DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

Nicole Van De Vaarst, Senior Manager
U.S. Commercial Regulatory Affairs, Bristol Myers Squibb
Karuna Therapeutics, Inc., a Bristol Myers Squibb Co.
3401 Princeton Pike
Lawrenceville, NJ 08648

RE: NDA 216158
COBENFY™ (xanomeline and trospium chloride) capsules, for oral use
MA 175

Dear Nicole Van De Vaarst:

The Office of Prescription Drug Promotion (OPDP) of the U.S. Food and Drug Administration (FDA) has reviewed the promotional communication, a direct-to-consumer broadcast advertisement (1629-US-2500690) (TV ad) for COBENFY™ (xanomeline and trospium chloride) capsules, for oral use (Cobenfy), submitted by Karuna Therapeutics, Inc., a Bristol Myers Squibb Co., under cover of Form FDA 2253. FDA has determined that the TV ad is false or misleading. Thus, the TV ad misbrands Cobenfy and makes the distribution of the drug in violation of the Federal Food, Drug, and Cosmetic Act (FD&C Act).

The TV ad begins with on-screen text of several schizophrenia symptoms appearing around the protagonist, Bryan, including, “Delusions”, “Disorganized thoughts”, “Voices”, “Lack of emotion”, “Low motivation”, and “Less social interaction.” Later, the TV ad includes the voiceover claim, “Cobenfy showed overall improvement across a range of schizophrenia symptoms . . .” in conjunction with the on-screen text (emphasis original), “**improvement** ACROSS A RANGE OF SYMPTOMS”, and an image of overlapping circles with the text (emphasis original), “POSITIVE SYMPTOMS” and “NEGATIVE SYMPTOMS.”

These claims and presentations create a misleading representation that treatment with Cobenfy will improve both the positive and negative symptoms of schizophrenia. However, the pivotal trials supporting the schizophrenia indication for Cobenfy were not designed to capture changes in positive or negative symptoms as distinct groups. According to the CLINICAL STUDIES section of the FDA-approved prescribing information (PI), “The primary efficacy measure was the change from baseline in the Positive and Negative Syndrome Scale (PANSS)[1] total score at Week 5.” Additionally, the pivotal trials for Cobenfy were not designed to evaluate the efficacy of the drug in treating negative symptoms because the patients in the studies were experiencing acute exacerbations of schizophrenia, which can confound the assessment of improvements in negative symptoms. Therefore, making representations that treatment with Cobenfy improves negative symptoms in patients with

[1] The PANSS is a 30-item scale that measures symptoms of schizophrenia. The PANSS total score may range from 30 to 210, with higher scores reflecting greater overall symptom severity.

schizophrenia is misleading. We acknowledge the SUPER, “In two 5-week clinical studies, a rating scale measured changes in schizophrenia symptoms overall versus a sugar pill in 470 adults. Individual results may vary.” However, inclusion of this statement does not mitigate the misleading representations or suggestions of efficacy in improving negative symptoms of schizophrenia with Cobenfy treatment.

In addition, the TV ad creates a misleading impression about the indication for Cobenfy. The TV ad includes the following claim in the voiceover, “If you still have symptoms, be bold and ask your healthcare provider about Cobenfy . . . .” This claim misleadingly suggests that Cobenfy has efficacy in treatment-refractory cases of schizophrenia, when this has not been demonstrated. The pivotal trials for Cobenfy were placebo-controlled studies that did not include an active comparator arm with another antipsychotic agent. We are not aware of any direct comparative efficacy data that could be used to support the implication that Cobenfy is effective when other antipsychotic treatments have failed. Furthermore, the pivotal studies did not specifically enroll a treatment-refractory population or patients with documented inadequate response to prior antipsychotic therapy. If you have data to support this claim, please submit them to FDA for review.

Moreover, the TV ad is misleading regarding the classification of Cobenfy. The TV ad includes the following claim in the voiceover, “Cobenfy is not an antipsychotic,” presented in conjunction with the on-screen text (emphasis original), “**not** an antipsychotic.” We acknowledge that the SUPER states, “A muscarinic agonist (xanomeline) and a muscarinic antagonist (trospium chloride)”. However, Cobenfy is considered a member of the antipsychotic drug class based on its therapeutic indication for treating schizophrenia and its effects on psychotic symptoms, not its mechanism of action.

The TV ad is also misleading because the compelling, attention-grabbing visuals (e.g., frequent camera angle changes showing Bryan skateboarding, greeting a friend, petting a dog, and setting up his DJ booth) during the presentation of the major statement interfere with comprehension of the major statement.

Conclusion and Requested Action

For the reasons described above, the TV ad misbrands Cobenfy and makes the distribution of the drug in violation of the FD&C Act.

This letter notifies you of our concerns and provides you with an opportunity to address them. FDA requests that Karuna Therapeutics, Inc., a Bristol Myers Squibb Co., take immediate action to address any violations (including, for example, ceasing and desisting promotional communications that are misleading as described above).

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 promotional communications (with the 2253 submission date) for Cobenfy that contain representations like those described above, and explaining your plan for the discontinuation of such communications, or for ceasing distribution of Cobenfy.

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.

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 175 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 Untitled 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 5174 under NDA 216158. Questions related to the submission of your response letter should be emailed to CDER-OPDP-RPM@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Emily Foltz, PharmD, RPh
Regulatory Review Officer
Division of Advertising & Promotion Review 1
Office of Prescription Drug Promotion

{See appended electronic signature page}

Taylor Burnett Mmagu, PharmD, RAC
Team Leader
Division of Advertising & Promotion Review 1
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/

EMILY M FOLTZ
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TAYLOR B BURNETT MMAGU
12/15/2025 12:07:58 PM