Pneumocystis carinii pneumonia (PCP)/leucopenia/thrombocytopenia (unlabeled). Four reported lack of efficacy. The unlabeled events constituted a very small number of the cases and the role of Cutivate in generalized edema, agitation/fatigue, and immunosuppression could not be determined due to underlying medical conditions and the absence of clinical information in the reports.

Five of 19 reports were adverse events in children younger than 16 years of age. The events included skin rash, immunodeficiency/PCP pneumonia, hyperglycemia/glycosuria, acute urticarial reaction (edema, urticaria, pruritus, and throat swelling), and lack of efficacy. Four children received cream and one child received an ointment formulation (unapproved in children). The outcomes included a hospitalization of a 3-year-old child for pneumocystis carinii pneumonia, insulin therapy for hyperglycemia/glycosuria and diphenhydramine for acute urticarial reaction. Three of 5 patients recovered. The outcomes were unknown in 2 patients. There were no fatalities.

The most important finding in this review was the inappropriate use of Cutivate cream/ointment in children. Misuse of the product included the use of the ointment in a 12-year-old (unapproved formulation in children), the use of the cream formulation under the age of 3 months (unapproved age), and excessive use of the product. The reported adverse events in these cases included hyperglycemia/glycosuria, immunosuppression /PCP, and acute urticarial reaction.

In general, most events were labeled, and the unlabeled events were few in number. The exact causal role of Cutivate in most cases could not be determined due to the concomitant use of topical corticosteroids, confounding medical conditions, and insufficient clinical information. We did not identify cases of eczema herpeticum, herpes simplex or influenza that were of particular interest to DDDDP. Four pediatric reports suggested that Cutivate cream/ointment was used inappropriately in children.

We did not identify any new safety issues and the information in the product labeling is adequate to communicate the safety information.

I. PRODUCT AND LABELING INFORMATION ^{1,2}

The FDA approved the fluticasone propionate ointment 0.005% (Cutivate®) and cream 0.05% (Cutivate®) on December 14 & 18, 1990, respectively. Both products are medium potency corticosteroids. They have anti-inflammatory, antipruritic, and vasoconstrictive properties and are indicated for the relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses. Cutivate Cream is approved for use in pediatric patients and the use of Cutivate Ointment in pediatric patients is not recommended.

Several sections of the product labeling indicate that topical corticosteroids can be absorbed from normal intact skin. Inflammation and/or other disease processes in the skin increase percutaneous absorption. Topically applied Cutivate Cream and ointment can be absorbed in sufficient amounts to produce systemic effects.

The products' labeling includes the following pertinent information.

Precautions

- Systemic absorption of topical corticosteroids can produce reversible hypothalamic-pituitary-adrenal (HPA) axis suppression with the potential for glucocorticosteroid insufficiency after withdrawal from treatment. Manifestations of Cushing's syndrome, hyperglycemia, and glycosuria can also be produced in some patients by systemic absorption of topical corticosteroids while on treatment.
- Cutivate Cream should not be applied in the diaper areas as diapers or plastic pants may constitute occlusive dressing
- Therapy should be discontinued when control is achieved. If no improvement is seen within 2 weeks, contact the physician.
- Pediatric Use: Cutivate Cream may be used with caution in pediatric patients 3 months of age or older. The safety and efficacy of drug use for longer than 4 weeks in this population have not been established. The safety and efficacy of Cutivate Cream in pediatric patients below 3 months of age have not been established. Cutivate Ointment is not recommended in children.

Adverse Reactions

Cutivate Ointment-

Pruritus, burning, hypertrichosis, increased erythema, hives, irritation, and lightheadedness are most frequently reported in clinical trials. Subnormal adrenal function and telangiectasia on the face reported in clinical trials.

Cutivate Cream-

Pruritus, dryness, numbness of fingers, and burning skin are most frequently reported in clinical trials. The other adverse events included skin infection, infected eczema, viral warts, herpes simplex, impetigo, atopic dermatitis, eczema, exacerbation of eczema, erythema, burning, stinging, skin irritation, pruritus, exacerbation of pruritus, folliculitis, blisters, dryness of skin, burning, dusky erythema, erythematous rash, facial telangiectasia, non-facial telangiectasia, and urticaria.

General statements in product labeling-

The following local adverse reactions have been reported infrequently with topical corticosteroids. They include dryness, folliculitis, acneiform eruptions, hypopigmentation, perioral dermatitis, allergic contact dermatitis, secondary infection, skin atrophy, striae, and miliaria. Also, there are reports of the development of pustular psoriasis from chronic plaque psoriasis following reduction or discontinuation of potent topical corticosteroid products.

Dosage and administration

Apply a thin film to the affected skin areas once or twice daily.

II. DRUG USE

The following table summarizes projected total prescriptions of Cutivate dispensed by retail pharmacies (chain, independent, food stores, mail order, and long-term care) in the U.S. from 1999 through June 2004 (product approved in December 1990).

Drug	TRx '99	TRx '00	TRx '01	TRx '02	TRx '03	TRx June '04	Total Rx
Cutivate Cream	[REDACTED]						
Cutivate Ointment	[REDACTED]						

(in thousands: ADD THREE 0's TO EACH FIGURE)

This information is not to be used outside of the FDA without prior clearance by IMS Health.

III. SELECTION AND SUMMARY OF CASES

We searched the AERS database on July 22, 2004 using both the brand and generic drug names, topical fluticasone propionate and Cutivate®. Thirty-five cases were retrieved, of which 16 cases were excluded from further review for the following reasons: the event was not related to the topical product (14); the event was unrelated to the use of a topical product (1) and no adverse event (1).

The demographics of the 19 remaining cases are summarized as follows:

Source	US- 19
Reporter	Consumer- 13; HCP: 6
Year	2002-1; 2000-1;1999-3; 1997-6; 1996-2; 1995-3; 1994-2; 1992-1
Report type	15-day:7; Periodic: 12
Age (years) (n=16)	Median: 40; Range: 2months-76 yrs
Gender	Males-6 ; Females- 13
Duration of therapy (days) (n=5)	Median: 5 weeks; Range: 1 week-2 years
Outcome (n=8)	Hospitalization- 3; Life-threatening-1; Required Intervention-4
Dechallenge	Positive-7; Negative-6; Not reported-6

A. Local Site Adverse Effects (9 cases)

There were 9 reports (adults-8; pediatric-1) of localized adverse reactions temporally associated with the use of Cutivate. The severity of reactions varied from localized rash, pain, burning, face edema, skin pigmentation to worsening of psoriasis. All local reactions were labeled adverse events.

There were 6 females and 3 males. The ages of patients ranged from 2 months to 64 years (n=8) with the median of 50 years. The dose, onset and duration were unavailable in most reports. A 2-month-old child received Cutivate cream (unapproved age) for diaper rash (use not recommended) and developed a localized reaction. Four adult patients reported either a history of contact dermatitis to cosmetics, seborrheic keratosis, psoriasis, or concomitant use of alclomethasone dipropionate ointment and calcipotriene that might have contributed to the reactions.

There was one hospitalization of a 64-year-old male who developed worsening of psoriasis, desquamation and pustular psoriasis after receiving Cutivate and calcipotriene (Dovonex®). Both drugs were suspect agents. Two patients received systemic prednisone and tetracycline treatments. Five patients recovered or improved after discontinuation of Cutivate. Three patients reported negative dechallenges. The outcome was unknown in one case. The narratives of a representative pediatric case and the most serious adult case are summarized below:

- ISR# 1553355, 1995, US

A 2-month-old male received Cutivate Cream for diaper rash and developed **localized red skin rash**. The dose and duration of use are unknown. The fluticasone discontinued and his symptoms resolved.

Reviewer's comment: The product is not recommended in children < 3 months of age.

- ISR# 1745706, 15-day, 1996, US

A 64-year-old male with a history of psoriasis received Cutivate Ointment and calcipotriene after completing a clinical trial involving tazarotene for psoriasis. He tolerated tazarotene therapy without problems. Four days later, he developed severe pruritus and erythema (~ 8-10 % total body surface area). Cutivate and calcipotriene were discontinued. The patient was treated with prednisone and Retin-A without improvement. Psoriasis continued to worsen and he was hospitalized due to severe pustular psoriasis.

Reviewer's comment: The reporting physician considered the event to be possibly related to Cutivate or calcipotriene(Dovonex). Both agents are considered suspect medications.

B. Systemic Adverse Effects (6 cases)

There were 6 unduplicated (adult-3; pediatric-3) reports of systemic adverse reactions with the use of Cutivate. Most events were unlabeled and occurred mostly in younger ages. The events were Cushing's syndrome (labeled), acute urticarial reaction (labeled), hyperglycemia/glucosuria (labeled), generalized body edema/blurred vision (unlabeled), and agitation/fatigue (unlabeled), and immunosuppression/thrombocytopenia /leucopenia (unlabeled).

The patients were 5 females and 1 male. The ages of patients ranged from 3 years to 45 years (n=6) with the median of 22 years. In four cases, dose or duration may have exceeded the labeled recommendations. Two pediatric cases described excessive use of Cutivate cream, and the reported events in these cases were hyperglycemia/glycosuria and immunosuppression/PCP/ leucopenia/thrombocytopenia. Another child developed acute urticarial reaction following the use of the ointment formulation (unapproved in children).

Three patients reported a history of atopic dermatitis, concomitant corticosteroids, or concurrent multiple systemic conditions (unspecified pancreatic and hepatic conditions) that might have contributed to the development of acute urticarial reaction, Cushing's syndrome and generalized body edema/blurred vision.

Two patients required hospitalizations as a result of immunosuppression/PCP and multiple medical events involving dermatological, psychiatric, and gastrointestinal systems. Two patients received insulin or diphenhydramine therapy and improved. Two patients recovered or improved after the discontinuation of Cutivate. Four patients reported negative dechallenges.

Narrative summaries of the cases are provided below.

- ISR#1506224, 1994, US

A 3-year-old female developed **immunosuppression** and was diagnosed with **Pneumocystis carinii pneumonia (PCP)** after receiving Cutivate Cream "liberally and multiple times daily" for a rash on her face, ears, and legs. A lesion on tongue was removed three weeks prior to the diagnosis of PCP. HIV serology was negative. She was hospitalized and improved. The fluticasone was re-started four times daily for a rash on her feet. About four months later, she developed leucopenia (2000/mm³) and thrombocytopenia (48,000/mm³). At the time of the report, her condition was unchanged.

Reviewer's comment: The product is not recommended to apply more than twice daily. The information on the report suggests that the patient may have received excessive doses of the product repeatedly. The causal role of Cutivate in the development of immunosuppression and subsequent bone marrow suppression could not be ruled out.

- ISR# 1553359, 1995, US

A 9-year-old female received Cutivate Cream twice daily for *several weeks* for rash and developed frequent urination, excessive thirst, fatigue, glycosuria and hyperglycemia and diagnosed with **insulin-dependent diabetes mellitus**. Serum glucose levels were > 300 mg/dl. She was treated with insulin and her symptoms improved.

Reviewer's comment: The patient developed IDDM after several weeks of Cutivate use. Systemic absorption of Cutivate leading to systemic toxicity could not be ruled out.

- ISR# 3443599, 2000, US

A 12-year old male with a history of atopic dermatitis received Cutivate Ointment twice daily and experienced hives, red confluent rash, itching, swelling at application site and throat swelling. Significant medical history includes immunotherapy for environmental and inhalant allergies and urticarial reaction to penicillin. He was diagnosed with **acute urticarial reaction**. The patient recovered after receiving diphenhydramine.

Reviewer's comment: The use of ointment formulation in children is not recommended. The patient's significant history of allergies and atopic dermatitis might have contributed to the events.

- ISR# 1878021, 1997, Periodic, Consumer, US

A 33-year-old female with a history of acne and dry lips applied Cutivate Ointment for the treatment of dry lips four times daily for about 2 months. Three weeks after the discontinuation of therapy she presented with swollen face and increased cortisol levels (254- units and time of blood sampling are not provided). She was diagnosed with **Cushing's syndrome**. Concomitant medications included isotretinoin, Ortho Cyclen, hydrocortisone butyrate, and Elocon (mometasone furoate). The outcome is unknown.

