DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

Daniel Bigelow
Director, Regulatory Affairs
Axsome Therapeutics, Inc.
One World Trade Center, 22nd Floor
New York, NY 10007

RE: NDA 215430
AUVELITY® (dextromethorphan hydrobromide and bupropion hydrochloride) extended-release tablets, for oral use
MA 148

Dear Daniel Bigelow:

The U.S. Food and Drug Administration (FDA) has reviewed the promotional communication, a direct to consumer (DTC) print advertisement (PP-AUV-US-2400051) (print ad) for AUVELITY® (dextromethorphan hydrobromide and bupropion hydrochloride) extended-release tablets, for oral use (Auvelity) submitted by Axsome Therapeutics, Inc. (Axsome) under cover of Form FDA 2253. FDA has determined that the print ad is false or misleading. Thus, the print ad misbrands Auvelity and makes the distribution of the drug in violation of the Federal Food, Drug, and Cosmetic Act (FD&C Act).

The print ad includes the following claims and presentations (in pertinent part, emphasis original, footnotes omitted):

> "**Do you ever feel a bit "meh"?"**
>
> "Not experiencing the same joy or pleasure in the things you used to **could be a major symptom of depression, called anhedonia."**
>
> **"~75% of people with depression** may experience lingering effects of anhedonia, even on treatment" preceded by a prominent graphic of a pie chart depicting a corresponding percentage.
>
> **"In a review of an AUVELITY study:"**
> **"People taking Auvelity experienced a greater reduction in their anhedonia scores** over 6 weeks vs placebo" preceded by a prominent graphic of a yellow arrow pointing down.
>
> **"More people taking AUVELITY achieved a 50% or greater improvement in their anhedonia scores** over 6 weeks vs placebo" preceded by a prominent graphic of a white arrow pointing up.

These claims and presentations, which appear next to an image of a woman smiling and appearing happy and joyous, create a misleading representation that treatment with Auvelity will provide a specific benefit of improving symptoms of anhedonia in patients with MDD, allowing patients to feel pleasure and joy, when this benefit has not been demonstrated. Axsome points to results from a 6-week post hoc analysis evaluating the effect of Auvelity vs. placebo in improving anhedonic symptoms in 327 adult patients with MDD to support their representation. This post hoc analysis utilized an "anhedonia rating sub-scale" to assess improvement in anhedonia, which is described in the footnotes to the above claims, as including five items: apparent sadness, reported sadness, concentration difficulties, physical or mental weariness, and inability to feel. These 5 items are a subset of the 10-item Montgomery-Åsberg Depression Rating Scale (MADRS). The MADRS is an instrument that is validated for use for the assessment of severity of symptoms of major depressive disorder (MDD). The change from baseline to Week 6 in the total score of the MADRS was the primary endpoint in the pivotal trials supporting the approval of Auvelity for the treatment of MDD.

However, the pivotal trials supporting the MDD indication for Auvelity were not designed to capture changes in anhedonia. In addition, there are significant limitations to this post hoc analysis where 5 of the 10 items of the MADRS were used to create an "anhedonia rating sub-scale" that would preclude the drawing of any conclusions regarding treatment of Auvelity resulting in improvement in anhedonia in patients with MDD. First, the "anhedonia rating sub-scale" is not validated to assess the efficacy of Auvelity in the treatment of anhedonia. Second, this analysis was conducted post hoc and there was no prespecified statistical procedure controlling for type 1 error, so it is not possible to ascertain whether the findings from the analysis were attributable to treatment with Auvelity or merely due to chance. As a result, these findings are exploratory (hypothesis-generating). Moreover, most of the items selected for the "anhedonia rating sub-scale" do not actually assess changes in anhedonia, and the subscale does not reflect the entire concept of anhedonia. Therefore, drawing conclusions or making representations that treatment with Auvelity improves anhedonia in patients with MDD based on this analysis of the five-item subset of the MADRS is misleading.

We acknowledge the inclusion of the statement, "The data was reviewed after the conclusion of a 6-week trial of AUVELITY; the results could have occurred at random because the review of anhedonia data was not planned at the start of the study" relegated below the representations described above. However, inclusion of this statement in this promotional communication does not correct or mitigate the misleading representations or suggestions of efficacy in improving anhedonia with Auvelity treatment.

Conclusion and Requested Action

For the reasons described above, the print ad misbrands Auvelity and makes the distribution of the drug in violation of the Federal Food, Drug, and Cosmetic Act (FD&C Act).

This letter notifies you of our concerns and provides you with an opportunity to address them. FDA requests that Axsome 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 Auvelity that contain representations like those described above, and explaining your plan for the discontinuation of such communications, or for ceasing distribution of Auvelity.

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 **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 148 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 0233 under NDA 215430. 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}

George Tidmarsh, M.D., Ph.D.
Director
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/

CARTER M BEACH
09/09/2025 05:09:46 PM
On behalf of George Tidmarsh, M.D., Ph.D