

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**021747Orig1s000**

**OTHER ACTION LETTER(s)**



NDA 21-747

**COMPLETE RESPONSE**

Boehringer Ingelheim  
900 Ridgebury Road  
P.O. Box 368  
Ridgefield, CT 06877-0368

Attention: Amy Van Anandel, DVM, MPH  
Senior Associate Director, Drug Regulatory Affairs

Dear Dr. Van Anandel:

Please refer to your new drug application (NDA) dated October 07, 2008, received October 08, 2008, submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act, for Combivent Respimat (ipratropium bromide and albuterol sulfate) Inhalation Spray.

We also refer to your submissions dated October 15, and November 06, 07, 11, 13, and 14, 2008, January 06, February 17, and 23, April 03, May 19, and 29, and July 14, and 17, 2009.

We have completed the review of your application, as amended, 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**

The submitted data do not provide substantial evidence of safety to support long-term use of Combivent Respimat Inhalation Spray in patients with chronic obstructive pulmonary disease (COPD). While efficacy of Combivent Respimat Inhalation Spray has been demonstrated, there is no data beyond 12 weeks to support long-term use of the product in patients with COPD.

To support approval of Combivent Respimat Inhalation Spray for use in patients with COPD, provide data from a long-term study (or studies) with treatment duration of at least one year. In the study compare the safety and efficacy of Combivent Respimat Inhalation Spray to the currently marketed Combivent Inhalation Aerosol, and to currently marketed albuterol and ipratropium single ingredient inhalation aerosols administered together. In the study also assess patient handling, and acceptance of Combivent Respimat Inhalation Spray.

### **PRODUCT QUALITY**

1. Explain how [redacted] (b) (4)  
Describe any [redacted] (b) (4)

2. Describe any instances in which the RespiMat nozzle was found to be clogged, before or after use of the entire number of labeled actuations.
3. Return all suspected or apparently malfunctioning drug product units discovered in your future one year clinical safety study for appropriate laboratory testing.
4. This pertains to your alternate Aerodynamic Particle Size Distribution (APSD) specification which utilizes a laser diffraction (LD) method. Develop a drug specific specification (e.g., using HPLC assay) to complement the APSD-LD method by determining and controlling the amount of each active ingredient present in the residue after actuation on the mouthpiece/adaptor in the APSD-LD assay.
5. This pertains to your response to our comment 2 in your May 19, 2009, amendment. Provide data to demonstrate that (b) (4)  

6. Respond to your agreement to provide in-use stability data for the drug product using drug product stored for 23 months under the long term storage condition. You will insert cartridges into the inhaler and store up to 3 months to cover the maximum in use period, and then test the product appropriately.

## LABELING

Submit draft labeling that incorporates revisions in the attached labeling and as listed below. In addition, submit 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>.

7. In Section 2 (Dosage and Administration section), it states that if the drug product is (b) (4)  
  
Revise (b) (4) Sections 2 (Dosage and Administration), Section 11 (Description), and Section 17 (Patient Counseling Information) of the package insert.
8. In Section 5 (Warnings and Precautions) revise the heading in subsection 5.6 to read "Hypersensitivity Reactions Including Anaphylaxis," and delete the word (b) (4)  
from the first line of first sentence. (b) (4)  


9. In Section 6 (Adverse Reactions) Subsection 6.1, revise the table to include the adverse reactions that occurred at a frequency of  $\geq 2\%$  in the COMBIVENT RESPIMAT treatment group. These events cannot be excluded from the Adverse Reactions table, because it is plausible that these events may be drug-related. Revise Table 1 to include these events. Also revise the rest of subsection 6.1 to incorporate the revisions noted in the marked up label.
10. In Section 8 (Use in Specific Populations) Subsection 8.1 (Pregnancy), add “and rabbits” to the sentence “However, albuterol sulfate has been shown to be teratogenic in mice *and rabbits*. In addition, add “*and rabbits*” to the first sentence under “Albuterol” in Section 13 (Nonclinical Toxicology) Subsection 13.2 (Animal Toxicology and Pharmacology).
11. In Section 8 (Use in Specific Populations), Subsection 8.5 (Geriatric Use) delete the words [REDACTED] <sup>(b) (4)</sup> from the last sentence as this minimizes the risk.
12. In Section 10 (Overdosage) change [REDACTED] <sup>(b) (4)</sup>  
[REDACTED]
13. In section 11 (Description) Retain the statement “*The actual amount of drug delivered to the lung may depend on patient factors, such as the coordination between the actuation of the device and inspiration, through the delivery system.*” The statement is consistent with language in other orally inhaled product labels.
14. In Section 12 (Pharmacology) Subsection 12.3 (Pharmacokinetics), revise the statement to read [REDACTED] <sup>(b) (4)</sup>  
[REDACTED]
15. In Section 14 (Clinical Trials), delete the sentence [REDACTED] <sup>(b) (4)</sup>  
[REDACTED]
16. Update the HIGHLIGHTS to incorporate the changes made to the Full Prescribing Information.

When responding to this letter, submit labeling that includes all previous revisions, as reflected in the most recently approved package insert. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should include annotations with the supplement number for previously-approved labeling changes.

17. Submit revised draft carton and container labeling revised as follows:

- a. On the labels indicate the delivered drug per actuation *from the mouthpiece*.
- b. Add a label space on the device where the patient can write the expiry date for the in-use shelf life of the drug product (e.g., discard by \_/\_/).
- c. Modify the cartridge label to indicate that the product is sterile.
- d. Modify the carton label to indicate that the product is sterile in the unopened cartridge.
- e. Provide actual size color mock ups of all labels.
- f. Move the statement “Each actuation delivers...” to the main panel of the carton.

The following comments pertain to the Structured Product Labeling (SPL)/Drug Listing Date Element (DLDE) Table.

18. Modify the proprietary name and names of active ingredient to include albuterol sulfate (i.e., under “Combivent Respimat”, the next line should be as follows: “albuterol sulfate and ipratropium bromide spray, metered”).
19. Under “packaging,” the first line under “packaging description” should read as follows: 1 CARTRIDGE and 1 INHALER in 1 CARTON. The first line under “multilevel packaging” should not include reference to a container within the cartridge, since the cartridge is not separable by the patient from the enclosed plastic container; modify this section accordingly.

## **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 regarding the extent and format of your safety update prior to responding to this letter.

## **OTHER**

20. As previously indicated, we recommend annual and expiry testing for sterility on stability for all of your Respimat drug products, including post approval stability batches.
21. Your stability data do not support a (b) (4) expiration dating period. Current stability data are considered to support an expiration dating period of (b) (4) for the drug product.

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's *Guidance for Industry - Formal Meetings Between the FDA and Sponsors or Applicants*, May 2009 at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.pdf>.

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 Sadaf Nabavian, Senior Regulatory Project Manager, at (301) 796-2777

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: Labeling

14 Page(s) of Draft Labeling has been Withheld in Full as B4 (CCI/TS)  
immediately following this page

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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BADRUL A CHOWDHURY  
08/07/2009