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RESEARCH**

APPLICATION NUMBER:
021936Orig1s000

OTHER ACTION LETTER(S)



NDA 21-936

COMPLETE RESPONSE

Boehringer Ingelheim
900 Ridgebury Road
PO Box 368
Ridgefield, CT 06877-0368

Attention: Jeffrey R. Snyder
Executive Director, Drug Regulatory Affairs

Dear Mr. Snyder:

Please refer to your new drug application (NDA) dated November 16, 2007, received November 16, 2007, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Spiriva Respimat (tiotropium bromide) inhalation spray.

We acknowledge receipt of your amendments dated January 4 and 10, February 16 and 27, March 18, April 4, 11, and 18, May 7 and 21, June 10, 20, and 23, July 1, 10, 18, 24, 25, 28 and 29, and August 5 and 13, 2008.

We have completed the review of your application, and have determined that we cannot approve this application in its present form. We have described below our reasons for this action and, where possible, our recommendations to address these issues.

CLINICAL

Deficiency

1. The submitted data do not provide substantial evidence of safety to support the use of Spiriva Respimat in patients with chronic obstructive disease (COPD). The safety concerns are death and stroke. Increased frequencies of death were observed in patients treated with Spiriva Respimat compared to placebo in the two 48-week studies submitted with this application, particularly in study 205.255. Increased frequencies of stroke were observed in patients treated with tiotropium bromide compared to placebo in a pooled analysis of clinical study data with Spiriva HandiHaler and Spiriva Respimat.

Information Needed to Resolve the Deficiency

To support the safety of Spiriva Respimat for use in COPD patients, provide data from an adequate and well-controlled study to address the concerns of death and stroke. The study should be of adequate duration and power that will allow evaluation of these two safety concerns. If study 205.235 (The UPLIFT study) is intended to be used to address these safety concerns, provide justification for use of safety data from Spiriva HandiHaler to support the safety of Spiriva Respimat.

Deficiency

2. The submitted data do not provide substantial evidence to support the proposed claim of reduction of COPD exacerbation. While the pre-specified combined analysis of the two 48-week clinical studies 205.254 and 205.255 show a decreased number of COPD exacerbations with Spiriva Respimat compared to placebo, replication of the finding is necessary to support a labeling claim. Results of the two individual 48-week studies are not sufficient for replication because only one of the two studies showed a statistically significant difference from placebo. The clinical study 205.266 is not acceptable for replication because the study was conducted with Spiriva HandiHaler, which is a distinct product in terms of efficacy.

Information Needed to Resolve the Deficiency

To support the proposed claim of reduction of COPD exacerbation, provide data from an adequate and well controlled clinical study that shows statistically significant reduction in COPD exacerbation with Spiriva Respimat compared to placebo.

LABELING

We reserve comment on the proposed labeling until the application is otherwise adequate. If you revise this labeling, your response must include updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/oc/datacouncil/spl.html>

SAFETY UPDATE

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). You are advised to contact the Division of Pulmonary and Allergy Products regarding the extent and format of your safety update prior to responding to this letter.

OTHER

Within one year after the date of this letter, you are required to resubmit or take one of the other actions available under 21 CFR 314.110. If you do not take one of these actions, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. A resubmission must fully address all the deficiencies listed. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

Under 21 CFR 314.102(d), you may request a meeting or telephone conference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the FDA Guidance for Industry *Formal Meetings With Sponsors and Applicants for PDUFA Products*, February, 2000 (<http://www.fda.gov/cder/guidance/2125fnl.htm>).

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

If you have any questions, call Miranda Raggio, Regulatory Project Manager, at (301) 796- 2109.

Sincerely,

{See appended electronic signature page}

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

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/s/

Badrul Chowdhury
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