Reviewer's comment: The patient used concomitant topical corticosteroids of unknown dose and duration. Systemic absorption of multiple corticosteroids may have played a role.

- ISR# 3342345, 1999, 15-day, Consumer, US

A 44-year-old female initially developed blurred vision and edema in her eyelids followed by generalized edema on extremities, headache, numbness, increased hair growth on her neck, arms and legs, severe scarring, exacerbation of unspecified hepatic and pancreatic conditions, urinary retention, sleep disorder, mood swings, gram negative bacterial infection and depression after using an unknown quantity of Cutivate Cream for nine months for the treatment of unspecified facial lesions. The concomitant medications included collagen, clobetasol, betamethasone and alprazolam.

Reviewer's comment: The patient received concomitant topical corticosteroids of unknown quantity and duration. The patient had complex multiple medical conditions and the report did not provide sufficient clinical information to determine the causal role of Cutivate.

- ISR# 1869003, 1997, Periodic, Consumer, US

A 45-year-old female experienced agitation, increased fatigue, feeling “out of control” while receiving Cutivate Cream twice daily for poison ivy. The medication was discontinued and the symptoms persisted. The outcome is unknown.

Reviewer’s comment: The report did not provide sufficient clinical information. Negative dechallenge after the discontinuation of Cutivate do not support the role of Cutivate.

C. Other- Drug ineffective (4 cases)

There were four reports where Cutivate failed to provide any relief to the patients’ symptoms. All were consumer reports. A 7 month-old male received a two-week course of treatment with Cutivate Cream for the treatment of mastocytoma and experienced lack of efficacy. Fluticasone was discontinued and switched to clobetasol. The outcome was unknown. It could not be determined if it was a lack of drug effect or worsening of his underlying disease. The remaining 3 reports did not provide sufficient clinical information.

CONCLUSION

We reviewed 19 cases of adverse events reported in association with the use of Cutivate cream/ointment. Most reports were from the consumers. The majority of the cases involved females, and the median age was 40 years. Most frequently observed reactions were labeled, localized reactions including rash, pain, burning, face edema, skin pigmentation and worsening of psoriasis. There were three systemic unlabeled adverse events including generalized body edema/blurred vision, agitation/fatigue, and immunosuppression /Pneumocystis carinii pneumonia (PCP) /leucopenia/ thrombocytopenia. The significance of Cutivate in these three cases could not be determined with certainty because of confounding medical conditions and insufficient clinical information in the reports.

There were three cases of labeled systemic events with serious outcomes. The first case which involved an adult patient with Cushing’s syndrome was confounded with the concomitant use of multiple topical corticosteroids, and the second case involved a pediatric patient with hyperglycemia / glycosuria that required insulin therapy. The third patient developed acute urticarial reaction and required antihistamine therapy. All three patients recovered. We did not identify cases of eczema herpeticum, herpes simplex or influenza.

Three of 19 patients required hospitalizations as a result of edema of lower extremities, severe pustular psoriasis, and immunodeficiency/pneumocystis carinii pneumonia. Four patients required interventions including prednisone, diphenhydramine, and insulin or tetracycline therapy. There were no fatalities.

Overall, most events were labeled and the unlabeled events were few in number. The most important finding was the inappropriate use of Cutivate cream/ointment in children. Misuse of the product included the use of unapproved formulation in children, the use of

the cream formulation for an unapproved age, and excessive use of the product. The reported adverse events in these cases included hyperglycemia/ glycosuria, immunosuppression/PCP, and acute urticarial reaction.

We did not identify any new safety issues and the information in the product labeling is adequate to communicate the safety information.

Renan A. Bonnel., Pharm.D., M.P.H.
Safety Evaluator

Concur:

Lauren Lee. Pharm.D.
Acting Team Leader, Division of Drug Risk Evaluation

REFERENCES

1. Cutivate Cream, 0.05%. 2002. GlaxoSmithKline
2. Cutivate Ointment, 0.005%. 2002. GlaxoSmithKline

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Renan Bonnel
8/4/04 03:23:46 PM
DRUG SAFETY OFFICE REVIEWER

Mark Avigan
8/4/04 04:51:19 PM
DRUG SAFETY OFFICE REVIEWER

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO (Division/Office): Division of Metabolic and Endocrine Drug Products/Enid M. Galliers and Kati Johnson, SCSOs, HFD-510, Parklawn Bldg, Rm 14-B-45

FROM: Dermatological and Dental Drug Products, HFD-540/Millie Wright, Project Manager/Abi Adebowale, PK Reviewer

DATE:
August 2, 2004

IND NO.

NDA NO.21-152

TYPE OF DOCUMENT:
Review of Protocol

DATE OF DOCUMENT: March 11, 2004

NAME OF DRUG: Cutivate (fluticason propionate), 0.05%

PRIORITY CONSIDERATION

CLASSIFICATION OF DRUG:
corticosteroid

DESIRED COMPLETION DATE:
August 31, 2004

NAME OF FIRM: GlaxoSmithKline

REASON FOR REQUEST

I. GENERAL

- | | | |
|--|--|---|
| <input type="checkbox"/> NEW PROTOCOL | <input type="checkbox"/> PRE-NDA MEETING | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER |
| <input type="checkbox"/> PROGRESS REPORT | <input type="checkbox"/> END OF PHASE II MEETING | <input type="checkbox"/> FINAL PRINTED LABELING |
| <input type="checkbox"/> NEW CORRESPONDENCE | <input type="checkbox"/> RESUBMISSION | <input type="checkbox"/> LABELING REVISION |
| <input type="checkbox"/> DRUG ADVERTISING | <input type="checkbox"/> SAFETY/EFFICACY | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE |
| <input type="checkbox"/> ADVERSE REACTION REPORT | <input type="checkbox"/> PAPER NDA | <input type="checkbox"/> FORMULATIVE REVIEW |
| <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION | <input type="checkbox"/> CONTROL SUPPLEMENT | <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): See Comments Below |
| <input type="checkbox"/> MEETING PLANNED BY | | |

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH

STATISTICAL APPLICATION BRANCH

- TYPE A OR B NDA REVIEW
 END OF PHASE II MEETING
 CONTROLLED STUDIES
 PROTOCOL REVIEW
 OTHER (SPECIFY BELOW):

- CHEMISTRY REVIEW
 PHARMACOLOGY
 BIOPHARMACEUTICS
 OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- DISSOLUTION
 BIOAVAILABILITY STUDIES
 PHASE IV STUDIES

- DEFICIENCY LETTER RESPONSE
 PROTOCOL-BIOPHARMACEUTICS
 IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
 DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
 CASE REPORTS OF SPECIFIC REACTIONS (List below)
 COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP

- REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
 SUMMARY OF ADVERSE EXPERIENCE
 POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

CLINICAL

PRECLINICAL

COMMENTS/SPECIAL

Please see attached page. If you have questions, either e-mail or call Millie Wright at 827-2084 or e-mail "wrightm" or Abi Adebowale at 827-2078 or e-mail "Adebowale" If you can not meet the requested due date, please let us know so that we determine a date that accommodates your work schedule. I will be sending the protocol through the DR. If you haven't received it in a couple of day, please let me know.

SIGNATURE OF REQUESTER
Millie Wright, Project Manager/Abi Adebowale, PK Reviewer

METHOD OF DELIVERY (Check one)
HAND X electronic MAIL & Fax

SIGNATURE OF RECEIVER

SIGNATURE OF DELIVERER

Attachment

Could you please take a look at Protocol FPL 10005, "An Open Label Adrenal Suppression Study of Fluticasone Propionate Lotion 0/05% Used Twice Daily in Pediatric Subjects Aged 3 Months to 5 Years with Moderate to Severe Eczema or Psoriasis," and let us know if you agree with the Sponsor's conclusion.

Basically, the statement of the problem is that we would like to know if your reviewer agrees with the Sponsor's endocrinologist evaluation of the HPA axis study (Protocol Number FPL10005). Specifically, the endocrinologist noted two subjects as having mild partial suppression even though their post-stimulation plasma cortisol levels were above the defined criteria for normal adrenal response. Does the Division of Endocrine agree that these patients are suppressed?

**Appears This Way
On Original**



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation V

FACSIMILE TRANSMITTAL SHEET

Date: July 29, 2004

To: **GlaxoSmithKline**
Attn: Tony Amitrano
Director, US Regulatory Affair
Phone: (973) 889-2566
Fax: (973) 889-2501

From: Millie Wright, Project Manager
Phone: (301) 827-2020
Fax: (301) 827-2091

This transmission includes 4 pages (including this page)

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED BY APPLICABLE LAW. If you are not the addressee, or a person authorized to deliver the document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is *unauthorized and strictly prohibited*. If you have received this facsimile in error, **please notify Millie Wright by telephone at 301-827-2020 immediately**, return it to HFD-540, 9201 Corporate Blvd, Room N243, Rockville, MD 20850 by US Mail.

FDA Fax Memorandum

Date: July 29, 2004

Subject: NDA 21-152/Cuticate ~~0.05%~~

Hi Tony,

We have the following informational request:

Phase 3 studies for NDA 21-152 used the Rajka/Langeland Severity Grading Scale to evaluate disease severity in order to determine enrollment eligibility. As indicated at the end-of-phase 2 meeting and Reviewer Comments, the Agency did not agree with the use of the Rajka/Langeland Severity Grading Scale. Specifically, Reviewer Comments faxed to you on March 17, 1999 stated: "The division does not agree with the use of the Rajka/Langeland Severity Grading Scale. In the end-of phase 2 meeting on May, 1998 with the sponsor, it was recommended that the clinical signs of eczema would be erythema, papulation/edema, and erosion/crusting/oozing with an ordinal grading scale that would contain these signs and that these signs would be used for the inclusion criteria. The patients enrolled in the study were also to have acute eczema for which these signs are the most predictive. The Rajka/Langeland Severity Grading scale does not distinguish acute from chronic eczema nor does it allow one to easily distinguish severity of eczema."

The Agency has concerns with the interpretability of studies in which many subjects had minimal clinical signs of atopic dermatitis at baseline. In addition, the Phase 3 studies did not follow the primary efficacy endpoint (clear or almost clear on a static Investigator's Global Assessment) recommended at the End of Phase 2 meeting, and the endpoint discussed at the pre-NDA meeting (at least 50% improvement and improvement or no change on 20 assessments) may have limited clinical utility.

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On Original

Please submit analyses where a treatment success is defined as achieving a score of 0 in all 4 body regions for the signs of erythema, infiltration/papulation, and erosion/oozing/crusting. Include in the analysis only the subset of subjects who meet the following baseline criteria: A minimum score of 2 for any two of the three parameters (i.e. erythema, induration/papulation, and erosion/crusting/oozing) in at least 1 of the 4 body areas (the scores of 2 may be in different body areas) AND a minimum combined score of 10 of 36

I will call you next week to discuss your projected target date for providing the Division with the requested information. We do need this information to assist us in the review of your NDA. A quick turn around would be appreciated.

I received the desk copies today. Thanks very much. Please note that you will need to submit the revised labeling, in both PDF format and as a Word document, to the electronic document room also. You can note in your cover letter that you are submitting electronic copies of the labeling that was submit in the July 23rd amendment.

