NDA 215430

NDA APPROVAL

Axsome Therapeutics, Inc.
Attention: Daniel Bigelow
Associate Director, Regulatory Affairs
22 Cortlandt St, 16th Floor
New York, NY 10007

Dear Mr. Bigelow:

Please refer to your new drug application (NDA) dated February 21, 2021, received February 22, 2021, and your amendments, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Auvelity (dextromethorphan hydrobromide and bupropion hydrochloride) extended-release tablets.

This NDA provides for the use of Auvelity (dextromethorphan hydrobromide and bupropion hydrochloride) extended-release tablets for the treatment of major depressive disorder (MDD) in adults.

APPROVAL & LABELING

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at FDA.gov.[1] Content of labeling must be identical to the enclosed labeling (text for the Prescribing Information and Medication Guide) as well as annual reportable changes not included in the enclosed labeling. Information on submitting SPL files using eLIST may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As.*[2]

The SPL will be accessible via publicly available labeling repositories.

[1] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm
[2] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

CARTON AND CONTAINER LABELING

We acknowledge your August 7, 2022, submission containing final printed carton and container labeling.

DATING PERIOD

Based on the stability data submitted to date, the expiry dating period for Auvelity (dextromethorphan hydrobromide and bupropion hydrochloride) extended-release tablets shall be 6 months from the date of manufacture when stored at 25 °C.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric studies requirement for ages ≤6 years old years because necessary studies are impossible or highly impracticable. A study in this age group would be impractical because of the rarity of the diagnosis of MDD in this patient population.

We are deferring submission of your pediatric studies for ages 7 to 12 years and adolescents aged 13 to 17 for this application because pediatric studies should be delayed until additional safety or effectiveness data have been collected and a juvenile animal study is completed.

Your deferred pediatric studies required by section 505B(a) of the Federal Food, Drug, and Cosmetic Act/FDCA are required postmarketing studies. The status of these postmarketing studies must be reported annually according to 21 CFR 314.81 and section 505B(a)(4)(C) of the Federal Food, Drug, and Cosmetic Act/FDCA. These required studies are listed below.

4233-1 Conduct a juvenile animal study to assess the safety of AXS-05 in animals of an age range and stage of development that are comparable to the population of children aged 7 to 12 years.

Final Protocol Submission:	05/2022
Study Completion:	04/2023
Final Report Submission:	06/2023

4233-2 Evaluate the pharmacokinetics, efficacy, and safety of AXS-05 in pediatric patients aged 7 to 17 years with MDD.

Final Protocol Submission:	05/2023
Study Completion:	11/2025
Final Report Submission:	05/2026

4233-3 Conduct a 1-year, open-label safety study in pediatric patients aged 7 to 17 years with MDD.

Final Protocol Submission:	05/2023
Study Completion:	11/2026
Final Report Submission:	05/2027

FDA considers the term *final* to mean that the applicant has submitted a protocol, the FDA review team has sent comments to the applicant, and the protocol has been revised as needed to meet the goal of the study or clinical trial.[3]

Submit the protocol(s) to your IND 124813, with a cross-reference letter to this NDA. Reports of these required pediatric postmarketing studies must be submitted as an NDA or as a supplement to your approved NDA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission "**SUBMISSION OF REQUIRED PEDIATRIC ASSESSMENTS**" in large font, bolded type at the beginning of the cover letter of the submission.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess risks to patients with severe renal or hepatic impairment, to assess risks during embryogenesis and early post-natal development, and to assess the carcinogenic potential of AXS-05. Furthermore, the active postmarket risk identification and analysis system as available under section 505(k)(3) of the FDCA will not be sufficient to assess these serious risks.

[3] See the guidance for Industry *Postmarketing Studies and Clinical Trials—Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (October 2019).* https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following studies:

4233-4 Evaluate the effect of severe renal impairment on the pharmacokinetics of AXS-05.

