WARNING LETTER

AstraZeneca Pharmaceuticals LP

MARCS-CMS 664789 — AUGUST 04, 2023

Product:

Drugs

Recipient:

Pascal Soriot

Executive Director and Chief Executive Officer

AstraZeneca Pharmaceuticals LP

1800 Concord Pike
Wilmington, DE 19850
United States

Issuing Office:

The Office of Prescription Drug Promotion (OPDP)

United States

RE: NDA 212122
BREZTRI AEROSPHERE™ (budesonide, glycopyrrolate, and formoterol fumarate) inhalation aerosol, for oral inhalation use MA 385

WARNING LETTER

Dear Pascal Soriot:

The Office of Prescription Drug Promotion (OPDP) of the U.S. Food and Drug Administration (FDA) has reviewed a promotional communication, a professional sales aid (US-68433), for BREZTRI AEROSPHERE™ (budesonide, glycopyrrolate, and formoterol fumarate) inhalation aerosol, for oral inhalation use (Breztri) submitted by AstraZeneca under cover of Form FDA 2253. The sales aid makes false or misleading claims and/or representations about the efficacy of Breztri. Thus, the sales aid misbrands Breztri within the meaning of the Federal Food, Drug, and Cosmetic Act (FD&C Act), and makes its distribution violative. 21 U.S.C. 352(a); 331(a). Cf. 21 CFR 202.1(e)(5). These violations are concerning from a public health perspective because the promotional communication creates a misleading impression regarding the overall benefits a patient may expect as a result of Breztri treatment.

Background

Below are the indication and summary of the most serious and most common risks associated with the use of Breztri.[1] According to the FDA-approved Prescribing Information (PI):

BREZTRI AEROSPHERE is indicated for the maintenance treatment of patients with chronic obstructive pulmonary disease (COPD).

Limitations of Use:

BREZTRI AEROSPHERE is not indicated for the relief of acute bronchospasm or for the treatment of asthma.

Breztri is contraindicated in patients who have demonstrated hypersensitivity to budesonide, glycopyrrolate, formoterol fumarate, or any of the excipients. The PI for Breztri includes the following Warnings and Precautions: serious asthma-related events—hospitalizations, intubations, and death; deterioration of disease and acute episodes; avoid excessive use of Breztri and avoid use with other long-acting beta2-agonists; oropharyngeal candidiasis; pneumonia; immunosuppression and risk of infections; transferring patients from systemic corticosteroid therapy; hypercorticism and adrenal suppression; drug interactions with strong cytochrome P450 3A4 inhibitors; paradoxical bronchospasm; hypersensitivity reactions including anaphylaxis; cardiovascular effects; reduction in bone mineral density; glaucoma and cataracts, worsening of narrow-angle glaucoma; worsening of urinary retention; coexisting conditions; and hypokalemia and hyperglycemia. The most common adverse reactions reported with use of Breztri are upper respiratory tract infection, pneumonia, back pain, oral candidiasis, influenza, muscle spasm, urinary tract infection, cough, sinusitis, and diarrhea.

False or Misleading Claims about Efficacy

Prescription drug advertisements and labeling (promotional communications) misbrand a drug if they are false or misleading with respect to efficacy. The determination of whether a promotional communication is misleading includes, among other things, not only representations made or suggested in the promotional communication, but also the extent to which the promotional communication fails to reveal facts material in light of the representations made or with respect to consequences that may result from the use of the drug as recommended or suggested in the promotional communication.

The sales aid includes the prominent headline claim (emphasis original), "**DIFFERENCE OBSERVED IN TIME TO ALL-CAUSE MORTALITY (OVER 52 WEEKS)**," in conjunction with a graph titled, "**SECONDARY ENDPOINT STUDY 1: Time to all-cause mortality in the ITT**

population," and the following claims (emphasis original):

- "**An observed relative difference with BREZTRI vs LAMA/LABA was shown in data published in 2020/2021, including in the *New England Journal of Medicine***"
- "**49% Observed relative difference with BREZTRI vs LAMA/LABA**"

These claims and presentation, in the context of a promotional communication describing the safety and efficacy of Breztri, are misleading because they suggest that Breztri treatment has been shown to have a positive impact on all-cause mortality (ACM) and reduce the risk of death in COPD patients. These suggestions are not supported by the cited references[2,3] that analyzed data from the Efficacy and Safety of Triple Therapy in Obstructive Lung Disease (ETHOS) trial. The ETHOS trial was designed with ACM as one of multiple secondary endpoints, and due to the failure of the study to show statistically significant results on endpoints higher in the analysis hierarchy, the trial does not allow for any conclusions to be drawn from the ACM data. In addition, as the ETHOS study design required removing patients from inhaled corticosteroids (ICS) prior to entering a treatment arm, abrupt withdrawal of ICS may have been a confounding factor when analyzing any positive effect on ACM. Due to the statistical testing hierarchy failure and to the fact that abrupt withdrawal of ICS may have been a confounding factor, no conclusions about the effect of Breztri on ACM can be drawn from the ETHOS trial. We note the statement below the graph, "These results are observational in nature, and any comparisons between treatment arms should be interpreted with caution." However, this does not mitigate the misleading impression. To date, no drug has been shown to improve ACM in COPD.[4] The results of the ETHOS trial do not exclude the possibility that the benefits in ACM claimed above may be attributable to

chance or to the withdrawal of ICS and not due to Breztri. These claims and presentation are concerning from a public health perspective because they overstate the efficacy of the drug and misleadingly suggest that Breztri will have a positive impact on ACM and reduce the risk of death in COPD patients.