Respectfully,
Millie

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Mildred Wright
7/29/04 04:27:45 PM
CSO

195

DUPLICATE

ORIGINAL



GlaxoSmithKline

July 23, 2004

N-000(B2)
ORIG AMENDMENT

GlaxoSmithKline
1500 Littleton Road
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07054-3884

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NDA 21-152

Jonathan K. Wilkin, M.D., Director
Division of Dermatologic and Dental Drug Products
Center for Drug Evaluation and Research
Document Control Room
Office of Drug Evaluation V
Food and Drug Administration
HFD-540
9201 Corporate Boulevard, Bldg. 2
Rockville, MD 20850

RECEIVED
JUL 23 2004
MEGACDER

Attention: Ms. Millie Wright, Project Manager

Re: NDA 21-152

CUTIVATE[®] (fluticasone propionate) 0.05%
Amendment to Pending Application: Chemistry, Pharmacology /
Toxicology, Clinical & Statistical

Dear Dr. Wilkin:

GlaxoSmithKline Consumer Healthcare (GSKCH) hereby submits, in duplicate, an amendment to pending NDA 21-152 for CUTIVATE[®] (fluticasone propionate) 0.05% consisting of Chemistry, Pharmacology / Toxicology, Clinical & Statistical information. This submission constitutes GSKCH's response to the FDA fax that was received on May 24, 2004 requesting the submission of information based on FDA's preliminary evaluation of this application. In order to facilitate the review process, the original FDA request is provided and is immediately followed by the response.

Chemistry

FDA Question

1. Please provide the following:
 - a. Complete stability study results for Batches 8B310, 8C283 and 8J257 of Cutivate Lotion, 0.05% that were manufactured in 1998. Include results from viscosity and weight loss studies. Perform statistical analysis of the data.

GSKCH Response

1. a. Updated drug product stability data for CUTIVATE[®] (fluticasone propionate) 0.05% is provided as Attachment I. This information represents the most current data and consists of stability data for up to 24 months on two batches of drug product manufactured using the drug substance manufactured at the facility and up to months of stability data on one batch of drug product manufactured using the drug substance manufactured at the facility. Analysis of the data support an expiry term of 24 months.

The data for the viscosity and weight loss studies is included in the updated stability report. GSKCH does not believe that a statistical analysis of the stability data is necessary since typically such an analysis is used to project the expiry date from limited data. The actual expiry term of 24 months has been verified with real-time data.

FDA Question

- b. Updated copies of all Letters of Authorization.

GSKCH Response

1. b. There are no DMF letters for the active ingredient and excipients used in the manufacture of CUTIVATE[®] GSKCH is in the process of obtaining updated copies of the letters of authorization for the

packaging components. It has since been discovered that the original mold for the bottle was discontinued by the supplier. Therefore, GSKCH is currently in the process of locating another supplier for the bottle. It is GSKCH's intention to keep all specifications for the packaging components identical or as close as possible to those provided in the original NDA submission. Any differences will be provided to the agency in a future amendment to NDA 21-152.

FDA Question

- c. Information to establish that the structures of the [REDACTED] products [REDACTED] are the ones displayed in v.2, p. 161.

GSKCH Response

1. c. Verification and confirmation for the [REDACTED] products, [REDACTED] is provided as Attachment II.

FDA Question

2. In light of the stability results to date, re-evaluate the acceptance criteria proposed in the submission (v. 2, p. 48).

GSKCH Response

2. Real-time stability data has been generated that supports an expiry term of 24 months for the 60mL [REDACTED] bottle. Please refer to Attachment I. Therefore, it is GSKCH's opinion that a re-evaluation of the acceptance criteria is not warranted.

FDA Question

3. We also remind you of the Agency's April 26, 2004, facsimile requesting the following information:
 - a. Please provide information on the manufacturing sites for drug substance and drug product using the following table format:

Name of Manufacturer	US or Foreign [U of F]	Address Street	Address City/State Zip Code (or Country)	CFN (or FEI) ¹	Responsibility Stage ² Process ³	Site Ready Y or N	Contact Person	Contact Phone No. [P], Fax No. [Fxn], and/or E-Mail address [EA]

1. If no manufacturer identification number is available, provide a copy of the facility registration form.
2. Drug substance [DS], intermediate [I], or finished dosage [FD].
3. Manufacturer [MF], Micronizer [MI], Packager [P], Sterilizer [S], Release Tester [RT], Stability Tester [ST], Sterility Tester [SxT], or Other [O].

GSKCH Response

3. a. This information was provided to the agency in an amendment dated May 13, 2004.

FDA Question

- b. Confirm that the proposed drug name is "CUTIVATE[®] (fluticasone propionate) _____, 0.05% (as designated in the Cover Letter dated 11-Mar-2004) and NOT CUTIVATE[®] (fluticasone propionate _____ 0.05% (as used in the Package Insert and label specimens).

GSKCH Response

3. b. GSKCH confirms that the proposed name is CUTIVATE[®] (fluticasone propionate _____ 0.05%. This confirmation was also provided to the agency in an amendment dated May 13, 2004.

Pharmacology/Toxicology

FDA Question

1. It is recommended that the Sponsor update the nonclinical portions of the Cutivate [REDACTED] label (i.e., Carcinogenesis, Mutagenesis, Impairment of Fertility and Pregnancy sections under the PRECAUTIONS heading of the label) to current labeling standards. It is recommended that the Sponsor use the labeling format for these sections of the label used in more recently approved fluticasone propionate drug products such as FLONASE[®] nasal spray and ADVAIR DISKUS[®].

The Division acknowledges receipt of the previously requested estimate of maximum daily human topical dose of Cutivate [REDACTED] in mg/kg and mg/m². It is recommended that the Sponsor include multiples of human exposure levels (based on mg/m² comparisons) in the nonclinical portions of the Cutivate [REDACTED] label based on the submitted estimate of the maximum daily human topical dose of Cutivate [REDACTED]. It is requested that the Sponsor submit the calculations used to determine the multiples of human exposure levels to be incorporated into the Cutivate [REDACTED] label.

GSKCH Response

1. The updated package insert incorporating all of the FDA's suggested changes is provided as Attachment III. The revisions are noted in blue type.

The requested calculations that were used to determine the multiples of human exposure levels are provided as Attachment IV.

FDA Question

2. It is recommended that the Sponsor conduct a study to determine the photo-carcinogenic potential of Cutivate [REDACTED] as a Phase IV commitment. The Division acknowledges that the Sponsor is not willing to commit to conducting a photo-carcinogenic study in hairless mice. However, alternative study designs for determining the photo-carcinogenic

potential of a topical drug product may be acceptable as noted in the guidance titled "Guidance for Industry - Photosafety testing" published in May, 2003. It would be appropriate to propose use of an alternative study design discussed in the photosafety testing guidance document. It is recommended that the Sponsor submit to the NDA their timeline for submitting a protocol and conducting the study to determine the photo-carcinogenic potential of Cutivate ~~_____~~

GSKCH Response

2. GSKCH does not believe that a photo-carcinogenic study is warranted in this case based on the published FDA guidance titled, "Photosafety Testing," May 2003. Justification for this position is provided as Attachment V.

Clinical and Statistical

FDA Question

1. Please submit a safety update for all fluticasone propionate products.

GSKCH Response

1. The 120-Day Safety Update for all fluticasone propionate topical products was submitted to the FDA as an amendment to pending NDA 21-152 on July 9, 2004.

FDA Question

2. Listing 8 for protocol FPL10003 (Listing of Induction Site Readings, Challenge, Application Site Readings and Tape Reactions; Vol. 13, p. 136- 209) is missing patients 31, 35, 76, 96, 97, 126, 204 and 205. Please submit these data. Listings for all studies in this NDA need to be complete; please review and submit any other missing data.

GSKCH Response

2. The data for patients 026, 031, 035, 076, 096, 097, 098, 126, 204 and 205 were not included in line listing 8 (Listing of Induction Site Readings, Challenge, Application Site Readings and Tape Reactions; Vol. 13, p. 136-209) due to the fact that these patients discontinued from study participation prior to the capture of these data parameters.

Please Note: Patients 026 and 098 were not included in the FDA's question, but were found to be missing after a review of the line listing. These two patients have been added for completeness.

Section 8 (Safety Results), Sub-Section 8.1 (Extent of Exposure) of the clinical report for Study FPL10003 (Volume 13, page 29) stated that 10 subjects who discontinued prematurely received only 1 application of drug. This would explain the absence of data in line listing 8 for the 10 patients listed above. This reference is provided as Attachment VI. The table below summarizes this conclusion and provides the source data from several line listings (Attachments VII - X).

**Appears This Way
On Original**

PATIENTS MISSING FROM LINE LISTING 8

Patient Number*	Reason for discontinuation**	Study Day of Completion or Discontinuation***
026	Withdrew Consent	3 Days
031	Adverse Event	3 Days
035	Withdrew Consent	6 Days
076	Withdrew Consent	3 Days
096	Withdrew Consent	3 Days
097	Withdrew Consent	3 Days
098	Withdrew Consent	3 Days
126	Withdrew Consent	3 Days
204	Withdrew Consent	5 Days
205	Withdrew Consent	3 Days

Source Data:

- * Patients 026 and 098 were added for completeness as they were not included in FDA's question
- ** Line Listing 11 [Listing of End of Study rug Records, Section 8, Volume 13, Pages 217-218 (Attachment VII)]; Line Listing 9 [Listing of All Adverse Events, Section 8, Volume 13, Pages 210-214 (Attachment VIII)]; Line Listing 10 [Listing of Treatment-Limiting Adverse Events, Section 8, Volume 13, Pages 215-216 (Attachment IX)]
- *** Line Listing 3 [Listing of Subject Accountability: End of Study Record, Section 8, Volume 13, Pages 68-80 (Attachment X)]

FDA Question

3. Please submit Case Report Form Tabulations for Study FPL10003.

GSKCH Response

3. The tabulations are located in Section 11, Volume 26, Pages 130-286 of the NDA. To facilitate FDA's review, they have been provided as Attachment XI.

FDA Question

4. Please see Agency's facsimile, dated April 21, 2004, requesting information related to certification of the absence of financial interests and arrangements of clinical investigators (Form FDA 3454) and disclosure of financial interests and arrangements of clinical investigators (Form 3455) in this submission.

GSKCH Response

4. This information was provided to the agency in an amendment on May 13, 2004.

FDA Question

5. Please indicate whether the final to-be-marketed formulation of fluticasone propionate lotion was used in studies FPL10003 (repeat insult patch test) and FPL10005 (adrenal suppression study) or whether a different formulation was used.

GSKCH Response

5. The formulation for fluticasone propionate [REDACTED] that was used in studies FPL10003 and FPL10005 is the same as the proposed marketed formulation.

FDA Question

6. Please submit Case Report Form Tabulations for Study FPL10003.

GSKCH Response

6. This question is identical to Question 3. Please see previous response.

FDA Question

7. Please submit revised labeling incorporating a Clinical Studies section with results from the 3 trials.

GSKCH Response

7. The revised label is provided as Attachment III. The revisions to the label are provided in blue type.

FDA Question

8. Two phase 3 studies of atopic dermatitis have been submitted. This does not fulfill the basic requirement for the indication of ' ██████████ ██████████ Please refer to the minutes for the April 19, 1999 meeting.

Note: This question was not addressed in the second half of the FDA fax. It has been added as question 8 for completeness.

GSKCH Response

8. GSKCH has reviewed the April 19 meeting minutes and is in agreement with the agency's conclusion. As a result, GSKCH has changed the indication to state "atopic dermatitis." The package insert has been revised accordingly (using blue color type). Please refer to Attachment III.

**Appears This Way
On Original**

If there are any questions concerning this submission, please contact me at 973-889-2566.

Sincerely,



Anthony Amirano

Director, US Regulatory Affairs

GlaxoSmithKline Consumer Healthcare, L.P.

182

ORIGINAL



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JUL 20 2004

MEGA/CDER

July 19, 2004

NDA 21-152

Jonathan K. Wilkin, M.D., Director
Division of Dermatologic and Dental Drug Products
Center for Drug Evaluation and Research
Document Control Room
Office of Drug Evaluation V
Food and Drug Administration
HFD-540
9201 Corporate Boulevard, Bldg. 2
Rockville, MD 20850

RECEIVED
ORIG AMENDMENT

Attention: Ms. Millie Wright, Project Manager

Re: NDA 21-152
CUTIVATE® (fluticasone propionate) 0.05%
Amendment to Pending Application: Chemistry

Dear Dr. Wilkin:

GlaxoSmithKline Consumer Healthcare (GSKCH) hereby submits, in duplicate, an amendment to pending NDA 21-152 for CUTIVATE® (fluticasone propionate) 0.05%. This submission is in response to the following question from the Chemistry Reviewer as stated in the FDA fax dated June 2, 2004:

In performing our filing review of the Chemistry, Manufacturing and Controls section of your submission, we evaluated the acceptability of [redacted] in the drug product name. Our recommendation is that the use of the dosage form term [redacted] is not acceptable.