Final Protocol Submission:	10/2022
Study Completion:	04/2023
Final Report Submission:	10/2023

4233-5 Evaluate the effect of severe hepatic impairment on the pharmacokinetics of AXS-05.

Final Protocol Submission:	10/2022
Study Completion:	04/2023
Final Report Submission:	10/2023

4233-6 Perform a lactation study (milk only) in lactating women who have received AXS-05 to assess concentrations of dextromethorphan and its metabolites in breast milk using a validated assay. A mother-infant pair study may be required in the future depending on the results of this milk-only study.

Final Protocol Submission:	03/2023
Study Completion:	09/2024
Final Report Submission:	03/2025

4233-7 Conduct an embryofetal toxicity study of AXS-05 in rabbits.

Final Report Submission:	06/2023

4233-8 Conduct a fertility and early embryonic developmental study to address the effect of AXS-05 on fertility.

Final Report Submission:	06/2023

4233-9 Conduct a pre- and postnatal developmental study to address the effect of AXS-05 on embryonic and post-natal development.

Final Report Submission:	12/2023

4233-10 Conduct carcinogenicity studies to address the carcinogenic potential of AXS-05.

Final Report Submission:	05/2025

4233-11 Conduct a study to address the neurotoxic potential of dextromethorphan using animals of an age range and stage of development that are comparable to the third trimester of gestation through the first several months of life but possibly extend to approximately three years of age in humans.

Final Report Submission: 02/2023

FDA considers the term *final* to mean that the applicant has submitted a protocol, the FDA review team has sent comments to the applicant, and the protocol has been revised as needed to meet the goal of the study or clinical trial.[4]

Submit clinical protocol(s) to your IND 124813, with a cross-reference letter to this NDA. Submit nonclinical and chemistry, manufacturing, and controls protocols and all final report(s) to your NDA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: **Required Postmarketing Protocol Under 505(o), Required Postmarketing Final Report Under 505(o), Required Postmarketing Correspondence Under 505(o).**

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

[4] See the guidance for Industry *Postmarketing Studies and Clinical Trials—Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (October 2019).* https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

4233-12 Conduct a bupropion-controlled, randomized withdrawal study to demonstrate whether the dextromethorphan component of AXS-05 contributes to the long-term efficacy of AXS-05 for the treatment of MDD.

Final Protocol Submission:	09/2022
Study Completion:	01/2024
Final Report Submission:	04/2024

4233-13 Develop and validate an optimized dissolution method for each of the two components (i.e., extended-release bupropion HCl and immediate-release dextromethorphan HBr) in AXS-05 Extended-Release Tablets, a fixed-dose combination (FDC) product.

Submit the proposed dissolution acceptance criteria for AXS-05 Extended-Release Tablets, based on the data generated from unexpired clinical and registration batches, and the first six commercial batches, using the new dissolution method(s).

Interim Report Submission:	01/2023
Final Report Submission:	04/2023

Submit clinical protocols to your IND 124813 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii) you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients/subjects entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled "**Postmarketing Commitment Protocol**," "**Postmarketing Commitment Final Report**," **or** "**Postmarketing Commitment Correspondence**."

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. For information about submitting promotional materials, see the final guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format—Promotional Labeling and Advertising Materials for Human Prescription Drugs.*[5]

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the Prescribing Information, at the time of initial dissemination or publication,

[5] For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/media/128163/download.

accompanied by a Form FDA 2253. Form FDA 2253 is available at FDA.gov.[6] Information and Instructions for completing the form can be found at FDA.gov.[7]

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, please email Simran Parihar, PharmD, at simran.parihar@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Tiffany R. Farchione, MD
Director
Division of Psychiatry
Office of Neuroscience
Center for Drug Evaluation and Research

ENCLOSURES:

- Content of Labeling
  - Prescribing Information
  - Medication Guide
- Carton and Container Labeling

[6] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf
[7] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf

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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.

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