CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:NDA 19958/S008

ADMINISTRATIVE DOCUMENTS

JUN 6 1996

NDA 19-958/S-008

Glaxo, Inc.
Attention: J. Christopher Prue, R.Ph.
Five Moore Drive
Research Triangle Park, North Carolina 27709

Dear Mr. Prue:

Please refer to your June 9, 1995, supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Cutivate (fluticasone propionate cream) Cream, 0.05%.

We acknowledge receipt of your correspondence dated April 8, 1996.

This supplemental new drug application provides for the proposed addition of a pediatric indication to the approved labeling for this drug product.

We have completed our review and find the information presented is inadequate, and the supplemental new drug application is not approvable under 505 (d) of the Act and 21 CFR 314.125 (b). The deficiencies may be summarized as follows:

CLINICAL:

1. Safety issues for pediatric indication:

A. Systemic toxicity in the pediatric age group needs to be assessed for each subdivision of patients; age 0 - 2 years, 3 - 5 years, 6 - 10 years, and 11 - 16 years. Specifically, a validated method of assessment of the HPA-axis, e.g. the acute Cortrosyn stimulation test, should be done to achieve this end in each patient.

B. There should be at least 20 patients in each of the above subdivisions evenly distributed in age within each group to ascertain safety of the drug for the dosage requested. Provide the exact age, weight, height, and heart rate for each pediatric patient within each arm of the trial. The evaluation should be conducted on individual data, not means of data classes.

C. A specific percentage of body surface area should be targeted to be treated in

an effort to decrease variance in the amount of drug to be evaluated for potential absorption. By keeping this constant, criteria for entry limited to a "signs" score of greater than or equal to 6 for severity could be used.

D. A form should be included to direct the investigator to look for signs of the more common side effects associated with topical steroid use, such as skin atrophy, dusky erythema, telangiectasia, etc.

E. Adverse event reports need to be examined to be certain that the actual incidence of local side effects is not higher than reported.

F. Investigators' qualifications need to be submitted.

2. Efficacy issues:

A. A second trial needs to be submitted comparing once a day dosage of the drug against its placebo, if once a day application is used to demonstrate efficacy.

B. Submit statistical analyses for both trials' "per protocol" and "total sample" populations.

C. Submit an analysis adjusted by investigator.

D. Demonstrate efficacy by age group with the appropriate data.

E. State the order of importance of the two primary efficacy variables, the global assessment and the signs and symptoms score.

F. The same criteria that were evaluated for entry into the study should be the basis for evaluation of success of the therapy. If adding vesiculation and crusting is important to the evaluation of the disease entity for efficacy, then they must be included in the baseline evaluation, and the severity score would have to be increased from 6.

G. Overall score for signs/symptoms should total 1.5 or less to be classified as a success.

Until the safety and effectiveness of this drug product for the proposed indication have been established, we reserve comment on the proposed labeling.

Within 10 days after the date of this letter, you are required to amend the

supplemental new drug application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.120. In the absence of any such action FDA may proceed to withdraw the supplemental new drug application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

Should you have any questions concerning this application, please contact:

Mary Jean Kozma-Fornaro, RN, MSA
Project Manager
Telephone: (301) 827-2020

Sincerely yours,

/S/ 6/6/96

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

cc:
Original NDA 19-958
HFD-540/Div File
HFD-2/Lumpkin
DISTRICT OFFICE
HFD-222/New Drug Chemistry Division Director
HFD-80
HFD-540/DIV DIR/Wilkin
HFD-540/DEP DIR/Katz
HFD-540/MO/Cook, Denise/6/5/96
HFD-540/CHEM/Pappas
HFD-540/PHARM/Avalos
HFD-713/BIOSTAT/Freidlin
HFD-540/PROJ MGR/Fornaro

Concurrence:
HFD-540/SPMS/Cook/ 6/5/96
HFD-713/BIOSTAT/Srinivasan

c:\wpfiles\19958sap

NOT APPROVABLE

EXCLUSIVITY SUMMARY FOR NDA #19-958 SUPPL #SE5-008

Trade Name: Cutivate Cream Generic Name: fluticasone propionate

Applicant Name: GlaxoWellcome HFD # 540

Approval Date If Known NDA approved 12/18/90
S-008 approved 6/17/99

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

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

a) Is it an original NDA?

YES /___/ NO /X/

b) Is it an effectiveness supplement?