[redacted]

We recommend that, in describing product

Appears This Way On Original

Appearance in the product specification, you employ terms that clearly describe or define "lotion" for the analyst in place of the term "lotion."

GSKCH has considered FDA's recommendation but upon further evaluation believes that the use of the term [REDACTED] in the drug product name should remain. This is supported by the following:

- A review of the following FDA website, Approved Drug Products with Therapeutic Equivalence Evaluations - Orange Book, demonstrated that since 1996, several Rx drugs have been approved by the FDA utilizing the term [REDACTED] in the name. This indicates that the FDA accepts the use of the term [REDACTED] in a drug product's name.

Please refer to the enclosed Attachment for additional information.

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Based on this information, GSKCH believes that the drug product CUTIVATE®
[redacted] more adequately satisfies the definition of an emulsion rather than
the definition of a lotion. Hence GSKCH would prefer to refer to the current
application product as an [redacted]

In order to address the agency's concern over the use of the term "lotion" when
describing the product Appearance in the product specification, GSKCH proposes
to revise the specification to state as follows: [redacted]

[redacted] An updated product specification document will be provided to the
agency in a subsequent submission. This document will replace the one
previously included in the original NDA (Volume 2, Section E2. Specifications,
page 48).

If there are any questions concerning this submission, please contact me at 973-
889-2566.

Sincerely,



Anthony Amitrano
Director, US Regulatory Affairs
GlaxoSmithKline Consumer Healthcare, L.P.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO (Division/Office):
Division of Medication Errors and Technical Support (DMETS),
HFD-420/ PKLN Rm. 6-34

FROM: Mike Albert, M.D./Millie Wright, Project Manager
Division of Dermatologic and Dental Drug Products/HFD-540

DATE: July 18, 2004

IND NO.

NDA NO. 21-152

TYPE OF DOCUMENT
NDA RS

DATE OF DOCUMENT:
March 11, 2004

NAME OF DRUG:
Cutivate (fluticasone propionate)
0.05%

PRIORITY CONSIDERATION

CLASSIFICATION OF DRUG:
3S

DESIRED COMPLETION DATE:
August 6, 2004

NAME OF FIRM: GlaxoSmithKline.

REASON FOR REQUEST

I. GENERAL

- | | | |
|--|--|--|
| <input type="checkbox"/> NEW PROTOCOL | <input type="checkbox"/> PRE-NDA MEETING | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER |
| <input type="checkbox"/> PROGRESS REPORT | <input type="checkbox"/> END OF PHASE II MEETING | <input type="checkbox"/> FINAL PRINTED LABELING |
| <input type="checkbox"/> NEW CORRESPONDENCE | <input type="checkbox"/> RESUBMISSION | <input type="checkbox"/> LABELING REVISION |
| <input type="checkbox"/> DRUG ADVERTISING | <input type="checkbox"/> SAFETY/EFFICACY | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE |
| <input type="checkbox"/> ADVERSE REACTION REPORT | <input type="checkbox"/> PAPER NDA | <input type="checkbox"/> FORMULATIVE REVIEW |
| <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION | <input type="checkbox"/> CONTROL SUPPLEMENT | <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): ODS consult |
| <input type="checkbox"/> MEETING PLANNED BY | | |

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH

STATISTICAL APPLICATION BRANCH

- TYPE A OR B NDA REVIEW
 END OF PHASE II MEETING
 CONTROLLED STUDIES
 PROTOCOL REVIEW
 OTHER (SPECIFY BELOW):

- CHEMISTRY REVIEW
 PHARMACOLOGY
 BIOPHARMACEUTICS
 OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- DISSOLUTION
 BIOAVAILABILITY STUDIES
 PHASE IV STUDIES

- DEFICIENCY LETTER RESPONSE
 PROTOCOL-BIOPHARMACEUTICS
 IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
 DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
 CASE REPORTS OF SPECIFIC REACTIONS (List below)
 COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP

- REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
 SUMMARY OF ADVERSE EXPERIENCE
 POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

CLINICAL

PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

NDA 21-152 has been submitted for fluticasone propionate lotion 0.05% (Cutivate Lotion). Fluticasone propionate cream 0.05% (Cutivate Cream) and fluticasone propionate ointment 0.05% (Cutivate Ointment) are currently approved products. An AERS/MedWatch database search for adverse events reported for fluticasone propionate dermatologic topical products is requested to assist in the safety review for this NDA.

If your schedule does not permit meeting the request due date of August 6, 2004, please let us know. Thanks, Millie (827-2084)

SIGNATURE OF REQUESTER

METHOD OF DELIVERY (Check one)

MAIL

HAND

SIGNATURE OF RECEIVER

SIGNATURE OF DELIVERER



GlaxoSmithKline

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July 9, 2004

NDA 21-152

Jonathan K. Wilkin, M.D., Director
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Center for Drug Evaluation and Research
Document Control Room
Office of Drug Evaluation V
Food and Drug Administration
HFD-540
9201 Corporate Boulevard, Bldg. 2
Rockville, MD 20850

RECEIVED
JUL 12 2004
MEGA/CDER

Attention: Ms. Millie Wright, Project Manager

**Re: NDA 21-152
CUTIVATE[®] (fluticasone propionate) 0.05%
Amendment to Pending Application: 120 DAY SAFETY
UPDATE**

Dear Dr. Wilkin:

In accordance with 21 CFR 314.50(d)(5), GlaxoSmithKline Consumer Healthcare (GSKCH) hereby submits, in duplicate, an amendment to pending NDA 21-152 for Cutivate[®] (fluticasone propionate) 0.05% consisting of the 120 Day Safety Update. This submission also represents GSKCH's response to question 1 (from Clinical and Statistical review: "Please submit a safety update for all your fluticasone propionate products") from a FDA fax dated May 21, 2004 that was received on May 24, 2004.

NDA 21-152 was first submitted to the FDA on December 13, 1999 and withdrawn due to business reasons on May 25, 2000. The original NDA was then re-submitted on March 11, 2004.

Based on a review of all the available safety information, there are no new data that significantly affect the established safety profile of the Cutivate[®] (fluticasone propionate) dermatologic preparations (i.e., Ointment, 0.005%; Cream, 0.05%; and the pending [REDACTED] 0.05%). This conclusion is based on the following:

A. General information

Fluticasone propionate topical preparations consist of dermatologic preparations (i.e., Cutivate[®]) and nasal/respiratory preparations (i.e., Flonase[®], Flovent[®], Advair[®]). It is GSKCH's position that the safety information for fluticasone propionate nasal/respiratory preparations has no clinically significant meaning for the evaluation of the safety of fluticasone propionate dermatologic preparations. This position is based on the fact that dermatologic and nasal/respiratory applications involve different anatomic sites and target diseases with significantly different pharmacokinetic profiles, use patterns and the magnitude of drug exposures among the target patients. Therefore, this safety update focuses on the review of safety information on topical fluticasone propionate preparations for dermatologic use.

Fluticasone propionate dermatologic preparations include:

- Cutivate[®] (fluticasone propionate ointment) Ointment, 0.005%, which is currently marketed. Safety information on this product has also been submitted via Periodic ADE Reports to NDA 19-957 in accordance with 21 CFR 314.90.
- Cutivate[®] (fluticasone propionate cream) Cream, 0.05%, which is currently marketed. Safety information on this product has also been submitted via Periodic ADE Reports to NDA 19-958 in accordance with 21 CFR 314.90.
- Cutivate[®] [REDACTED] (fluticasone propionate [REDACTED]) 0.05%, which is under evaluation by the FDA.

B. Summary of all post-marketing adverse events associated with currently marketed Cutivate® Ointment and Cream

Please refer to the Attachment containing information on all post-marketing adverse events reported to GSK (as of May 31, 2004) that are associated with Cutivate® Ointment and Cream marketed worldwide. Evaluation of the attached information reveals no clinically significant safety data that is beyond the scope of the current labels/warnings for the two drug products.

C. Summary of published clinical studies on fluticasone propionate dermatologic preparations

Literature searches in several biomedical databases were conducted on all topical fluticasone propionate preparations under dermatologic applications, including Cutivate® drug products. Based on a review of the existing literature, there is no information that significantly impacts the safety of Cutivate® (fluticasone propionate) dermatologic preparations.

D. Summary of unpublished clinical studies on fluticasone propionate dermatologic preparations

There are no ongoing clinical studies on any fluticasone propionate topical preparations under dermatologic applications. For NDA 21-152, no further safety data from clinical trials were reviewed after the original submission since all studies were completed prior to and included in the original NDA submission. Therefore, the incidence of adverse events concerning clinical trials remains unchanged.

Since there were no ongoing clinical studies on any fluticasone propionate topical preparation, there were no additional deaths or discontinuations due to adverse events in patients enrolled in clinical trials. The case report forms for all patients who dropped out due to death or adverse events were included in the original NDA submission (please refer to Volume 31, Page 2 - 345 and Volume 32, Page 2 - 258).

E. Summary of information on submissions in other countries

Cutivate® [REDACTED] has not been approved in any other country, however, applications are currently pending in France, Finland, Greece, Italy, Netherlands, Norway, Egypt, India, Madagascar, Maritius, Morocco and Pakistan. To date, these applications remain under review by the respective country's health authorities.

In summary, based on a review of relevant safety information on all fluticasone propionate topical preparations for dermatologic use, no revisions to the package insert concerning safety of Cutivate® [REDACTED] (fluticasone propionate [REDACTED]) 0.05% are deemed necessary.

If you have any questions concerning this submission, please contact me at 973-889-2566.

Sincerely,



Anthony Amitrano
Director, US Regulatory Affairs
GlaxoSmithKline Consumer Healthcare, L.P.

196



GlaxoSmithKline

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JUL 08 2004

CDR/CDER

July 7, 2004

NDA 21-152

Jonathan K. Wilkin, M.D., Director
Division of Dermatologic and Dental Drug Products
Center for Drug Evaluation and Research
Document Control Room
Office of Drug Evaluation V
Food and Drug Administration
HFD-540
9201 Corporate Boulevard, Bldg. 2
Rockville, MD 20850

RECEIVED

JUL 13 2004

MEGA/CDER

NJ-000-BL

ORIG AMENDMENT

Re: NDA 21-152
CUTIVATE[®] (fluticasone propionate) 0.05%
Amendment to Pending Application: Labeling

Dear Dr. Wilkin:

GlaxoSmithKline Consumer Healthcare (GSKCH) hereby submits an amendment to pending NDA 21-152 for CUTIVATE[®] (fluticasone propionate) 0.05% consisting of the package insert in Word and PDF formats as requested by the agency in a fax dated 7/7/04. This package insert is identical to the PDF version that was provided in the submission dated 3/11/04.

Please note that the package insert is being provided on a disk as a reviewer's aid and is not part of an electronic submission.

ORIGINAL

If there are any questions concerning this submission, please contact me at 973-889-2566.

Sincerely,


Anthony Amatrano

Director, US Regulatory Affairs

GlaxoSmithKline Consumer Healthcare, L.P.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO (Division/Office):

Division of Medication Errors and Technical Support
(DMETS), HFD-420
PKLN Rm. 6-34

FROM:

Millie Wright, Project Manager
Division of Dermatologic and Dental Drug Products/HFD-540

DATE: July 7, 2004

IND NO.

