CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-833

APPROVAL LETTER(S)

NDA 20-833

GlaxoWellcome Inc.
Five Moore Drive
Research Triangle Park, NC 27709

Attention: Kathleen A. Prodan
Director, Regulatory Affairs

Dear Ms. Prodan:

Please refer to your new drug application (NDA) dated March 30, 1998, received March 31, 1998, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Flovent Diskus 50 mcg, Flovent Diskus 100 mcg and Flovent Diskus 250 mcg (fluticasone propionate inhalation powder).

We acknowledge receipt of your submissions dated April 29, May 4, 27, and 28, June 5, July 23, October 12, and December 22, 1998, February 15, June 7, 10, 24, and 30, September 13, October 22, November 11, and December 2, and 14, 1999, March 30, April 13, August 25, September 6, 7, 14, 20, 27, 28, and 29, 2000. Your submission of March 30, 2000, constituted a complete response to our December 8, 1999, action letter.

This new drug application provides for the use of Flovent Diskus 50 mcg, Flovent Diskus 100 mcg and Flovent Diskus 250 mcg (fluticasone propionate) Inhalation Powder for the maintenance treatment of asthma as prophylactic therapy in adults and pediatric patients 4 years of age and older. It is also indicated for patients requiring oral corticosteroid therapy for asthma. Many of these patients may be able to reduce or eliminate their requirement for oral corticosteroids over time.

We have completed the review of this application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed upon labeling text. Accordingly, the application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the submitted draft labeling (package insert submitted September 29, 2000, patient's instructions for use and immediate container and carton labels submitted September 28, 2000). Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit 20 paper copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. Alternatively, you may submit the FPL electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDAs* (January 1999). For administrative purposes, this submission should be designated "FPL for approved NDA 20-833." Approval of this submission by FDA is not required before the labeling is used.

We remind you of your post marketing commitment specified in your submission dated September 27, 2000. This commitment, along with any completion dates agreed upon, are listed below.

[ ]. This information will be submitted as a prior approval supplement by January 1, 2001.

Protocols, data, and final reports should be submitted to your IND for this product and a copy of the cover letter sent to this NDA. If an IND is not required to meet your post marketing commitments, please submit protocols, data and final reports to this NDA as correspondence. In addition, under 21 CFR 314.81(b)(2)(vii), we request that you include a status summary of each commitment in your annual report to this NDA. The status summary should include the number of patients entered in each study, expected completion and submission dates, and any changes in plans since the last annual report. For administrative purposes, all submissions, including labeling supplements, relating to these post marketing commitments must be clearly designated "Post Marketing Commitments."

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

Be advised that, as of April 1, 1999, 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 (63 *FR* 66632). We note that you have not fulfilled the requirements of 21 CFR 314.55 (or 601.27) for patients < 4 years of age. We are deferring submission of your pediatric studies until July 31, 2003.

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Please submit one market package of the drug product when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call Sandy Barnes, Chief, Project Management Staff, at (301) 827-1055.

Sincerely,

Robert J. Meyer, M.D.
Director
Division of Pulmonary and Allergy Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-833

APPROVABLE LETTER(S)

NDA 20-833

DEC 8 1999

Glaxo Wellcome
Five Moore Drive
Research Triangle Park, NC 27709

Attention: Kathleen A. Prodan
Director, Regulatory Affairs

Dear Ms. Prodan:

Please refer to your new drug application (NDA) dated March 30, 1998, received March 31, 1998, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Flovent ® Diskus ® 50 mcg, Flovent ® Diskus ® 100 mcg, and Flovent ® Diskus ® 250 mcg (fluticasone propionate) Inhalation Powder.

We acknowledge receipt of your submissions dated April 29, May 4, 27, and 28, June 5, July 23, October 12, and December 22, 1998, February 15, June 7, 10, 24, and 30, September 13, October 22, November 11, December 2, 1999. Your submission of June 7, 1999, constituted a complete response to our March 31, 1999, action letter.

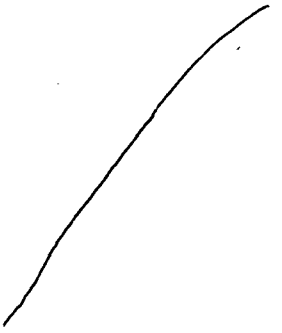
We have completed the review of this application, as amended, and it is approvable. Before this application may be approved, however, it will be necessary for you to address the following comments.

1. There are insufficient data to allow for the approvability and proper labeling of the proposed once-daily dosing. To support once-daily dosing,

2.