YES /X/ NO /___/

If yes, what type? (SE1, SE2, etc.) SE5

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 /X/ 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:

Form OGD-011347 Revised 10/13/98
cc: Original NDA 19-958 Division File HFD-93 Mary Ann Holovac
HFD-540/Wright

d) Did the applicant request exclusivity?

YES /___/ NO /X/

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

e) Has pediatric exclusivity been granted for this Active Moiety?
NO

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule, previously been approved by FDA for the same use? (Rx to OTC switches should be answered NO-please indicate as such)

YES /X/ NO /___/

If yes, NDA #:19-958. Drug Name : Cutivate Cream

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

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

YES /___/ NO /___/

IF THE ANSWER TO QUESTION 3 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# _____ _____

NDA# _____ _____

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. IF "YES" GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S 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:

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 /___/

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

_____ _____

_____ _____

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

_____ _____

_____ _____

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 !

IND # _____ YES /___/ ! NO /___/ Explain: _____

Investigation #2 !

IND # _____ YES /___/ ! NO /___/ Explain: _____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1 !

YES /___/ Explain _____ ! NO /___/ Explain _____

_____ ! _____

_____ ! _____

Investigation #2 !

YES /___/ Explain _____ ! NO /___/ Explain _____

_____ ! _____

_____ ! _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /___/

If yes, explain: _____

_____

/S/

Signature _____ Date 6/14/99

Title: Project Manager

/S/

Signature of ~~Office~~ _____ Date 6/17/99

Division Director

S-008

cc: Original NDA 19-958/S-008 Division File HFD-93 Mary Ann Holovac
HFD-540/Wright

PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

NDA/BLA Number:	19958	**Trade Name:**	CUTIVATE CREAM
Supplement Number:	8	**Generic Name:**	FLUTICASONE PROPIONATE
Supplement Type:	SE5	**Dosage Form:**	Cream; Topical
Regulatory Action:	AP	**Proposed Indication:**	Use in pediatric patients 3 months of age or older with corticosteroid-reponsive dermatoses.

ARE THERE PEDIATRIC STUDIES IN THIS SUBMISSION?
YES, Pediatric data exists for at least one proposed indication which supports pediatric approval

What are the INTENDED Pediatric Age Groups for this submission?

____NeoNates (0-30 Days) _X_ Children (25 months-12 Years)
____Infants (1-24 Months) _X_ Adolescents (13-16 Years)

Label Adequacy	Adequate for SOME pediatric age groups
Formulation Status	-
Studies Needed	No further STUDIES are needed
Study Status	-

Are there any Pediatric Phase 4 Commitments in the Action Letter for the Original Submission? NO

COMMENTS:
Application is not approved for neonates (birth to 1 month) or infants (1-2 months). 6/18/99

This Page was completed based on information from a PROJECT MANAGER/CONSUMER SAFETY OFFICER, MILDRED WRIGHT

Signature /S/ Date 6/18/99

cc:
NDA 19-958/S-008, Divfile
HFD-540/Wright

MEMORANDUM OF TELECON

DATE: June 3, 1999

APPLICATION NUMBER: NDA 19-958/SE5-008

BETWEEN:
Name: Janice McKellar, Associate Director
Dermatology Regulatory Affairs
Representing Glaxo Wellcome, Inc
Name: Susan Walker, M.D., Medical Team Leader
Mary Jean Kozma-Fornaro, Chief, Project Management Staff 6/17/99
Representing Division of Dermatologic and Dental Drug Products/HFD-540

Topic: Laboratory Values for Subjects

Discussion:
The Sponsor was requested to provide data showing the percentage of subjects with laboratory values outside normal range for each laboratory variable at baseline and end-of-treatment.

Action Items: The Sponsor agreed to provide the requested information

Minutes drafted by Mary Jean Kozma-Fornaro

CC:
Orig NDA 19-958-S-008
Div File
HFD-540/M.Wright

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:NDA 19958/S008

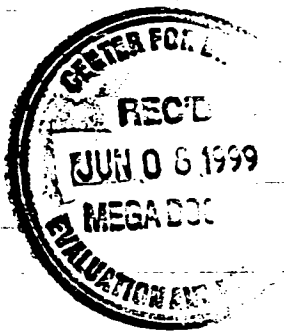
CORRESPONDENCE

GlaxoWellcome

Glaxo Dermatology

SE5-008 BS BM
NDA SUPPL AMENDMENT

June 4, 1999



Millie Wright, Project Manager
Division of Dermatologic and Dental Drug Products, HFD-540
Center for Drug Evaluation and Research
Pilot Drug Evaluation Staff
Food and Drug Administration
HFD-170, PKLN, 9B45
5600 Fishers Lane
Rockville, MD 20857

Re: NDA 19-958/S-008; CUTIVATE® (fluticasone propionate cream) Cream, 0.05%
Response to FDA Request/Comment: Statistical

Dear Ms. Wright:

Ms. Kozma-Fornaro and Dr. Walker phoned me June 3, 1999, with an additional clarification of FDA requested information.

