

**TRANSMITTED BY FACSIMILE**

Michael Castagna, PharmD, MBA
Chief Executive Officer
MannKind Corporation
One Casper Street
Danbury, CT 06810

RE: NDA 022472
AFREZZA® (insulin human) inhalation powder, for oral inhalation use
MA 439

WARNING LETTER

Dear Dr. Castagna:

The Office of Prescription Drug Promotion (OPDP) of the U.S. Food and Drug Administration (FDA) has reviewed a Facebook post (post) for AFREZZA® (insulin human) inhalation powder, for oral inhalation use (Afrezza) posted on on MannKind Corporation's (MannKind) Facebook page for Afrezza on February 9, 2018, and March 19, 2018.¹ The OPDP Bad Ad Program also received a complaint regarding posts on the Afrezza Facebook page. The post reviewed by OPDP makes false or misleading claims and/or representations about the risks associated with Afrezza by suggesting that there are no safety concerns associated with the use of the drug. Therefore, the post misbrands Afrezza within the meaning of the Federal Food, Drug and Cosmetic Act (FD&C Act), making its distribution violative. 21 U.S.C. 352(a), (n); 321(n), 331(a). See 21 CFR 202.1(e)(3); (e)(5). These violations are especially concerning from a public health perspective because Afrezza is a drug with multiple serious, potentially life-threatening risks, including a BOXED WARNING for the risk of acute bronchospasm in patients with chronic lung disease.

Background

Below are the indication and summary of the most serious and most common risks associated with the use of Afrezza.² According to the FDA-approved product labeling (PI):

AFREZZA is a rapid acting inhaled insulin indicated to improve glycemic control in adult patients with diabetes mellitus.

¹ Afrezza Facebook page, at <https://www.facebook.com/DiscoverAfrezza/photos/a.447839262229858.1073741828.442343219446129/600058867007896/?type=3> (Last accessed, July 17, 2018).

² This information is for background purposes only and does not necessarily represent the risk information that should be included in the promotional piece cited in this letter.

Limitations of Use:

- AFREZZA is not a substitute for long-acting insulin. AFREZZA must be used in combination with long-acting insulin in patients with type 1 diabetes mellitus.
- AFREZZA is not recommended for the treatment of diabetic ketoacidosis.
- The safety and efficacy of AFREZZA in patients who smoke has not been established. The use of AFREZZA is not recommended in patients who smoke or who have recently stopped smoking.

This product is associated with a number of serious risks. The PI for the drug contains a boxed warning for the risk of acute bronchospasm in patients with chronic lung disease. Afrezza is contraindicated during episodes of hypoglycemia; in patients with chronic lung disease, such as asthma or chronic obstructive pulmonary disease; and in patients with hypersensitivity to regular human insulin or any of the Afrezza excipients. The PI for Afrezza includes warnings and precautions regarding changes in insulin regimen, hypoglycemia, decline in pulmonary function, lung cancer, diabetic ketoacidosis, hypersensitivity reactions, hypokalemia, and fluid retention and heart failure with concomitant use of PPAR-gamma agonists. In addition, the most common adverse reactions associated with Afrezza are hypoglycemia, cough, and throat pain or irritation.

False or Misleading Risk Presentation

Promotional materials misbrand a drug if they are false or misleading with respect to risks or benefits. The determination of whether promotional materials are misleading includes, among other things, not only representations made or suggested in promotional materials, but also failure 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 materials.

The post includes the following claims and presentations (emphasis original):

- **“Afrezza Inhalation Powder”**
...
- “Insulin is not the bad guy. If your doctor is advising you start taking insulin it will help your body work its best and protect you from health complications.”
- “Type 2 diabetes
My body stopped making insulin. So I take insulin. No drama.” (Prominently presented in a white box with large bold text, superimposed over a photo with the image of a woman)

This post suggests that there are no risks associated with the use of the drug. Specifically, in the context of a promotional piece for Afrezza, the post claims that “Afrezza Inhalation Powder” “will help your body work its best and protect you from health complications” with “no drama,” when this may not be the case. As discussed in the Background section above,

Afrezza is associated with multiple serious, and potentially life-threatening risks, such as those contained in the product's BOXED WARNING. By suggesting that there are no risks associated with use of Afrezza, this post is misleading with respect to the drug's safety. We note the inclusion of the statement, "Please see full Prescribing Information, including boxed WARNING, Medication Guide, and Instructions for Use" with a link to the PI in the post. However, this statement does not mitigate the misleading impression from the claims in the post.

We also note that information regarding the risk of acute bronchospasm in patients with chronic lung disease appears together with Afrezza's indication in text format in a separate pop-up box that is visible when hovering a cursor over the thumbnail of the Afrezza logo in the top left corner of the post. However, presenting risk information for Afrezza in this manner does not mitigate the misleading impression from the claims in the post. Moreover, neither the post nor the pop-up box include information regarding two of the conditions for which Afrezza is contraindicated (i.e., during episodes of hypoglycemia and in patients with hypersensitivity to regular human insulin or any of the Afrezza excipients) nor any of the other warnings and precautions associated with the drug. This is especially problematic from a public health perspective given the multiple serious and potentially life-threatening risks associated with the drug.

Conclusion and Requested Action

For the reasons discussed above, the post misbrands Afrezza within the meaning of the FD&C Act and makes its distribution violative. 21 U.S.C. 352(a), (n); 321(n), 331(a). See 21 CFR 202.1(e)(3); (e)(5).

OPDP requests that MannKind immediately cease misbranding Afrezza and/or cease introducing the misbranded drug into interstate commerce. Please submit a written response to this letter on or before October 19, 2018, stating whether you intend to comply with this request, listing all promotional materials (with the 2253 submission date) for Afrezza that contain statements such as those described above, and explaining your plan for discontinuing use of such materials, or, in the alternative, for ceasing distribution of Afrezza. Because the violations described above are serious, we request, further, that your submission include a comprehensive plan of action to disseminate truthful, non-misleading, and complete corrective messages about the issues discussed in this letter to the audience(s) that received the violative promotional materials. In order to clearly identify the violative promotional piece(s) and/or activity and focus on the corrective message(s), OPDP recommends that corrective piece(s) include a description of the violative promotional piece(s) and/or activity, include a summary of the violative message(s), provide information to correct each of the violative message(s), and be free of promotional claims and presentations. To the extent possible, corrective messaging should be distributed using the same media, and generally for the same duration of time and with the same frequency that the violative promotional material was disseminated.

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 Amundson Avenue, Beltsville, Maryland 20705-1266**. A courtesy copy can be sent by facsimile to (301) 847-8444. To ensure timely delivery of your submissions, please use the

full address above and include a prominent directional notation (e.g., a sticker) to indicate that the submission is intended for OPDP. Please refer to MA 439 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. OPDP reminds you that only written communications are considered official.

The violations discussed in this letter do not necessarily constitute an exhaustive list. It is your responsibility to ensure that your promotional materials for Afrezza comply with each applicable requirement of the FD&C Act and FDA implementing regulations. If you believe that your products are not in violation of the FD&C Act, include your reasoning and any supporting information for our consideration.

Failure to correct the violations discussed above may result in FDA regulatory action, including seizure or injunction, without further notice.

Sincerely,

{See appended electronic signature page}

Robert Dean
Division 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/

ROBERT T DEAN
10/05/2018