NDA NO. 21-152

TYPE OF DOCUMENT
NDA RS

DATE OF DOCUMENT:
March 11, 2004

NAME OF DRUG:

Cutivate (fluticasone propionate)
0.05%

PRIORITY CONSIDERATION

CLASSIFICATION OF DRUG:
3S

DESIRED COMPLETION DATE:
Labeling mtg. scheduled 12/6/04

NAME OF FIRM: GlaxoSmithKline.

REASON FOR REQUEST

I. GENERAL

- | | | |
|--|--|--|
| <input type="checkbox"/> NEW PROTOCOL | <input type="checkbox"/> PRE-NDA MEETING | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER |
| <input type="checkbox"/> PROGRESS REPORT | <input type="checkbox"/> END OF PHASE II MEETING | <input type="checkbox"/> FINAL PRINTED LABELING |
| <input type="checkbox"/> NEW CORRESPONDENCE | <input type="checkbox"/> RESUBMISSION | <input type="checkbox"/> LABELING REVISION |
| <input type="checkbox"/> DRUG ADVERTISING | <input type="checkbox"/> SAFETY/EFFICACY | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE |
| <input type="checkbox"/> ADVERSE REACTION REPORT | <input type="checkbox"/> PAPER NDA | <input type="checkbox"/> FORMULATIVE REVIEW |
| <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION | <input type="checkbox"/> CONTROL SUPPLEMENT | <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): Tradename |
| <input type="checkbox"/> MEETING PLANNED BY | | |

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH

STATISTICAL APPLICATION BRANCH

- | | |
|--|---|
| <input type="checkbox"/> TYPE A OR B NDA REVIEW | <input type="checkbox"/> CHEMISTRY REVIEW |
| <input type="checkbox"/> END OF PHASE II MEETING | <input type="checkbox"/> PHARMACOLOGY |
| <input type="checkbox"/> CONTROLLED STUDIES | <input type="checkbox"/> BIOPHARMACEUTICS |
| <input type="checkbox"/> PROTOCOL REVIEW | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> OTHER (SPECIFY BELOW): | |

III. BIOPHARMACEUTICS

- | | |
|--|---|
| <input type="checkbox"/> DISSOLUTION | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS |
| <input type="checkbox"/> PHASE IV STUDIES | <input type="checkbox"/> IN-VIVO WAIVER REQUEST |

IV. DRUG EXPERIENCE

- | | |
|--|--|
| <input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) | <input type="checkbox"/> POISON RISK ANALYSIS |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP | |

V. SCIENTIFIC INVESTIGATIONS

CLINICAL

PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

Please review the requested tradename "Cutivate [REDACTED]". The labeling for this NDA can be found in the electronic document room. I have requested a Word document. Labeling meeting is scheduled for July 19, 2004.

PDUFA DATE: January 12, 2005

SIGNATURE OF REQUESTER

METHOD OF DELIVERY (Check one)

MAIL

HAND

SIGNATURE OF RECEIVER

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this page is the manifestation of the electronic signature.**

/s/

Mildred Wright
7/7/04 11:59:59 AM



**Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation V**

FACSIMILE TRANSMITTAL SHEET

Date: July 7, 2004

To: GlaxoSmithKline
Attn: Tony Amitrano
Director, US Regulatory Affairs
Phone: (973) 889-2566
Fax: (973) 889-2501

From: Millie Wright, Project Manager
Phone: (301) 827-2020
Fax: (301) 827-2091

This transmission includes 3 pages (including this page)

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NDA 21-152 label request

FDA Fax Memorandum

Date: July 7, 2004

Subject: NDA 21-152/Cuticate . 0.05%

Hi Tony,

When I checked your electronic labeling submissions, I noted that you have only submitted PDF files. Please submit the labeling as a Word document also.

If you have questions, please call.

Respectfully,
Millie

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Mildred Wright
7/7/04 11:01:08 AM
CSO

Memorandum

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research**

PID#: D030651

DATE: May 24, 2004

FROM: LCDR David Moeny, USPHS, R.Ph. Drug Use Specialist
Division of Surveillance, Research and Communication Support, HFD-410

Aaron B. Mendelsohn, Ph.D., MPH, Epidemiologist
Division of Surveillance, Research and Communication Support, HFD-410

THROUGH: Laura Governale, Pharm.D., MBA, Drug Use Specialist Team Leader
Division of Surveillance, Research and Communication Support, HFD-410

THROUGH: Judy Staffa, R.Ph., Ph.D., Epidemiology Team Leader
Division of Surveillance, Research and Communication Support, HFD-410

THROUGH: Gerald Dal Pan, MD, MHS, Director
Division of Surveillance, Research and Communication Support, HFD-410

TO: Jonathan Wilkin, M.D. Director
Division of Dental and Dermatologic Drug Products, HFD-540.

Shirley Murphy, M.D., Director
Division of Pediatric Drug Development, HFD-960

Claudia Karwoski, Pharm.D., Safety Team Leader Evaluator

Marilyn Pitts, Pharm.D, D., Safety Team Evaluator

SUBJECT: Topical corticosteroid use among pediatric patients.

Executive Summary

Approximately [REDACTED] prescriptions for topical corticosteroids were dispensed in 2003. Triamcinolone, betamethasone, and hydrocortisone products were the most commonly dispensed products, accounting for roughly [REDACTED] of topical corticosteroid prescriptions dispensed in 2003. Approximately [REDACTED] of dispensing to the 1 to 3 year old age group was for a medium or low

potency steroid product. During a 2 year period from 12/01/2001 through 11/30/2003 the cumulative use of topical corticosteroids in this age group was predominantly 30 grams or less per patient. Over 80% of the prescription dispensing to adults aged 17 years and older was with a medium or high potency product; the most common cumulative amount used during the time period 12/01/2001 through 11-30-2003 was 31-60 grams. Our analysis showed that adults used higher quantities and higher potency products than children and adolescents.

For patients aged 0 through 64 years the most common single diagnosis for a topical corticosteroid among patients who visited a physician was eczema (80% of topical corticosteroid use in 2003), however all instances of dermatitis constitute 85% of uses. In patients age 65 years and older, the most common single diagnosis for topical corticosteroid use was dermatitis (80%) in 2003.

Introduction

The Pediatric subcommittee of the Anti-infective committee met on October 29th, 2003 and began with a discussion of Clinical Risk Management of HPA Axis Suppression in Children with atopic dermatitis being treated with topical corticosteroids. During the exploration of this issue, questions of the prevalence of use of these products among children were raised. In addition, the Agency's question 3 to the committee addressed HPA axis suppression, asking if the subcommittee thought that this represented a clinically significant (or relevant) concern for pediatric patients exposed to topical corticosteroids. The committee felt that there was significant risk and recommended further studies in children, including epidemiological studies of steroid exposure and its effects. In subsequent internal discussions in the Office of Drug Safety, specific interest in the use of topical corticosteroids to treat diaper dermatitis, and the duration of therapy in children in general were also raised as key use issues to explore. This analysis describes the outpatient drug use patterns for topical corticosteroids in the pediatric, adolescent, and adult populations in attempt to provide a context of use in which to better examine potential risks. Full transcripts of the Pediatric subcommittee meeting are available online at <<http://www.fda.gov/ohrms/dockets/ac/cder03.html#Anti-Infective>>.

Data Sources

This analysis utilizes three databases: the IMS Health National Prescription Audit (NPA™ Plus), the IMS National Disease and Therapeutic Index™ (NDTI™) and AdvancePCS Dimension Rx™. AdvancePCS data were analyzed using two methods: an online analysis for the time period of March 2001 through February 2004 for cross-sectional analyses and a more complex dataset analysis for evaluating longitudinal use during the time period of December 2001 through November 2003. The IMS Health National Prescription Audit™ and the National Disease and Therapeutic Index™ data were examined for the years from January 1999 through December 2003. These data sources are described in detail below.

IMS HEALTH, NATIONAL PRESCRIPTION AUDIT PLUS™ (NPA PLUS™)

The IMS Health, National Prescription Audit Plus™ (NPA Plus™) measures the retail dispensing of prescriptions, or the frequency with which drugs move out of retail pharmacies

into the hands of consumers via formal prescriptions. These retail pharmacies include chain, independent, food store, mail order, discount houses, and mass merchandiser pharmacies, as well as nursing home (long-term care) pharmacy providers. Information on the specialty of the prescribing physician is also collected, except for in the long-term care and mail order pharmacy settings.

The number of dispensed prescriptions is obtained from a sample of approximately [REDACTED] pharmacies throughout the United States and projected nationally. The pharmacies in the database account for approximately [REDACTED] of all pharmacy stores and represent approximately [REDACTED] of prescription coverage in the U.S.

IMS HEALTH, NATIONAL DISEASE AND THERAPEUTIC INDEX™ (NDTI™)

NDTI™ is an ongoing survey designed and conducted by IMS Health to provide descriptive information on the patterns and treatment of disease encountered in office-based practice in the continental United States by collecting data on drug products mentioned during visits to office-based physicians. The data are gathered by a panel of roughly [REDACTED] office-based physicians who complete and submit a survey of their practice patterns to IMS Health for two consecutive days per quarter. These data may include profiles and trends of diagnoses, patients, and treatment patterns and are collected and projected nationally to reflect national prescribing patterns.

NDTI uses the term drug uses for mentions of a drug in association with a diagnosis during an office-based patient visit. This term may be duplicated by the number of diagnosis for which the drug is mentioned. It is important to note that a drug use does not necessarily result in prescription being generated. Rather, the term indicates that a given drug was mentioned during an office visit.

ADVANCEPCS DIMENSION RX™

AdvancePCS is one of the largest pharmacy benefit manager (PBM) companies in the U.S., which, at the time of this analysis, covered 50 million patient lives and processed [REDACTED] prescription claims annually. FDA has access to AdvancePCS' database of paid claims for prescriptions filled in [REDACTED] pharmacies across the country. At any time, FDA has on-line access to the most recent 36 months of data. Patients whose claims are processed by AdvancePCS include those covered under various types of insurance plans that cover prescription drugs, including some employers' self-insured plans, selected managed care plans, Blue Cross/Blue Shield plans, and selected other traditional insurers. Demographically, these patients appear to represent all 50 states, and include elderly patients, children and women of childbearing age. Their representativeness to all patients receiving dispensed prescriptions in the U.S., however, is not known.

The data in this prescription database include the drug name, strength, dosage form, and dispensing date of the prescription, the quantity and days' supply, and the prescriber specialty. For all patients, a unique identifier is assigned, making it possible to follow patients longitudinally (regardless of where the prescriptions are filled), as long as they remain enrolled

in the same prescription plan. Therefore, patterns of drug utilization over time, such as duration of use and concomitant medication use can be explored using these data.

Methods for dataset analysis

For the dataset analysis, a subset of topical corticosteroid prescription claims consisting of 1.2 million patients with continuous coverage from March 2001 through February 2004 were extracted from the AdvancePCS system and examined. The number of patients receiving topical corticosteroids, the amount and strength of the product dispensed, and the cumulative exposure in each potency range for assigned age groups were examined. Products were assigned to standard potency ranges of "low", "medium", "high", and "very high"¹. Patients were assigned to the following age groups: 1, 2, and 3 years (to assess diaper dermatitis use), 4-16 years, 17-64 years, 65 years and older. For this analysis, prescription size is given in terms of 15 gram equivalents.

The potency of a topical corticosteroid is determined experimentally with products classified by measuring the amount of skin blanching due to vasoconstriction which occurs when applied to the skin of Caucasian patients and then compared to reference products in each class. The class a product is placed into depends on the active ingredient, product strength (concentration), and the formulation of the vehicle (cream, ointment, solution). For instance, betamethasone may be classified into one of 3 ranges: Augmented betamethasone dipropionate 0.05% ointment is classed as very high potency, augmented betamethasone dipropionate 0.05% cream and betamethasone dipropionate 0.05% cream or ointment are classed as high potency, and betamethasone dipropionate 0.05% lotion is classed as medium potency.