The request was to show the percentage of subjects with laboratory values outside normal range for each laboratory variable at baseline and end-of-treatment.

This information is provided in the enclosed table for age groups 3 months – 2 years and 2 years – 5 years, separately and combined. In addition, we have displayed the low and high values separately.

Sincerely,

Janice P. McKellar

Janice P. McKellar
Associate Director
Dermatology Regulatory Affairs

Glaxo Wellcome Inc.
Five Moore Drive
PO Box 13398
Research Triangle Park
North Carolina 27709-3398
Telephone
919 483 2100

ORIGINAL

ORIGINAL

SE5-008/BA

GlaxoWellcome

Glaxo Dermatology

199

June 3, 1999

NDA SUPPL AMND

Millie Wright, Project Manager
Division of Dermatologic and Dental Drug Products, HFD-540
Center for Drug Evaluation and Research
Pilot Drug Evaluation Staff
Food and Drug Administration
HFD-170, PKLN, 9B45
5600 Fishers Lane
Rockville, MD 20857

Re: NDA 19-958/S-008; CUTIVATE® (fluticasone propionate cream) Cream, 0.05%
Response to FDA Request/Comment: Statistical

Dear Ms. Wright:

Reference is made to the FDA FAX memo dated June 2, 1999.

Item 1. How many children (out of 51) had their faces treated with Cutivate Cream?

The protocol required that each subject enrolled into the study had to have a minimum baseline body surface area of disease involvement of at least 35%, excluding the diaper area for subjects wearing diapers, the eyelids, the perioral area, around the nostrils, and atrophic areas. In addition, all lesional areas of the body could be treated throughout the study (with exceptions as noted above), and cleared areas could be treated for up to one week in order to assure a minimum exposure of 35% total BSA.

Given the protocol requirements, the case report forms collected information on the body surface area extent and location of eczematous lesions on the skin. However, the case report forms did not collect specific information on what areas of the body were treated. The specific areas to be treated were left to the investigators' discretion as long as the investigators met the protocol requirements as outlined above. The protocol intent was to treat all allowed lesions, therefore, it is presumed that lesional areas on the face were treated, at least until cleared.

Upon review of the diagrams denoting disease locations, 41 of 51 subjects had atopic dermatitis on the facial areas at the baseline visit.

Glaxo Wellcome Inc.
Five Moore Drive
PO Box 13398
Research Triangle Park
North Carolina 27709-3398

Telephone
919 483 2100

Item 2. For each laboratory adverse event, send us a table showing the percentages of patients that were abnormal at baseline and at end-treatment for each category where there was an abnormality at end-treatment.

Addendum Table 3 (attachement1) displays the number and percent of subjects with abnormal (i.e., outside of normal range) end of treatment laboratory values whose baseline value was also abnormal.

Regarding the FDA FAX from Mary Jean Kozma-Fornaro dated June 3, 1999:

Request A complete assay validation report for assessing fluticasone propionate in the plasma. The sponsor has only mentioned the limit of quantification. We need to know the percentage accuracy, precision, linearity of the assay, recovery, etc.

The following summarizes the information requested:

Calibration Model	Weighted 1/X
Validated Ranged	20-1520pg/mL
Precision (%CV) intra-assay inter-assay	<5.3% <3.3%
Accuracy (%bias)	< + 7.7%
Recovery	71.9%
Long Term Stability	At least 123 days at -20°C
Matrix Stability	At least 48 hours at room temperature
Freeze-Thaw Stability	At least 3 cycles
Processed Extract Stability	At least 48 hours at room temperature
Precision/Accuracy	There are no details of precision or accuracy given for this assay as there was only one assay performed. Only when there is more than one assay, is it possible to perform these calculations.

The complete validation report is included in attachment 2.