5 Page(s) Withheld

11. The following comments relate to the — of the drug product.



12. The following comment refers to the —

13. Submit revised draft labeling that incorporates the following comments.

    a. The Diskus products are a series of drug products using the same device. Provide consistent labeling for the drug products to the extent possible, particularly for the instructions for use of the Diskus device.

    b. Increase the size and prominence of the discard instructions on the overwrap.

    c. Place the statement ' — ." on the overwrap.

    d. Incorporate a — in use period for the 50 and 100 mcg strength drug products and two months for the 250 mcg strength drug product into the following labeling sections.

        (1) How Supplied Section of the package insert.

(2) Patient Instructions for Use.

(3) Discard Instructions on the overwrap.

(4) Discard instructions on the carton.

e. Include the following on the Diskus device label.

(1) "Pouch opened ____."

(2) "Use by ____."

f. We note that an expiration date of only numbers will be ambiguous (e.g., 03/02). Provide an unambiguous format (e.g., FEB/02).

g. We note that the patient inhalation instructions in the proposed labeling (". — ") are different from the inhalation instructions used in the clinical trials ("...breathe in quickly and deeply ... through the Inhaler, not through your nose....") and studies of flow rates achieved by patients — . Change the patient inhalation instructions for the labeling to be consistent with the inhalation instructions used in the clinical trials or provide appropriate documentation that the proposed patient inhalation instructions for labeling ensure that patients can be expected to receive the demonstrated benefits of the drug product. If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

Additional labeling comments will be forwarded following satisfactory resolution of the above issues.

You are advised to contact the Division regarding the extent and format of your safety update prior to responding to this letter.

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-40
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of any such action FDA may proceed to withdraw the 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.

The drug product may not be legally marketed until you have been notified in writing that the application is approved.

If you have any questions, contact LCDR James Lindsay Cobbs, Regulatory Project Manager, at (301) 827-1051.

Sincerely,

Robert J. Meyer, M.D.
Director
Division of Pulmonary and Allergy Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

cc:
Archival NDA 20-833
HFD-570/Div. Files
HFD-570/J.L.Cobbs
HFD-570/PURUCKER
HFD-570/POOCHIKIAN
HFD-570/MEYERRO
HFD-570/KOBLE
HFD-570/GEBERT
HFD-570/WILSON
HFD-570/UPPOOR
HFD-570/CHEN
HFD-570/Barnes
HFD-570/SANCILIO
HFD-570/SUN
HFD-002/ORM
HFD-102/ADRA
HFD-95/DDMS
HFD-820/DNDC Division Director
DISTRICT OFFICE
Drafted by: LCOBBS/December 7, 1999
Initialed by: Barnes/12-7-99
GEBERT/12-8-99
WILSON/12-8-99
CHEN/12-8-99
UPPOOR/12-8-99
KOBLE/12-8-99
POOCHIKIAN/12-8-99
PURUCKER/12-8-99
MEYER/12-8-99
VOGEL/12-8-99
final:LCOBBS/DECEMBER 8, 1999
filename: MY DOCUMENTS/FLOVENT/AE2

APPROVABLE (AE)

NDA 20-833

Glaxo Wellcome
Five Moore Drive
Research Triangle Park, NC 27709

Attention: Kathleen A. Prodan
Director, Regulatory Affairs

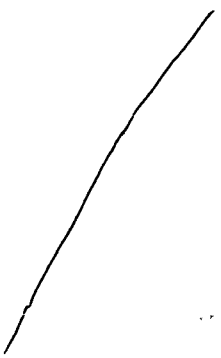
Dear Ms. Prodan:

Please refer to your new drug application (NDA) dated March 30, 1998, received March 31, 1998, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Flovent ® Diskus ® 50 mcg, Flovent ® Diskus ® 100 mcg, and Flovent ® Diskus ® 250 mcg (fluticasone propionate) Inhalation Powder.

We acknowledge receipt of your submissions dated May 4, 27, and 28, June 5, July 23, October 12, and December 2, 1998.

We have completed the review of this application, as amended, and it is approvable. Before this application may be approved, however, it will be necessary for you to address the following comments.

1. The available clinical and Chemistry, Manufacturing & Controls (CMC) data related to the once daily dosing recommendation for the Flovent Diskus are insufficient to support such a claim. The following must be provided to support a claim for once daily dosing.