Results

Utilization

Nationally, topical corticosteroid use has remained fairly constant over the past 5 years, hovering around [redacted] prescriptions dispensed annually (Table 1). The most commonly dispensed active ingredients in 2003 were triamcinolone [redacted] prescriptions), betamethasone [redacted] prescriptions), and hydrocortisone [redacted] prescriptions). The top 3 molecules were the same in previous years (Table 1).

Total claims for topical corticosteroids processed through AdvancePCS for all age ranges declined slightly from [redacted] during the interval March 2001 - February 2002 to [redacted] during the interval March 2003 - February 2004 (Table 2). Claims for children aged 1 through 3 declined during the same period. Patients aged 1 year accounted for [redacted] claims during the interval March 2003 - February 2004 while patients aged 2 years and 3 years accounted for [redacted] claims, respectively.

Dispensing by potency was stable from March 2002 - February 2004 (Table 2). Patients aged 1-

¹ Relative Potency of Topical Corticosteroid Products, *Lexi Comp Drug Information Handbook*, 11th edition, page 1529

3 years most commonly received medium potency products ([redacted] of claims). Low potency products accounted for approximately [redacted] of dispensing while high and very high potency products accounted for [redacted] of claims. For the age 4-16 year group, [redacted] of claims for all topical corticosteroids were for low potency steroid products, [redacted] were for medium potency products, [redacted] were for high potency products, and [redacted] were for very high potency products during the interval March 2003 - February 2004. In the same time period, [redacted] of all topical corticosteroid claims in adults aged 65 and older group were for low potency products, [redacted] of claims were for medium potency products, [redacted] of claims were for high potency products, and [redacted] of claims were for very high potency products. In general, as age increased, the percentage of high and very high potency prescription claims also increased.

Longitudinal (Cumulative) Use

A longitudinal analysis by potency and cumulative amount of product dispensed over the period of December 2001 through November 2003 mirrored the potency distributions seen in the general AdvancePCS population (Table 3, summarized below). For each pediatric age group, [redacted] received only 1-2 15-gram equivalents over a two year period. A little over one-third received 3-4 equivalents and [redacted] received 5 or more. In contrast, adults aged 17-64 and 65 and older received 1-2 equivalents at a rate of [redacted] respectively, 3-4 equivalents at [redacted] and 5 or more equivalents at [redacted] (Table 3). This analysis, when combined with the distribution of potencies from table 3, suggests that adults use larger quantities of higher potency products while children use lower quantities of lower potency products, given that half of the pediatric population used only 1-2 15 gram equivalents over a 2 year period.

Claims Filed for Topical Corticosteroids by Age and			
Number of 15 Gram Equivalents			
	1-2	3-4	5 +
Age 1	[redacted]	[redacted]	[redacted]
Age 2	[redacted]	[redacted]	[redacted]
Age 3	[redacted]	[redacted]	[redacted]
Age 4-16	[redacted]	[redacted]	[redacted]
Age 17-64	[redacted]	[redacted]	[redacted]
Age 65 +	[redacted]	[redacted]	[redacted]

SOURCE: AdvancePCS™ Dataset Analysis (12/1/2001 - 11/30/2004)

Indications

In each of the four pediatric age groups analyzed, the 3 most common diagnoses in 2003 were eczema and “contact dermatitis” or “atopic dermatitis” which account for approximately [redacted] of all uses in 2003 (Table 4). Of note is the finding that together, diaper rash was the 7th most common diagnosis in patients aged less than 4 years, accounting for [redacted] of the use in 2003. Among adults aged 17 and over, eczema, “dermatitis, contact nos”, “dermatitis, nos” and psoriasis were the 3 most common diagnoses which together accounted fo. [redacted] of topical corticosteroid use. While the single most common diagnosis was eczema, when the multiple

subtypes were taken together dermatitis was the most common. In all age groups, the top 3 diagnoses were unchanged from 1999 through 2003.

Limitations

NPA Plus™ data provide an estimate of the total number of prescriptions dispensed in the U.S. The dispensing of these prescriptions do not necessarily reflect actual use by the patient.

NDTI™ data provide estimates of patient demographics and indications for use of medicinal products in the U.S. Due to the sampling and data collection methodologies, the small sample size can make these data unstable. For patients who were seen by a physician, NDTI™ data provides estimates of patient demographics and indications for use of medicinal products in the U.S. This survey is unable to capture patients who self diagnose and purchase an OTC product, likely biasing the results towards prescription products. This represents a major limitation of this analysis.

AdvancePCS data cannot be projected to make national level estimates of use therefore the proportions of children using these products in this database may not be representative of all U.S. experience. Although the data may not be nationally representative, they provide a useful description of prescription drug use in the U.S. for a large proportion of the population with prescription drug coverage. In addition, reliable information for patients less than the age of 1 year is not available.

Ideally, we would have analyzed the dataset for continuous duration of therapy and patient switching between product potencies. However, due to dataset and methodological limitations, cumulative exposure by potency range was used instead. AdvancePCS cannot provide height and weight data to conduct an analysis of grams of product use per unit of body surface area, which we would have preferred to use to characterize the differences in use between adults and children.

Conclusions

Approximately ██████ prescriptions for topical corticosteroids were dispensed in 2003. Triamcinolone, betamethasone, and hydrocortisone products were the most commonly dispensed products, accounting for roughly ██████ of topical corticosteroid prescriptions dispensed in 2003. Approximately ██████ of dispensing to the 1 to 3 year old age group was for a medium or low potency steroid product. During a 2 year period from 12/01/2001 through 11/30/2003 the cumulative use of topical corticosteroids in this age group was predominantly 30 grams or less per patient. Over ██████ of the prescription dispensing to adults aged 17 years and older was with a medium or high potency product; the most common cumulative amount used during the time period 12/01/2001 through 11-30-2003 was 31-60 grams. Our analysis showed that adults used higher quantities and higher potency products than children and adolescents.

For patients aged 0 through 64 years the most common single diagnosis for a topical corticosteroid among patients who visited a physician was eczema (██████ of topical corticosteroid use in 2003), however all instances of dermatitis constitute ██████ uses

— In patients age 65 years and older, the most common single diagnosis for topical corticosteroid use was dermatitis — in 2003.

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Appears This Way
On Original

Accompanying Tables and Figures

Table 1. Total Number of Prescriptions Dispensed in the U.S. for Topical Corticosteroids for 1999 through 2003. (IMS Health, National Prescription Audit).

Copyright IMS HEALTH										
Projected Number of Total ¹ Prescriptions Dispensed										
by Retail Pharmacies										
(Chain, Independent, Food Stores, Long Term Care, and Mail Order) in the US										
for Dermatological Corticosteroids										
Stratified by Generic Drug										
Distributed by Calendar Year 1999 through 2003										
(in thousands; ADD THREE 0's TO EACH FIGURE)										
Copyright IMS HEALTH										
	1999	1999	2000	2000	2001	2001	2002	2002	2003	2003
TOTAL PRESCRIPTIONS										
TRIAMCINOLONE ACET										
BETAMETHASONE										
HYDROCORTISONE										
CLOBETASOL										
FLUCINONIDE										
MOMETASONE										
FLUOCINOLONE ACET										
DESONIDE										
FLUTICASONE										
DESOXIMETASONE										
HALOBETASOL										
DIFLORASONE										
ALCLOMETASONE										
PREDNICARBATE										
FLURANDRENOLIDE										
AMCINONIDE										
CLOCORTOLONE										
HALCINONIDE										
SOURCE: IMS HEALTH; National Prescription Audit Plus TM , On-line										
Notes:										
* a blank means no data; a zero means less than total projected										
¹ Total includes New and Refill prescriptions										
**NOTE: DATA NOT TO BE SHARED OUTSIDE OF FDA OR WITH non-FDA STAFF WITHOUT PRIOR CLEARANCE BY IMS HEALTH.										

Table 2. Topical Steroid Use in a Large, Pharmacy Benefits Manager March 1, 2001 through February 28, 2004. (AdvancePCS DimensionRx)

Copyright ADVANCE PCS Dimension Rx							
*NOTE: NOT TO BE SHARED OUTSIDE OF FDA OR WITH NON-FDA STAFF WITHOUT PRIOR CLEARANCE BY ADVANCEPCS.							
Clearance must be requested from AdvancePCS through the FDA Office of Drug S							
Total number of prescription claims							
Dispensed by Retail Pharmacies in the Advance PCS™ pharmacy claims processing network ²							
for Topical corticosteroids							
Stratified by Age, Potency							
Time Period-Rolling years 3/1/01 - 2/28/2004							
Counts are ACTUAL. Data are NOT projected to represent a national estimate.							
		3/1/01 - 2/28/02		3/1/02 - 2/28/03		3/1/03 - 2/28/04	
		Claims	Percent	Claims	Percent	Claims	Percent
Total							
Age 1							
	Low						
	Medium						
	High						
	Very High						
Age 2							
	Low						
	Medium						
	High						
	Very High						
Age 3							
	Low						
	Medium						
	High						
	Very High						
Age 4-16							
	Low						
	Medium						
	High						
	Very High						
Age 17-64							
	Low						
	Medium						
	High						
	Very High						
Age 65+							
	Low						
	Medium						
	High						
	Very High						

Table 3. Cumulative Amount of Topical Corticosteroid Product Dispensed, as processed through a Large Pharmacy Benefits Manager December 1, 2001 – November 20, 2003. (AdvancePCS DimensionRx)

Copyright ADVANCE PCS Dimension Rx									
Number of 15 gram equivalents dispensed per prescription ¹									
Dispensed by Retail Pharmacies in the Advance PCS™ pharmacy claims processing network ²									
for Topical Corticosteroids									
Stratified by Patient Age, Product Potency									
Time Period 12/1/2001 - 11/30/03									
15 Gram Equivalents									
		1-2		3-4		5 +		Total	Percent
		Total	Percent	Total	Percent	Total	Percent		
Total									
Age 1									
Low									
Medium									
High									
Very High									
Age 2									
Low									
Medium									
High									
Very High									
Age 3									
Low									
Medium									
High									
Very High									
Age 4-16									
Low									
Medium									
High									
Very High									
Age 17-64									
Low									
Medium									
High									
Very High									
Age 65 +									
Low									
Medium									
High									
Very High									

SOURCE: AdvancePCSTM Dataset Analysis									
Notes:									
* A blank cell indicates that "zero" claims were processed for that drug product.									
¹ Equivalents = number of grams dispensed in a prescription divided by 15									
² AdvancePCSTM is a pharmacy benefits manager in the U.S. that processes ██████████ third-party payer prescription claims annually and covers 75 million Patient Lives throughout the U.S.									
Data are NOT projected to represent a national total, do not include non-AdvancePCS reimbursed Rx's or mail order Rx claims, and do not include prescriptions where the patient paid cash at the pharmacy without subsequent third-party insurance reimbursement.									
*NOTE: NOT TO BE SHARED OUTSIDE OF FDA OR WITH NON-FDA STAFF WITHOUT PRIOR CLEARANCE BY ADVANCEPCS.									
Clearance must be requested from AdvancePCS through the FDA Office of Drug Safety*									

Table 4. Indications for Use of Topical Corticosteroids in the U.S. for Calendar Years 1999 - 2003. (IMS National Disease and Therapeutic Index)

Copyright IMS Health										
Projected Total Number of Drug Uses ¹										
During Patient Visits ² in Office-Based Practices in the Continental US										
For Topical Steroids										
Stratified by Age and Diagnosis										
For Calendar Year 1999 through 2003										
(in thousands; ADD THREE 0's TO EACH FIGURE)										
(percents are absolute numbers)										
Variable : Uses (Thousands)										
	1999	1999 %V	2000	2000 %V	2001	2001 %V	2002	2002 %V	2003	2003 %V
Age 0-3										
	ECZEMA NOS									
	DERMATITIS ATOPIC									
	DERMATITIS CONTACT NOS									
	SEBORRHEA									
	RASH NOS									
	DERMATITIS NOS									
	DIAPER RASH									
Age 4-16										
	ECZEMA NOS									
	DERMATITIS CONTACT NOS									
	DERMATITIS ATOPIC									
	DERMATITIS NOS									
	DERMATITIS POISON IVY									
	INSECT BITE NOS									
	RASH NOS									
Age 17-64										
	ECZEMA NOS									
	DERMATITIS CONTACT NOS									
	PSORIASIS ANY TYPE NOS									
	DERMATITIS NOS									
	DERMATITIS SEBORRHEIC NOS									
	RASH NOS									
	ALLERGIC DERMATITIS									
Age 65+										
	DERMATITIS NOS									
	ECZEMA NOS									
	PSORIASIS ANY TYPE NOS									
	DERMATITIS SEBORRHEIC NOS									
	DERMATITIS CONTACT NOS									
	RASH NOS									
	VARICOSE ECZEMA									
SOURCE: IMS HEALTH, National Disease and Therapeutic Index, CD-ROM										
NOTES:										
* -- means no data; a zero means less than total projected;										
¹ A drug use is the mention of a drug in association with a diagnosis during a patient visit.										
The drug uses are duplicated by the number of diagnoses for which the drug is mentioned.										
² Every patient contact reported is considered a patient visit, regardless of location										
**NOTE: DATA NOT TO BE SHARED OUTSIDE OF FDA OR WITH non-FDA STAFF WITHOUT PRIOR CLEARANCE BY IMS HEALTH.										
Clearance must be requested from IMS HEALTH through the FDA Office of Drug Safety										

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

David Moeny
5/24/04 01:04:01 PM
DRUG SAFETY OFFICE REVIEWER

Toni Piazza Hepp
5/26/04 09:34:58 AM
DRUG SAFETY OFFICE REVIEWER
for Gerald Dal Pan

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO (Division/Office):
Division of Drug Risk Evaluation (DDRE), HFD-430
(Room 15B-08, PKLN Bldg.)