This document is being submitted in duplicate. If you have any further questions please feel free to contact me at 919-483-3030.

Sincerely,

Janice P. McKellar

Janice P. McKellar
Associate Director
Dermatology Regulatory Affairs

202

GlaxoWellcome

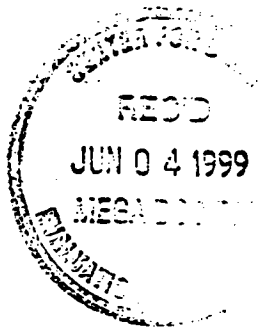
Glaxo Dermatology

ORIGINAL

SE5-009 /BR

June 2, 1999

NDA SUPPL ALLEGED



Millie Wright, Project Manager
Division of Dermatologic and Dental Drug Products, HFD-540
Center for Drug Evaluation and Research
Food and Drug Administration
HFD-170, PKLN, 9B45
5600 Fishers Lane
Rockville, MD 20857

Re: NDA 19-958/S-008; CUTIVATE® (fluticasone propionate cream) Cream, 0.05%
Response to FDA Request/Comment: Statistical

Dear Ms. Wright:

The information contained herein is provided in response to the request you made in our telecommunication on May 27, 1999. The attached documents consist of Addendum Tables 1 and 2. The information includes the mean cortisol values, with Standard Deviations, as determined by method (Addendum Table 1) and by method (Addendum Table 2).

Each table displays the mean cortisol values at baseline, and at end of treatment by scheduled visit, i.e., Day 22 ± 2 and Day 29 ± 1. Values collected outside of the scheduled visit are displayed by the unscheduled visit day, e.g., Day 11, Day 25, Day 33 and Day 36.

In addition, the mean cortisol values for the end of treatment visit at any visit day is included for the sake of completeness. These values were reported in the sNDA submission of December 16, 1999.

Glaxo Wellcome Inc.

Five Moore Drive
PO Box 13398
Research Triangle Park
North Carolina 27709-3398

Telephone
919 483 2100

This document is being submitted in duplicate. If you need any additional information or if you have any other questions feel free to contact me at 919-483-5787.

Sincerely,

Janice P. McKellar

Janice P. McKellar
Associate Director
Dermatology Regulatory Affairs

cc: Dr. Dennis Bashaw
Dr. Venetta Tandon

(126)

GlaxoWellcome

Glaxo Dermatology

February 11, 1999

ORIGINAL

SES-008 BC

Jonathan K. Wilkin, M.D., Director
Division of Dermatologic and Dental Drug Products, HFD-540
CDER ODE V
Food and Drug Administration
Attn: Room N115
9201 Corporate Blvd., Bldg. 2
Rockville, MD 20850

Re: NDA 19-958/S-008; CUTIVATE® (fluticasone propionate cream) Cream, 0.05%
Amendment to Pending Application: CMC

Dear Dr. Wilkin:

Reference is made to a telephone conversation between Ms. Millie Wright and the undersigned, Janice McKellar on January 21, 1998. The questions asked are shown below with their responses:

1. A cross-reference is needed to the chemistry, manufacturing, and controls section of the approved NDA. If there is no difference as a result of this pediatric supplement, this needs to be stated.

Response: The chemistry, manufacturing, and controls section is unchanged and is submitted by cross-reference to the original approved NDA 19-958, supplements and annual reports, thereto.

2. Does the currently approved batch production size change as a result of adding the pediatric population? If so, a waiver for the Environmental Assessment should be submitted.

Response: The currently approved batch size is unchanged from the approved NDA and its supplements and annual reports, thereto.

If there are any questions regarding this submission, please contact me at 919-483-3030.

Glaxo Wellcome Inc.
Five Moore Drive
PO Box 13398
Research Triangle Park
North Carolina 27709-3398

Telephone
919 483 2100

Sincerely,

Janice P. McKellar

Janice P. McKellar
Associate Director
Dermatology Regulatory Affairs

DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

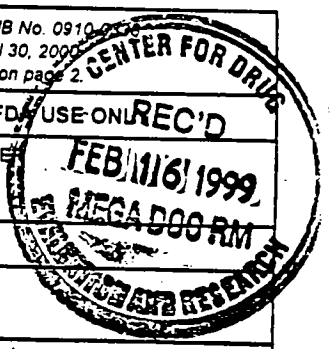
APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314 & 601)

Form Approved : OMB No. 0910-0338
Expiration Date: April 30, 2000
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER



APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Glaxo Wellcome Inc.	02/11/99
TELEPHONE NO. *(Include Area Code)* (919) 483-2100	FACSIMILE (FAX) Number *(Include Area Code)* (919) 941-5883 or (919) 483-3012

APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued)*:
P.O. Box 13398
Five Moore Drive
Research Triangle Park, NC 27709

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

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued) 19-958

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
Fluticasone propionate	Cutivate Cream, 0.05%

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(if any)*

CODE NAME *(if any)*

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
Cream	0.05%	Topical

(PROPOSED) INDICATION(S) FOR USE:
Dermatologic indications

APPLICATION INFORMATION

APPLICATION TYPE
(check one) ☒ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED APPLICATION (ANDA, AADA, 21 CFR 314.94)
☐ BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☒ 505 (b) (1) ☐ 505 (b) (2) ☐ 507

IF AN ANDA, OR AADA, 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 ☐ SUPAC SUPPLEMENT
☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

REASON FOR SUBMISSION
To provide additional information, as requested, regarding the pending supplement #008 (pediatric labeling)

PROPOSED MARKETING STATUS (check one) ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER-THE-COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 1 THIS APPLICATION IS ☒ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION

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)

This application contains the following items: *(Check all that apply)*	
	1. Index
	2. Labeling (check one) ☐ Draft Labeling ☐ Final Printed Labeling
	3. Summary (21 CFR 314.50 (c))
	4. Chemistry section
X	A. Chemistry, manufacturing, and controls information (e.g. 21 CFR 314.50 (d) (1), 21 CFR 601.2)
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	15. Establishment description (21 CFR Part 600, if applicable)
	16. Debarment certification (FD&C Act 306 (k)(1))
	17. Field copy certification (21 CFR 314.50 (k) (3))
	18. User Fee Cover Sheet (Form FDA 3397)
	19. OTHER (Specify)

CERTIFICATION

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:

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2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations 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 21 CFR 314.70, 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.

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.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: a willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE
Janice P. McKellar	Janice P. McKellar Associate Director, Dermatology Regulatory Affairs	02/11/99

ADDRESS *(Street, City, State, and ZIP Code)*	Telephone Number
Glaxo Wellcome Inc. Five Moore Drive, P. O. Box 13398, Research Triangle Park, NC 27709	(919) 483-3030

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DHHS, Reports Clearance Officer
Paperwork Reduction Project (0910-0338)
Hubert H. Humphrey Building, Room 531-H
200 Independence Avenue, S.W.
Washington, DC 20201

Please DO NOT RETURN this form to this address.

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.

FORM FDA 356h (7/97)

GlaxoWellcome

Glaxo Dermatology

NDA SUPPL AMEND
SE5-008 BL DUPLICATE

December 16, 1998

Jonathan K. Wilkin, M.D., Director
Division of Dermatologic and Dental Drug Products, HFD-540
CDER, ODE V
Food and Drug Administration
Attn: Room N115
9201 Corporate Blvd., Bldg. 2
Rockville, MD 20850

Re: NDA 19-958; CUTIVATE® (fluticasone propionate cream) Cream, 0.05%
S-008: Pediatric Labeling
Amendment to Pending Application

Dear Dr. Wilkin:

Enclosed for your review is the final report for **Study FPC40001: An Open Label Adrenal Suppression Study of Fluticasone Propionate Cream, 0.05% Used Twice Daily in Pediatric Subjects Aged 3 Months to 5 Years with Moderate to Severe Eczema or Psoriasis.** This report is submitted to complete our commitment to provide additional safety information in pediatric patients in support of the approval of a pediatric indication for Cutivate Cream, 0.05%.

BACKGROUND

On June 9, 1995 a supplemental NDA (S-008) was submitted to NDA 19-958, Cutivate (fluticasone propionate) Cream, 0.05%, to provide for the addition of a pediatric indication to the approved labeling. Three clinical studies were provided to support the application:

FLT/411: Cutivate Cream, 0.05% versus Hydrocortisone Cream, 1% in the Treatment of Moderate to Severe Atopic Dermatitis in Children. Investigators: RT Garrett, CT Kennedy, NM Birchell, and M Kirkup.

FLT/412: Cutivate Cream, 0.05% versus Hydrocortisone Butyrate Cream, 0.01% in the Treatment of Moderate to Severe Atopic Dermatitis in Children. Investigators: RT Garrett, CT Kennedy, NM Birchell, and M Kirkup.