7 Page(s) Withheld

16. Submit revised draft package insert and carton and container labeling that incorporate the following preliminary comments as well as the preliminary revisions shown in the enclosed marked-up draft package insert.

a. Provide clarification of the statement (page 38, Volume 1.1) that [redacted] Our records do not indicate approval of this for Flovent Rotadisk. Provide a detailed reference for this agreement.

b. Modify the emitted dose delivery data in the Description section based on *in vitro* testing using a flow rate of 60 L/min for 2 seconds; i.e., a two liter volume.

c. These comments refer to the Pharmacodynamic subsection of the CLINICAL PHARMACOLOGY section.

(i) Amend the description of the short term cosyntropin stimulation test to use either [redacted] or peak serum cortisol <18 mcg/dL [redacted] the criteria for an abnormal response.

(ii) Amend the description of the 2-year safety study found in paragraph 3 to clarify the use of the Rotadisk device instead of the Diskus device since both can generally be referred to as fluticasone propionate inhalation powder.

(iii) In addition, remove the reference in this study description to [redacted]

d. Remove the graph in the Clinical Trials subsection of the CLINICAL PHARMACOLOGY section and revise the related text appropriately so that [redacted] are not presented. The graph may be replaced with graphs representing individual trials.

e. Revise the PRECAUTIONS section of the package insert to include [redacted] s requested in our correspondence dated November 6, 1998, to NDAs 20-548 and 20-549.

f. Revise the tabulation of the adverse events data to refer only to the twice daily dosing and modify the headers and accompanying text accordingly.

g. Insert the statement "Because individual responses may vary, children previously maintained on fluticasone propionate Rotadisk 50 or 100 mcg twice daily may require dosage adjustments upon transfer to Flovent Diskus." into the **DOSAGE AND ADMINISTRATION** section.

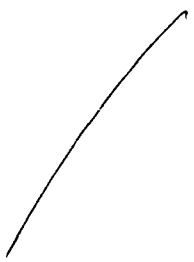
h. Modify the patient use period in the HOW SUPPLIED section of the package insert, based on adequate data and agreement with the agency.

i. Modification of the patient use period in the "How to Use Your Flovent Diskus" and "STORING YOUR FLOVENT DISKUS" sections in the PATIENT INSTRUCTIONS FOR USE will be required once agreement is reached with the agency.

j. Revise the storage statement on the label for the over-wrap to:

k. Update the discard instructions on the label for the over-wrap, once an agreement with the agency is reached for a patient use period.

l. The following comments refer to the label for the cartons.



m. Modify the device label storage statement to:

17. The following comments refer to the analytical test sites.

    a. Identify the analytical test sites used for release and stability testing of batches provided in support of this application.

    b. Identify the analytical tests to be performed at each of the proposed analytical testing sites for the drug substance and drug product.

    c. Limit the test sites for the [redacted] to the sites that have demonstrated satisfactory laboratory to laboratory reproducibility and provide data supporting the reproducibility for these tests.

During recent inspections of the manufacturing facilities for your NDA, a number of deficiencies were noted and conveyed to you or your suppliers by the inspector. Satisfactory inspections will be required before this application may be approved.

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of any such action FDA may proceed to withdraw the 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.

The drug product may not be legally marketed until you have been notified in writing that the application is approved.

If you have any questions, contact Mr. J. Lindsay Cobbs, Project Manager, at (301) 827-1051.

Sincerely,

John K. Jenkins, M.D., F.C.C.P.
Director
Division of Pulmonary Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure

A

16 Draft Labeling Page(s) Withheld

cc:
Archival NDA 20-833
HFD-570/Div. Files
HFD-570/J.L.Cobbs
HFD-570/PURUCKER
HFD-570/POOCHIKIAN
HFD-570/MEYERRO
HFD-570/KOBLE
HFD-570/GEBERT
HFD-570/WILSON
HFD-570/UPPOOR
HFD-570/CHEN
HFD-570/SCHUMAKER
HFD-570/JAFARI
HFD-570/SANCILIO
HFD-570/SUN
HFD-002/ORM
HFD-102/ADRA
HFD-95/DDMS
HFD-820/DNDC Division Director
DISTRICT OFFICE

Drafted by: LC/March 25, 1999
Initialed by: SUN/3-31-99
SANCILIO/3-31-99
BARNES/3-30-99, 3-31-99
SCHROEDER/3-31-99
PURUCKER/3-31-99
MEYER/3-31-99
JENKINS/3-31-99
final:
filename: MY DOCUMENTS/FLOVENT/N20833AE

APPROVABLE (AE