NDA 215431

CORRECTED
NDA APPROVAL

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

Dear Daniel Bigelow:

Please refer to your new drug application (NDA) dated and received June 30, 2021, and your amendments, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Symbravo (meloxicam and rizatriptan) tablets.

We also refer to our letter dated January 30, 2025. That letter contained the following errors in the Prescribing Information:

1. Section 14, Study 1, Figure 2: The line representing the meloxicam data was previously tracking the placebo data, rather than the meloxicam data for MBS. The revised figure corrects this to show the meloxicam line with the correct trajectory.
2. Section 14, Study 1, in the text below Figure 2: The original language states that the incidence of symptom freedom was reduced with Symbravo, however it is meant to say that the incidence of each symptom was reduced with Symbravo. Removing the word "freedom" corrects this.
3. Section 14, Study 2, in the text below Figure 4: Same as above.

This corrected letter incorporates the enclosures with the correction of the error.

The effective date will remain January 30, 2025, the date of the original letter.

We acknowledge receipt of your amendment dated July 31, 2024, which constituted a complete response to our action letter dated April 29, 2022.

This NDA provides for the use of Symbravo (meloxicam and rizatriptan) for the acute treatment of migraine with or without aura 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.

WAIVER OF ½ PAGE LENGTH REQUIREMENT FOR HIGHLIGHTS

We are waiving the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of Prescribing Information. This waiver applies to all future supplements containing revised labeling unless we notify you otherwise.

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.

CARTON AND CONTAINER LABELING

Submit final printed carton and container labeling that are identical to the carton and container labeling submitted on November 27, 2024, as soon as they are available, but no more than 30 days after they are printed. Please submit these labeling electronically according to the guidance for industry *SPL Standard for Content of Labeling Technical Qs & As.* For administrative purposes, designate this submission "**Final Printed Carton and Container Labeling for approved NDA 215431**." Approval of this submission by FDA is not required before the labeling is used.

[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.

DATING PERIOD

Based on the stability data submitted to date, the expiry dating period for Symbravo (meloxicam and rizatriptan) tablets shall be six (6) months from the date of manufacture when stored at 20°C to 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 children 0 to 5 years of age because necessary studies are impossible or highly impracticable. This waiver is being granted because very few children of this age can be definitively diagnosed with migraine.

We are deferring submission of your pediatric studies for children 6 to 17 years of age for this application because this product is ready for approval for use in adults and the pediatric studies have not been completed.

Your deferred pediatric studies required by section 505B(a) of the Federal Food, Drug, and Cosmetic Act are required postmarketing studies. The status of these postmarketing studies must be reported annually, according to 21 CFR 314.81 and section 505B(a)(3)(B) of the Federal Food, Drug, and Cosmetic Act. These required studies are listed below:

4782-1 A randomized, double-blind, placebo-controlled efficacy and safety study to evaluate Symbravo for the acute treatment of migraine in pediatric patients ages 6 to less than 18 years. This study should include an initial blinded placebo run-in period to identify placebo nonresponders for enrollment into the efficacy portion of the study. This efficacy study must be designed to show superiority of Symbravo over placebo.

Draft Protocol Submission:	02/2026
Final Protocol Submission:	08/2026
Study Completion:	02/2028
Final Report Submission:	08/2029

4782-2 A long-term open-label safety study in pediatric patients ages 6 years to less than 18 years. The long-term safety study must provide a descriptive analysis of safety data in at least 200 pediatric patients treated with Symbravo for a duration of at least 6 months and 75 pediatric patients treated with Symbravo for 12 months, treating on average at least one migraine attack per month, at doses evaluated in the efficacy study.

Draft Protocol Submission:	02/2026
Final Protocol Submission:	08/2026
Study Completion:	02/2029
Final Report Submission:	08/2029

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 identify an unexpected serious risk of adverse maternal, fetal, and infant outcomes resulting from the use of Symbravo during pregnancy.

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.

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

4782-3 A prospective pregnancy exposure registry cohort study in the United States that compares the maternal, fetal, and infant outcomes of women with migraine exposed to Symbravo during pregnancy with two unexposed control populations: one consisting of women with migraine who have not been exposed to Symbravo before and during pregnancy and the other consisting of women without migraine. The registry will identify and record pregnancy complications, major and minor congenital malformations, spontaneous abortions, stillbirths, elective terminations, preterm births, small-for-gestational-age births, and any other adverse outcomes, including postnatal growth and development. Outcomes

will be assessed throughout pregnancy. Infant outcomes, including effects on postnatal growth and development, will be assessed through at least the first year of life.

The timetable you submitted January 9, 2025, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	09/2025
Final Protocol Submission:	09/2026
Interim Report Submissions:	11/2029
	11/2033
	11/2036
Study Completion:	09/2039
Final Report Submission:	09/2040

4782-4 A pregnancy outcomes study using a different study design than provided for in PMR 4782-3 (for example, a retrospective cohort study using claims or electronic medical record data with outcome validation or a case-control study) to assess pregnancy complications, major congenital malformations, spontaneous abortions, stillbirths, preterm births, and small-for-gestational-age births in women exposed to Symbravo during pregnancy compared to an unexposed control population.

Draft Protocol Submission:	09/2025
Final Protocol Submission:	09/2026
Interim Report Submission:	09/2029
Study Completion:	09/2033
Final Report Submission:	09/2034

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 clinical protocol(s) to your IND 135972 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**

[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.

POSTMARKETING FINAL REPORT UNDER 505(o), REQUIRED POSTMARKETING CORRESPONDENCE UNDER 505(o).

Submission of the protocol(s) for required postmarketing observational studies to your IND is for purposes of administrative tracking only. These studies do not constitute clinical investigations pursuant to 21 CFR 312.3(b) and therefore are not subject to the IND requirements under 21 CFR part 312.

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(a)(1) 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(a)(1) and 21 CFR 314.81(b)(2)(vii) to 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.

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.*[4]

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, accompanied by a Form FDA 2253. Form FDA 2253 is available at FDA.gov.[5] Information and Instructions for completing the form can be found at FDA.gov.[6]

[4] For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/media/128163/download.
[5] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf
[6] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf

REPORTING REQUIREMENTS

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

COMPENDIAL STANDARDS

A drug with a name recognized in the official United States Pharmacopeia or official National Formulary (USP-NF) generally must comply with the compendial standards for strength, quality, and purity, unless the difference in strength, quality, or purity is plainly stated on its label (see FD&C Act § 501(b), 21 USC 351(b)). FDA typically cannot share application-specific information contained in submitted regulatory filings with third parties, which includes USP-NF. To help ensure that a drug continues to comply with compendial standards, application holders may work directly with USP-NF to revise official USP monographs. More information on the USP-NF is available on USP's website[7].

If you have any questions, contact Lana Chen, Regulatory Project Manager, at lana.chen@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Paul R. Lee, MD, PhD, MA
Director (Acting)
Division of Neurology 2
Office of Neuroscience
Center for Drug Evaluation and Research

ENCLOSURES

- Content of Labeling
  - Prescribing Information
  - Medication Guide

[7] https://www.uspnf.com/

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/

PAUL R LEE
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