FLT/001: A Four-Week Multicentre Double-Blind Study to Compare Safety and Efficacy Between once-Daily and Twice Daily Administration of Fluticasone Propionate 0.05%

Glaxo Wellcome Inc.
Five Moore Drive
PO Box 13398
Research Triangle Park
North Carolina 27709-3398

Telephone
919 483 2100

Cream in the Treatment of Atopic Eczema. Investigators: S Bleehen, A Chu, I Hamann, C Holden, J Hunter, and R Marks.

In a meeting with the Agency on November 24, 1997, the Agency agreed that adequate efficacy data had been provided in the above-cited studies to support pediatric labeling. However, to support final approval of the supplemental application, the Agency requested additional safety information, specifically, an assessment of HPA axis function in an age stratified pediatric population using a validated method of assessment.

A draft protocol (Study FPC40001) was submitted to the Agency for comment in the pre-meeting package submitted November 7, 1997. The study design was based on discussion between Dr. J. Wilkin and Dr. J. Kallal and Ms. J. Ferrell on April 24, 1997 and was modified following comments received in a November 24, 1997 meeting. A final protocol was submitted to IND . The protocol was subsequently amended twice based on comments provided during Institutional Review Board review. These amendments were provided to the Agency on May 5, 1998 (S.N. 047) and July 1, 1998 (S.N. 050). This study has been completed. A summary of the study is described below and a final study report is enclosed.

SUMMARY OF STUDY FPC40001

Study Design: This was an open-label, safety study conducted at 10 centers in the United States. The objective of the study was to evaluate the response to cosyntropin stimulation test (CST) following a 3- or 4-week course of twice-daily fluticasone propionate cream 0.05% in pediatric subjects with moderate to severe eczema or psoriasis covering more than 35% of their body surface area (BSA). The study was age-stratified into two groups, 3 months to 2 years of age and 3 to 5 years of age. Cortisol was assayed using two methods: the primary determinant, and a secondary determinant. A normal adrenal response to cosyntropin by was defined as a post-stimulation cortisol value of >18 µ/dL. Other variables used to assess safety included plasma fluticasone levels, serum chemistry and hematology tests, signs of cutaneous atrophy and changes in skin pigmentation, and the incidence of adverse events. The severity of signs and symptoms of disease and % BSA affected were collected in order to assess the extent of exposure to study drug in any subject with a safety concern.

Results: All 51 subjects enrolled had a diagnosis of eczema with an average treated BSA of 68%, almost twice the protocol-defined minimum treated BSA. A total of 46 subjects completed the study, including 32 in the younger group and 14 in the older group. Of these, 43 subjects had an end-treatment post-stimulation CST test. There was no clinically significant difference in cortisol levels at baseline and end-treatment. Two subjects had

end-treatment post-stimulation cortisol values not >18μg/dL. One of these subjects, a 5-year old male, had been treated for 4 weeks over 95% of BSA. Within 2 weeks after last treatment this patient had returned to normal. The other subject, a 2-year old male, was treated for 5 weeks over 35% of BSA. This patient was lost to follow-up. Two additional subjects had downward trending in cortisol levels at end-treatment. Two observations of reversible mild telangectasia were reported and described as pre-existing conditions unmasked by the resolution of lesional inflammation. No subject was discontinued due to adverse events and there were no serious adverse events or deaths.

Conclusion: Fluticasone propionate 0.05% cream is safe when used in the treatment of extensive eczema for up to 4 weeks in pediatric subjects 3 months of age and older.

PROPOSED LABELING

Attachment 1 contains four copies of proposed package insert language incorporating usage in pediatric patients 3 months of age and older.

On July 9, 1998 a supplemental application was submitted to NDA 19-958 (S-011) to provide for revisions to the Cutivate Cream package insert. These revisions were proposed to update product information and to standardize wording between the Cutivate Cream and Cutivate Ointment package inserts where appropriate. Additionally, S-011 addressed product information issues raised during the review and approval of S-009 (addition of once daily dosing). Supplement S-011 is currently under Agency review.

With new product information presented in this amendment to S-008, additional revision to the current approved package insert for Cutivate Cream, and further revision of some proposed changes as submitted in S-011 are required. To facilitate review of this submission, a complete copy of the revised Cutivate Cream package insert submitted under S-011 is included in Attachment 2. Only those sections of the package insert requiring revision as a result of the clinical data reviewed under S-008, are included in Attachment 1.