FROM:
Millie Wright, Project Manager
Division of Dermatologic and Dental Drug Products/HFD-540

DATE: May 24, 2004

IND NO.

NDA NO. 21-152

TYPE OF DOCUMENT
NDA RS

DATE OF DOCUMENT:
March 11, 2004

NAME OF DRUG:
Cutivate  fluticasone
propionate  0.05%

PRIORITY CONSIDERATION

CLASSIFICATION OF DRUG:
3S

DESIRED COMPLETION DATE:
Labeling mtg. will be in early
Dec. 2004

NAME OF FIRM: GlaxoSmithKline.

REASON FOR REQUEST

I. GENERAL

- | | | |
|--|--|--|
| <input type="checkbox"/> NEW PROTOCOL | <input type="checkbox"/> PRE-NDA MEETING | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER |
| <input type="checkbox"/> PROGRESS REPORT | <input type="checkbox"/> END OF PHASE II MEETING | <input type="checkbox"/> FINAL PRINTED LABELING |
| <input type="checkbox"/> NEW CORRESPONDENCE | <input type="checkbox"/> RESUBMISSION | <input type="checkbox"/> LABELING REVISION |
| <input type="checkbox"/> DRUG ADVERTISING | <input type="checkbox"/> SAFETY/EFFICACY | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE |
| <input type="checkbox"/> ADVERSE REACTION REPORT | <input type="checkbox"/> PAPER NDA | <input type="checkbox"/> FORMULATIVE REVIEW |
| <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION | <input type="checkbox"/> CONTROL SUPPLEMENT | <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> MEETING PLANNED BY | | ODS consult |

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH

STATISTICAL APPLICATION BRANCH

- | | |
|--|---|
| <input type="checkbox"/> TYPE A OR B NDA REVIEW | <input type="checkbox"/> CHEMISTRY REVIEW |
| <input type="checkbox"/> END OF PHASE II MEETING | <input type="checkbox"/> PHARMACOLOGY |
| <input type="checkbox"/> CONTROLLED STUDIES | <input type="checkbox"/> BIOPHARMACEUTICS |
| <input type="checkbox"/> PROTOCOL REVIEW | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> OTHER (SPECIFY BELOW): | |

III. BIOPHARMACEUTICS

- | | |
|--|---|
| <input type="checkbox"/> DISSOLUTION | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS |
| <input type="checkbox"/> PHASE IV STUDIES | <input type="checkbox"/> IN-VIVO WAIVER REQUEST |

IV. DRUG EXPERIENCE

- | | |
|--|--|
| <input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) | <input type="checkbox"/> POISON RISK ANALYSIS |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP | |

V. SCIENTIFIC INVESTIGATIONS

CLINICAL

PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

The labeling for this NDA can be found in the electronic document room. I did note that the Sponsor has not submitted the labeling in a Word document, I will request that they do so. The labeling mtg. will be scheduled in early December.

PDUFA DATE: January 11, 2005

SIGNATURE OF REQUESTER

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MAIL (DFS)

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/s/

Mildred Wright
5/24/04 04:34:49 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-152

GlaxoSmithKline
Attention: Anthony Amitrano
Director, US Regulatory Affairs
1500 Littleton Road
Parisippany, New Jersey 07054-3884

Dear Mr. Amitrano:

Please refer to your March 11, 2004, new drug application (NDA), received March 12, 2004, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for CUTIVATE[®] (fluticasone propionate) 0.05%.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application has been filed under section 505(b) of the Act on May 10, 2004, in accordance with 21 CFR 314.101(a).

We are providing the following comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application.

Chemistry

1. Complete stability study results for certain batches of drug product are lacking.
2. Letters of Authorization need to be updated.
3. The structures of at least [redacted] products have not been established.
4. The manufacturing site information has not been provided.
5. The proposed drug name is unclear.

Pharmacology/Toxicology

1. The proposed package insert does not use the current labeling format for the Carcinogenesis, Mutagenesis, Impairment of Fertility, and Pregnancy sections under the PRECAUTIONS heading of the label.
2. A study to determine the photoco-carcinogenic potential of Cutivate [redacted] is lacking in the NDA submission.

Clinical and Statistical

1. Two phase 3 studies of atopic dermatitis have been submitted. This does not fulfill the basic requirement for the indication of [REDACTED]. Please refer to the minutes for the April 19,1999 meeting.
2. A safety update that includes all fluticasone propionate products is lacking.
3. There appears to be missing patient data from one study report (FPL10003).
4. Financial disclosure information is incomplete.
5. A descriptive Clinical Studies section is lacking in the proposed package insert.

We request that you submit the following information:

Chemistry

1. Please provide the following:
 - a. Complete stability study results for the Batches 8B310, 8C283, and 8J257 of Cutivate Lotion, 0.05% that were manufactured in 1998. Include results from viscosity and weight loss studies. Perform statistical analyses of the data.
 - b. Updated copies of all Letters of Authorization.
 - c. Information to establish that the structures of the [REDACTED] are the ones displayed in v. 2, p. 161.
2. In light of the stability results to date, re-evaluate the acceptance criteria proposed in the submission (v. 2, p. 48).
3. We also remind you of the Agency's April 26, 2004, facsimile requesting the following information:
 - a. Please provide information on the manufacturing sites for drug substance and drug product using the following table format:

Name of Manufacturer	US or Foreign [U or F]	Address -Street	Address- City/State Zipcode (or Country)	CFN (or FEI) ¹	Responsibility Stage ² Process ³	Site Ready Y or N	Contact Person	Contact Phone No. [P], Fax No. [FxN], and/or E-mail address [EA]

1. If no manufacturer identification number is available, provide a copy of the facility registration form.
2. Drug substance [DS], intermediate [I], or finished dosage [FD].
 Manufacturer [MF], Micronizer [MI], Packager [P], Sterilizer [S], Release Tester [RT], Stability Tester [ST], Sterility Tester [SxT], or Other [O]

- b. Confirm that the proposed drug name is "CUTIVATE^d (fluticasone propionate) 0.05% (as designated in the Cover Letter date 11-MAR 2004) and NOT CUTIVATE^e (fluticasone propionate) 0.05% (as used in the Package Insert and label specimens).

Pharmacology/Toxicology:

1. It is recommended that the Sponsor update the nonclinical portions of the Cutivate label (i.e., Carcinogenesis, Mutagenesis, Impairment of Fertility and Pregnancy sections under the PRECAUTIONS heading of the label) to current labeling standards. It is recommended that the Sponsor use the labeling format for these sections of the label used in the more recently approved fluticasone propionate drug products such as FLONASE[®] nasal spray and ADVAIR DISKUS[®].

The Division acknowledges receipt of the previously requested estimate of maximum daily human topical dose of Cutivate in mg/kg and mg/m². It is recommended that the Sponsor include multiples of human exposure levels (based on mg/m² comparisons) in the nonclinical portions of the Cutivate label based on the submitted estimate of the maximum daily human topical dose of the Cutivate. It is requested that the Sponsor submit the calculations used to determine the multiples of human exposure levels to be incorporated into the Cutivate label.

2. It is recommended that the Sponsor conduct a study to determine the photoco-carcinogenic potential of Cutivate as a Phase 4 commitment. The Division acknowledges that the Sponsor is not willing to commit to conducting a photoco-carcinogenicity study in hairless mice. However, alternative study designs for determining the photoco-carcinogenic potential of a topical drug product may be acceptable as noted in the guidance titled "Guidance for Industry – Photosafety testing" published in May, 2003. It would be appropriate to propose use of an alternative study design discussed in the photosafety testing guidance document. It is recommended that the Sponsor submit to the NDA their timeline for submitting a protocol and conducting the study to determine the photoco-carcinogenic potential of Cutivate.

Clinical and Statistical:

1. Please submit a safety update for all your fluticasone propionate products
2. Listing 8 for protocol FPL10003 (Listing of Induction Site Readings, Challenge, Application Site Readings and Tape Reactions; Vol 13, p. 136-209) is missing patients 31, 35, 76, 96, 97, 126, 204 and 205. Please submit these data. Listings for all studies in this NDA need to be complete; please review and submit any other missing data.
3. Please submit Case Report Form Tabulations for study FPL10003.

4. Please see Agency's facsimile, dated April 21, 2004, requesting information related to certification of the absence of financial interests and arrangements of clinical investigators (Form FDA 3454) and disclosure of financial interests and arrangements of clinical investigators (form FDA 3455) in this submission.
5. Please indicate whether the final to-be-marketed formulation of fluticasone propionate lotion was used in studies FPL10003 (repeat insult patch test) and FPL10005 (adrenal suppression study) or whether a different formulation was used.
6. Please submit Case Report Form Tabulations for Study FPL10003.
7. Please submit revised labeling incorporating a *Clinical Studies* section with results from the Phase 3 trials.

If you have any questions, call Millie Wright, Project Manager, at (301) 827-2020.

Sincerely,

{See appended electronic signature page}

Jonathan Wilkin, M.D.
Director
Division of Dermatologic & Dental Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research

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/s/

Stanka Kukich
5/21/04 02:34:50 PM
Signing off for Dr. Wilkin, Division Director

158

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MAY 18 2004

CDR / CDER



GlaxoSmithKline

GlaxoSmithKline
1500 Littleton Road
Parsippany, NJ
07054-3884

Tel. 973 889 2100
Fax. 973 889 2390
www.gsk.com

May 13, 2004

NDA 21-152

Jonathan K. Wilkin, M.D., Director
Division of Dermatologic and Dental Drug Products
Center for Drug Evaluation and Research
Document Control Room
Office of Drug Evaluation V
Food and Drug Administration
HFD-540
9201 Corporate Boulevard, Bldg. 2
Rockville, MD 20850

N-000(BC)
ORIG AMENDMENT

RECEIVED

MAY 20 2004

MEGA / CDER

Re: NDA 21-152
CUTIVATE[®] (fluticasone propionate) 0.05%
Amendment to Pending Application: Response to FDA Questions

Dear Dr. Wilkin:

GlaxoSmithKline Consumer Healthcare (GSKCH) hereby submits, in duplicate, an amendment to NDA 21-152 for CUTIVATE[®] (fluticasone propionate) 0.05% to address questions that were received from the agency in fax communications dated 4/21/04 and 4/26/04. The questions are provided below along with GSKCH's response.

