DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-077/S-003

GlaxoSmithKline
P. O. Box 13398
Five Moore Drive
Research Triangle Park, NC 27709

Attention: Patrick D. Wire, Pharm.D.
Product Director, Respiratory Group

Dear Dr. Wire:

Please refer to your supplemental new drug application dated May 4, 2001, received May 7, 2001, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Advair Diskus 250/50 (fluticasone propionate 250 mcg and salmeterol 50 mcg inhalation powder).

We acknowledge receipt of your submissions dated August 31, October 17, and 26, and November 9, 2001. and February 28, March 22, June 20, July 10, October 25, and November 13, 2002, and January 14, May 30, October 10, 2003, November 6, 12, and 17, 2003.

Your submission of May 30, 2003, constituted a complete response to our December 12, 2002, action letter.

This supplemental new drug application provides for the use of Advair Diskus 250/50 (fluticasone propionate and salmeterol xinafoate inhalation powder) for Chronic Obstructive Pulmonary Disease associated with Chronic Bronchitis.

We completed our review of this application, as amended. This application is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert submitted on November 17, 2003, and text for the patient instruction leaflet submitted on November).

Please submit the FPL electronically according to the guidance for industry titled Providing Regulatory Submissions in Electronic Format – NDA. Alternatively, you may 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 15 of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved supplement NDA 21-077/S-003." Approval of this submission by FDA is not required before the labeling is used.

We remind you of your postmarketing study commitments in your submission dated November 17, 2003. These commitments are listed below.

1. Conduct a randomized double-blind parallel-group study to evaluate the effect of Advair 250/50 via Diskus on bone mineral density in subjects with chronic obstructive pulmonary disease. The agreed upon timelines for the submission of the final protocol is April 2004, and the final report is due in December 2007.

2. Conduct a randomized double-blind, parallel-group study to evaluate the effect of Advair 250/50 via Diskus on exacerbations in subjects with chronic obstructive pulmonary disease. The agreed upon timelines for the submission of the final protocol is April 2004, and the final report is due in August 2007.

Submit clinical protocols to your IND for this product. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii), you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies, number of patients entered into each study. All submissions, including supplements, relating to these postmarketing study commitments must be prominently labeled "Postmarketing Study Protocol," "Postmarketing Study Final Report," or "Postmarketing Study Correspondence."

In addition, we remind you of the following agreements as stated in your submission dated November 17, 2003.

1. Review all new serious unexpected cases (spontaneous cases and attributable clinical trial cases) within 1-2 days of receipt and follow up on the cases for full documentation using targeted questions.

2. Submit a quarterly listing and review of all serious adverse events occurring during clinical trials with Advair.

3. Review all new spontaneous cases describing adverse events of special interest within 1-2 days of receipt and follow up on the cases for full documentation using targeted questions. Adverse events of special interest are (a) decrease bone mineral density, osteoporosis, and fractures (b) cataract and glaucoma, (c) adrenal suppression and (d) lower respiratory tract infections [pneumonia].

4. Maintain monthly listings and review all newly reported adverse events, and perform monthly data mining of your spontaneous adverse event database for adverse events of special interest as listed in item 3 above. Submit the results with quarterly reports.

5. Submit a quarterly cumulative review of all spontaneous adverse event reports, and clinical trial cases of adverse events of special interest as listed in item 3 above.

6. Submit cumulative review of all spontaneous reports describing pneumonia, categorized by patient age, total daily dose and indication at six month intervals.

7. Submit a plan for evaluating the performance of the elements of the risk management plan with details of the timeline and the methodology that will be applied in the plan.

8. Specify a time when you will report back to the Agency to provide data on (a) the extent of high-dose use of Advair Diskus among patients with COPD and (b) the extent of compliance with the risk management plan and complications of product use (through surveys of COPD patients and/or physicians using claims databases).

9. Produce patient and health care provider educational material describing the possible risks of Advair use in COPD patients, such as bone demineralization, glaucoma, and cataract formation. In addition, advise physicians and patients on the appropriate use of Advair Diskus for the treatment of COPD associated with chronic bronchitis.

In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to the Division of Pulmonary & Allergy Drug Products 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, MD 20857

If you issue a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HFD-410
FDA
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Ms. Ladan Jafari, Regulatory Project Manager, at (301) 827-1084.

Sincerely,

{See appended electronic signature page}

Badrul A. Chowdhury, M.D., Ph.D.
Director
Division of Pulmonary and Allergy Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure (Package insert & Patient Instruction leaflet)

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

/s/

Badrul Chowdhury

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