NDA EXCLUSIVITY – PEDIATRIC INDICATION

This supplemental application (S-008) contains reports of new clinical investigations conducted by Glaxo Wellcome which are essential to the approval of the supplemental application. Consequently, under the provisions of the Drug Price Competition and Patent Restoration Act (1984 Amendments), upon final approval of a pediatric indication the sNDA qualifies Cutivate Cream, 0.05% for a period of exclusivity of three years for the pediatric indication.

Additionally, on September 16, 1998 a request was submitted to the Agency for a Written Request to support an additional six months exclusivity for fluticasone propionate under the provisions of Section 505A of the FDA Modernization Act of 1997. The protocol proposed to support this additional exclusivity is the subject of the enclosed final clinical report. While the results of this clinical study are being provided to the Agency to complete the approval of this sNDA prior to receiving an official Written Request, we believe the listing of fluticasone propionate in the Agency's "List of Approved Drugs for Which Additional Pediatric Information May Produce Health Benefits in the Pediatric Population" supports the Agency's interest in receiving pediatric labeling information on Cutivate Cream. In the spirit of meeting this request, GW has decided to not withhold submission of this additional pertinent information needed to complete the Agency's review of this pending supplemental application.

On page 3 of the Agency's Guidance for Industry which addresses the process for requesting additional exclusivity under Section 505A, it states that the holder of the approved application must submit reports of the studies in accordance with a written agreement, or if there is no written agreement, in accordance with commonly accepted scientific principles. The design of this clinical study is based on commonly accepted scientific principles and was formally discussed with the Agency in a meeting on November 24, 1997. Within the spirit and intent of the provisions provided under Section 505A, and if the Agency agrees that the submitted study meets their requirements to support pediatric labeling, then the approval of this sNDA should support an additional 6 months extended exclusivity.

Additionally, on December 15, 1998 a second request was submitted to the Agency under IND , requesting the Agency. provide a Written Request based on pediatric studies currently ongoing under this IND. A copy of our request was also provided to the Division of Pulmonary Drug Products, HFD-570, to facilitate your joint review.

CONCLUSION

We believe that the clinical data previously submitted and reviewed by the Agency and the additional safety data submitted herein provides an adequate assessment of efficacy and safety in the pediatric population to support the final approval of a pediatric indication for Cutivate Cream under S-008.

This submission is submitted in duplicate. If you have any questions, please contact William Stagner, Ph.D., Group Director, Dermatology Product Development at (919) 483-5787.

Sincerely,

Joy E. Ferrell

Joy E. Ferrell
Director
Dermatology Regulatory Affairs

Attachments:

Form FDA 356h
Final Clinical Study Report for Study FPC40001

DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314 & 601)

Form Approved : OMB [illegible]
Expiration Date: April 30, 2000
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Glaxo Wellcome Inc.	12/16/98
TELEPHONE NO. *(Include Area Code)* (919) 483-2100	FACSIMILE (FAX) Number *(Include Area Code)* (919) 941-5883 or (919) 483-3012
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued)*: P.O. Box 13398 Five Moore Drive Research Triangle Park, NC 27709	AUTHORIZED U.S. AGENT NAME & ADDRESS *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued) 19-958

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
Fluticasone propionate	Cutivate Cream, 0.05%

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*

CODE NAME *(If any)*

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
Cream	0.05%	Topical

(PROPOSED) INDICATION(S) FOR USE:
Dermatologic indications

APPLICATION INFORMATION

APPLICATION TYPE (check one)

☒ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED APPLICATION (ANDA, AADA, 21 CFR 314.94)

☐ BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☒ 505 (b) (1) ☐ 505 (b) (2) ☐ 507

IF AN ANDA, OR AADA, 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 ☐ SUPAC SUPPLEMENT

☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

REASON FOR SUBMISSION
Submission for the dissemination of information on an unapproved/new use

PROPOSED MARKETING STATUS (check one) ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER-THE-COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 3

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SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE
Joy E. Ferrell	Joy E. Ferrell, Director, Dermatology Regulatory Affairs	12/16/98

ADDRESS *(Street, City, State, and ZIP Code)*	Telephone Number
Glaxo Wellcome Inc. Five Moore Drive, P. O. Box 13398, Research Triangle Park, NC 27709	(919) 483-5211

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