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RESEARCH**

APPLICATION NUMBER:

212122Orig1s000

OTHER ACTION LETTERS



NDA 212122

COMPLETE RESPONSE

AstraZeneca AB
c/o AstraZeneca Pharmaceuticals
1800 Concord Pike
Wilmington, DE 19803

Attention: Monique Small, PharmD
Director, Global Regulatory Affairs

Dear Dr. Small:

Please refer to your new drug application (NDA) dated and received on November 30, 2018, and your amendments, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Breztri Aerosphere (budesonide, glycopyrrolate and formoterol fumarate) 160/9/4.8 mcg Inhalation Aerosol.

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

CLINICAL

The submitted data do not provide substantial evidence of the efficacy and safety for the use of Breztri Aerosphere (budesonide, glycopyrrolate and formoterol fumarate) 160/9/4.8 mcg Inhalation Aerosol for the proposed indication of the (b) (4), maintenance treatment of (b) (4) patients with chronic obstructive pulmonary disease (COPD) (b) (4). The single Breztri Aerosphere phase 3 pivotal trial failed on the co-primary endpoint of change from baseline in trough FEV₁ for the comparison of Breztri Aerosphere and the glycopyrrolate and formoterol fumarate combination. Therefore, the submitted data do not establish the contribution of budesonide to the Breztri Aerosphere combination product. Furthermore, due to failure at the co-primary endpoint, all secondary endpoints in the single phase 3 pivotal trial failed to show statistical significance and did not provide supportive evidence of efficacy. Moreover, as only a single Breztri Aerosphere phase 3 pivotal trial was submitted with this application, there was no additional data to directly support the efficacy and safety of Breztri Aerosphere.

Information to Resolve Deficiency

In order to address the above deficiency, conduct an additional trial or trials to provide data to demonstrate the efficacy of the Breztri Aerosphere combination product and the contribution of budesonide to the combination product.

PRESCRIBING INFORMATION

- (1) We reserve comment on the proposed labeling until the application is otherwise adequate. We encourage you to review the labeling review resources on the PLR Requirements for Prescribing Information¹ and Pregnancy and Lactation Labeling Final Rule² websites, including regulations and related guidance documents and the Selected Requirements for Prescribing Information (SRPI) – a checklist of important format items from labeling regulations and guidances.

If you revise labeling, use the SRPI checklist to ensure that the Prescribing Information conforms with format items in regulations and guidances. Your response must include updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at FDA.gov.³

PROPRIETARY NAME

- (2) Please refer to correspondence dated, March 8, 2019, which addresses the proposed proprietary name, Breztri Aerosphere. This name was found acceptable pending approval of the application in the current review cycle. Please resubmit the proposed proprietary name when you respond to the application deficiencies.

SAFETY UPDATE

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). The safety update should include data from all nonclinical and clinical studies/trials of the drug under consideration regardless of indication, dosage form, or dose level.

- (1) Describe in detail any significant changes or findings in the safety profile.

¹ <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm>

² <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Labeling/ucm093307.htm>

³ <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>

- (2) When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:
- Present new safety data from the studies/clinical trials for the proposed indication using the same format as in the original submission.
 - Present tabulations of the new safety data combined with the original application data.
 - Include tables that compare frequencies of adverse events in the original application with the retabulated frequencies described in the bullet above.
 - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.
- (3) Present a retabulation of the reasons for premature trial discontinuation by incorporating the drop-outs from the newly completed trials. Describe any new trends or patterns identified.
- (4) Provide case report forms and narrative summaries for each patient who died during a clinical trial or who did not complete a trial because of an adverse event. In addition, provide narrative summaries for serious adverse events.
- (5) Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original application data.
- (6) Provide updated exposure information for the clinical studies/trials (e.g., number of subjects, person time).
- (7) Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.
- (8) Provide English translations of current approved foreign labeling not previously submitted.

OTHER

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 314.110. If you do not take one of these actions, we may consider your lack of response a request to withdraw the application under 21 CFR 314. You may also request an extension of time in which to resubmit the application.

A resubmission must fully address all the deficiencies listed in this letter and should be clearly marked with "**RESUBMISSION**" in large font, bolded type at the beginning of the cover letter of the submission. The cover letter should clearly state that you consider this resubmission a complete response to the deficiencies outlined in this letter. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

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 Linda Ebonine, Regulatory Project Manager, at 240-402-4483.

Sincerely,

{See appended electronic signature page}

Sally Seymour, MD
Division Director
Division of Pulmonary, Allergy, and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

SALLY M SEYMOUR
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