4/21/04 Fax Communication (Financial Disclosure)

Question:

Please update any relevant changes that may have occurred in the course of the investigation or for 1 year following completion of the study (21-CFR 54.4(3)(c)). The agency requests written confirmation that no changes occurred affecting these forms after they were signed and dated, and that they are complete and accurate.

ORIGINAL

Response:

GSK has conducted a search of all relevant documents from the 9/30/99 (worldwide cut-off date imposed to allow sufficient time to prepare all relevant information to be included in the NDA submission) to 4/30/00 (1 year after termination of studies. [REDACTED]). To the best of our knowledge the FDA Forms 3454 and 3455 are complete and accurate as no changes affecting the forms after they were signed and dated were found during this search.

Question:

The agency also requests clarification of the payment made to [REDACTED]. [REDACTED] Was a single \$40,000 payment made to this institution or was this payment made for more than one investigator listed in Form FDA 3455? If so, what was the total payment made to the institution?

Response:

Due to the fact that 5 years has transpired since the collection of the financial disclosure information and that the originators of the information are no longer employees of the company or have moved on to other areas within the company, locating the pertinent files proved to be a difficult task. According to the internal documents that were retrieved, GSKCH has ascertained that to the best of our knowledge only one payment in the amount of \$40,000 was made to [REDACTED].

4/26/04 Fax Communication (Chemist's Request for Information)

Question:

Provide information on the manufacturing sites for drug substance and drug product.

Response:

The information is contained in Table No. 1 and 2 that is included in this submission.

Question:

Confirm that the proposed drug name is "CUTIVATE[®] (fluticasone propionate) 0.05%" (as designated in the cover letter dated 11-Mar-2004) and NOT "CUTIVATE[®] (fluticasone propionate 0,05%" (as used in the Package Insert and label specimens).

Response:

GSK apologizes for any confusion, but the proposed name should be the same as that used in the Package Insert and label specimens, i.e., CUTIVATE[®] (fluticasone propionate 0,05%.

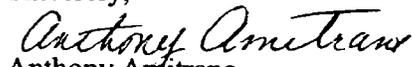
The cover letter and FDA Form 356h are included in both paper and electronic format. The remainder of the submission is electronic only.

This submission is contained on one CDROM of approximately 30 megabytes in size. The CDROM has been confirmed as virus free using Norton Antivirus software (version 8.00.9374, scan engine 4.1.0.15, updated 5/12/04, rev. 9) from Symantec.

Please note: Any future amendments to this NDA will be submitted in electronic format.

If there are any questions concerning this submission, please contact me at 973-889-2566.

Sincerely,


Anthony Amitrano

Director, US Regulatory Affairs

GlaxoSmithKline Consumer Healthcare, L.P.



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation V

FACSIMILE TRANSMITTAL SHEET

DATE: April 26, 2004

To: Anthony Armitrano	From: Melinda Harris, M.S. for Millie Wright Project Manager
Company: GlaxoSmithKline	Division of Dermatologic & Dental Drug Products
Fax number: (973) 889-2501	Fax number: (301) 827-2091 or 2075
Phone number: (973) 889-2566	Phone number: (301) 827-2020

Subject: NDA 21-152

Total no. of pages including cover: 3

Comments: CMC request for information

Document to be mailed: YES NO

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

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Please respond to the following request for information by 03-MAY-2004. Please let us know if this deadline cannot be met. If you have any questions about specific items in the list or any other points in need of clarification, call the project manager Millie Wright (301-827-2020).

NDA Number: 21-152
Drug Name: CUTIVATE [REDACTED] 0.05%

Applicant: GlaxoSmithKline
26-APR-2004

These comments are being provided to you prior to completion of our review of the application to give you preliminary notice of issues that have been identified. Per the user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and are subject to change as the review of your application is finalized. In addition, we may identify other information that must be provided prior to approval of this application. If you choose to respond to the issues raised in this letter during this review cycle, depending on the timing of your response, as per the user fee reauthorization agreements, we may or may not be able to consider your response prior to taking an action on your application during this review cycle.

NOTE: If your response can be found in the contents of your submission, just cite those sections of the submission that are relevant to the issue under consideration. Otherwise, please provide the appropriate information as an amendment to the submission.

Chemist's Request for Information

1. Provide information on the manufacturing sites for drug substance and drug product.

Name of Manufacturer	US or Foreign [U or F]	Address-Street	Address-CityState Zipcode (or Country)	CFN (or FEL) ¹	Responsibility Stage ² Process ³	Site Ready Y or N	Contact Person	Contact Phone No. [P], Fax No. [Fxn], and/or E-mail address [EA]

1. If no manufacturer identification number is available, provide a copy of the facility registration form.
2. Drug substance [DS], intermediate [I], or finished dosage [FD].
3. Manufacturer [MF], Micronizer [MI], Packager [P], Sterilizer [S], Release Tester [RT], Stability Tester [ST], Sterility Tester [SxT], or Other [O].

2. Confirm that the proposed drug name is "CUTIVATE@ [REDACTED] (fluticasone propionate) [REDACTED] 0.05%" (as designated in the Cover Letter dated 11-MAR-2004) and NOT "CUTIVATE@ [REDACTED] (fluticasone propionate) [REDACTED] 0.05%" (as used in the Package Insert and label specimens).

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/s/

Melinda Harris
4/27/04 10:16:19 AM
CSO



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation V

FACSIMILE TRANSMITTAL SHEET

DATE: 4/21/04

To: Anthony Amitrano	From: Mary Jean Kozma-Fornaro Supervisor, Project Management Staff
Company: GlaxoSmithKline	Division of Dermatologic & Dental Drug Products
Fax number: 973 889-2501	Fax number: (301) 827-2091
Phone number: 973 889-2566	Phone number: (301) 827-2020
Subject: NDA 21-152 Cultivate [REDACTED] 0.05%	

Total no. of pages including cover:

Comments: NDA 21-152: Please provide a response to the following:

Forms related to certification of the absence of financial interests and arrangements of clinical investigators (Form FDA 3454) and disclosure of financial interests and arrangements of clinical investigators (Form FDA 3455) in submission NDA 21-152 are dated December 6, 1999, or less than 1 year following the completion of protocols [REDACTED]. Please update any relevant changes that may have occurred in the course of the investigation or for 1 year following completion of the study (21 CFR 54.4(3)(c)). The Agency requests written confirmation that no changes occurred affecting these forms after they were signed and dated, and that they are complete and accurate.

The Agency also requests clarification of the payment made to [REDACTED]. Was a single \$40,000 payment made to this institution or was this payment made for more than one investigator listed in Form FDA 3455? If so, what was the total payment made to the institution?

Document to be mailed:

YES

NO

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2020. Thank you.**

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/s/

Mary Jean Kozma Fornaro
4/21/04 04:16:42 PM
CSO



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-152

GlaxoSmithKline Consumer Healthcare, LP
Attention: Anthony Amitrano
Director, US Regulatory Affairs
1500 Littleton Road
Parsippany, NJ 07054-3884

Dear Mr. Amitrano:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Cutivate (fluticasone propionate) , 0.05%

Review Priority Classification: Standard (S)

Date of Application: March 11, 2004

Date of Receipt: March 12, 2004

Our Reference Number: NDA 21-152

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on May 11, 2004 in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be January 12, 2005.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have submitted pediatric studies with this application. Once the review of this application is complete we will notify you whether you have fulfilled the pediatric study requirement for this application.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. Address all communications concerning this NDA as follows:

NDA 21-152

Page 2

U.S. Postal Service:

Center for Drug Evaluation and Research
Division of Dermatologic & Dental Drugs
HFD-540
5600 Fishers Lane
Rockville, Maryland 20857

Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Dermatologic & Dental Drugs
HFD-540
9201 Corporate Boulevard
Rockville, MD 20850

If you have any questions, call Millie Wright, Regulatory Project Manager, at (301) 827-2020.

Sincerely,

{See appended electronic signature page}

Mary Jean Kozma-Fornaro
Supervisor, Project Management Staff
Division of Dermatologic & Dental Drugs
Office of Drug Evaluation V
Center for Drug Evaluation and Research

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/s/

Mildred Wright
3/25/04 03:02:30 PM
Signing for M.J. Kozma-Fornaro



GlaxoSmithKline

GlaxoSmithKline
1500 Littleton Road
Parsippany, NJ
07054-3884

Tel. 973 889 2100
Fax. 973 889 2390
www.gsk.com

March 11, 2004

RECEIVED

MAR 12 2004

NDA 21-152

MEGA/CDER

N. 000(RS)

Jonathan K. Wilkin, M.D., Director
Division of Dermatologic and Dental Drug Products
Center for Drug Evaluation and Research
Document Control Room
Office of Drug Evaluation V
Food and Drug Administration
HFD-540
9201 Corporate Boulevard, Bldg. 2
Rockville, MD 20850

ORIG AMENDMENT

Re: NDA 21-152
CUTIVATE[®] (fluticasone propionate) 0.05%
Re-submission of original NDA

Dear Dr. Wilkin:

GlaxoSmithKline Consumer Healthcare (GSKCH), is hereby, re-submitting the original NDA for CUTIVATE[®] (fluticasone propionate) 0.05% (NDA 21-152) per the agency's March 2, 2004 telephone conference request. This NDA was originally submitted by GlaxoWellcome (GW), Research Triangle Park, North Carolina to the FDA on December 13, 1999. It was voluntarily withdrawn without prejudice (May 25, 2000) six months into the review process, as this product line was not in the strategic plan for GW. The subsequent merger of GW and SmithKline Beecham and the transfer of ownership of the Dermatology Drug Products resulted in renewed interest in the CUTIVATE[®] drug product. Although this NDA remained inactive for several years, it is now GSKCH's intention to move the approval process forward. As previously conveyed to the agency in the original application, throughout the development of the product, the formulation was referred to as "Lotion", however, the marketed formulation will be identified as

DUPLICATE

In the March 2, 2004 telephone conference and subsequent fax, the FDA stated the following:

1. Appreciate correspondence dated February 27, 2004 of intent of re-filing NDA 21-152 subsequent to withdrawal of NDA 21-152 on May 25, 2000.
2. A complete resubmission of all volumes for all relevant disciplines needs to be resubmitted per CFR 314. References to previous submission of NDA 21-152 on December 13, 1999 can be made.
3. Consider all updated elements for NDA submission by current standards i.e., electronic case report forms, financial disclosure etc. if not previously submitted in current content and format.
4. A meeting request for a pre-NDA meeting (content and format) can be made.
5. Application not subject to a user fee.
6. Standard review with a 10 month review cycle with the new NDA submission.

While we acknowledge that the standard user fee review cycle is 10 months, GSKCH is committed to working with the agency to accelerate the review and approval process if at all possible. To this end:

- GSKCH has complied with FDA's March 2nd request and is providing a paper copy of the original NDA submission that was previously filed on December 13, 1999. As requested by the agency, we have ensured that all of the relevant NDA sections meet current standards. To further assist in the review of this NDA application, the following has been included as electronic files: updated draft labeling, clinical case report forms and SAS data sets for the pivotal clinical trials. It is believed that this will further assist in the review of this NDA application.
- The February 27, 2004 GSKCH submission augments the new NDA submission as it provides the following:

- (a). Reviewer's Guide consisting of a correspondence chronology between GW and FDA during the initial NDA review period as well as hyperlinks to the relevant documents.
- (b). FDA Reviewer's questions/outstanding issues that were precipitated during the agency's initial review of the application and GSKCH's responses to these requests.

While GSKCH appreciates the FDA's suggestion to hold a pre-NDA meeting, we believe that such a meeting would not be mutually beneficial at this time. However, GSKCH is committed to working with the agency to maintain an open dialog and exchange of information so that a timely review and approval of this NDA application can be achieved.

If there are any questions concerning this submission please contact me at 973-889-2566.

Sincerely,



Anthony Amitrano
Director, US Regulatory Affairs
GlaxoSmithKline Consumer Healthcare, L.P.