The sales aid also includes the following claims (bolded emphasis original, underlined emphasis added):

- "In a 52-week study where patients had a history of exacerbations within the last year, **BREZTRI was the ONLY triple therapy vs ICS/LABA to show a significant reduction in severe exacerbations**"
- "**20% EXACERBATION REDUCTION VS ICS/LABA**[;] rate ratio: 0.80[;] *P=0.02*"

The presentation of these claims with the associated p-value creates a misleading impression regarding the benefit of the drug by suggesting that Breztri will have a statistically significant reduction in severe exacerbations. This suggestion is not supported by the ETHOS trial data analyzed in the cited reference[5] because the reduction in severe exacerbations was not statistically significant for patients treated with Breztri relative to comparator groups. A pvalue is generally understood to indicate statistical significance if it is less than 0.05. Therefore, the inclusion of a p-value of 0.02 in conjunction with the above presentation creates the impression that the reduction in severe exacerbations was statistically significant. However, for the Breztri to inhaled corticosteroid/long-acting beta agonist (ICS/LABA) comparison (i.e., "20% REDUCTION VS ICS/LABA"), the result was not statistically significant due to the p-value being greater than the significance threshold (critical value) established in the testing strategy. In the ETHOS trial[6] testing strategy the raw p-value of each hypothesis test was compared to the corresponding critical value to determine whether the test was statistically significant. As the p-value for the Breztri to ICS/LABA comparison (p=0.02) was greater than the critical value (0.008) for that hypothesis test, the result, per the threshold set by the testing strategy, is not statistically significant. Therefore, the presentation of these claims (i.e., with a p-value of 0.02) creates the misleading impression that Breztri provides a *statistically significant* reduction in severe exacerbations compared to ICS/LABA by 20% when this has not been demonstrated. We acknowledge the footnote, "*Based on predefined Type-1 error control plan" is included following these claims and related presentations. However, this does not mitigate the misleading impression. The presentation is concerning from a public health perspective because it overstates the efficacy of the drug and misleadingly represents that Breztri significantly reduces severe exacerbations.

Conclusion and Requested Action

For the reasons discussed above, the detail aid misbrands Breztri within the meaning of the FD&C Act and makes its distribution violative. 21 U.S.C. 352(a); 331(a). Cf. 21 CFR 202.1(e)(5).

This letter notifies you of our concerns and provides you with an opportunity to address them. OPDP requests that AstraZeneca cease any violations of the FD&C Act. Please submit a written response to this letter within 15 working days from the date of receipt, addressing the concerns described in this letter, listing all other promotional communications (with the 2253 submission date) for Breztri that contain representations such as those described above, and explaining any plan for discontinuing use of such communications, or for ceasing distribution of Breztri.

Failure to adequately address this matter may lead to regulatory action. If you believe that your products are not in violation of the FD&C Act, please include in your submission to us your reasoning and any supporting information for our consideration within 15 working days from the date of receipt of this letter.

Additionally, we request that your submission include a comprehensive plan of action to disseminate truthful, non-misleading, and complete corrective communication(s) about the concern(s) discussed in this letter. The corrective communication(s) should be disseminated to the audience(s) that received the promotional communication(s) identified in the opening paragraph of this letter. OPDP recommends that corrective communication(s) include a description of the promotional communication(s) identified in this letter, which

misbrand Breztri; include a summary of the concern(s) described in this letter; and provide information to correct each of these concern(s). Corrective communication(s) should be free of promotional claims and presentations. To the extent possible, corrective communication(s) should be distributed using the same media, and generally for the same duration of time and with the same frequency as the promotional communication(s) identified in the opening paragraph of this letter.

The concerns discussed in this letter do not necessarily constitute an exhaustive list of potential violations. It is your responsibility to ensure compliance with each applicable requirement of the FD&C Act and FDA implementing regulations.

Please direct your response to the undersigned at the **Food and Drug Administration, Center for Drug Evaluation and Research, Office of Prescription Drug Promotion, 5901-B Ammendale Road, Beltsville, Maryland 20705-1266**. A courtesy copy can be sent by facsimile to (301) 847-8444. Please refer to MA 385 in addition to the NDA number in all future correspondence relating to this particular matter. All correspondence should include a subject line that clearly identifies the submission as a Response to Warning Letter. You are encouraged, but not required, to submit your response in eCTD format. All correspondence submitted in response to this letter should be placed under eCTD Heading 1.15.1.6. Additionally, the response submission should be coded as an Amendment to eCTD Sequence 0454 under NDA 212122. Questions related to the submission of your response letter should be emailed to the OPDP RPM at CDER-OPDP-RPM@fda.hhs.gov.

Sincerely,
{See appended electronic signature page}
Twyla Mosey, Pharm.D.
Director
Division of Advertising & Promotion Review 2
Office of Prescription Drug Promotion

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/

MATTHEW J FALTER on behalf of TWYLA N MOSEY
08/04/2023 10:20:52 AM

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1 This information is for background purposes only and does not necessarily represent the risk information that should be included in the promotional communications cited in this letter.

2 Martinez FJ, Rabe KF, Ferguson GT, et al. Reduced all-cause mortality in the ETHOS trial of budesonide/glycopyrrolate/formoterol for COPD: a randomized, double-blind, multi-center, parallel-group study. Am J Respir Crit Care Med. 2021;203(5):553-564.

3 Rabe KF, Martinez FJ, Ferguson GT, et al. Triple inhaled therapy at two glucocorticoid doses in moderate-to-very severe COPD. N Engl J Med. 2020;383(1):35-48.

4 Through the issuance of this letter, FDA does not intend to convey any views on whether data that did show that Breztri improved ACM in COPD would support a change to the FDA-approved labeling for Breztri.

5 See FN3.

6 The ETHOS trial used a combination of hierarchical and Hochberg test procedures to control the overall Type I error among different endpoints and different doses.

PROMOTIONAL MATERIAL (/media/171157/download?attachment)

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