CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

215431Orig1s000

OTHER ACTION LETTERS

NDA 215431

COMPLETE RESPONSE

Axsome Therapeutics, Inc.
Attention: Amanda Jones, PharmD
22 Cortlandt St
16th Floor
New York, NY 10007

Dear Dr. Jones:

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

We have completed our review of this application, as amended, and have determined that we cannot approve this application in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

PRODUCT QUALITY

Drug Product

1. As you committed in the response dated March 1, 2022, develop validated sensitive methods to demonstrate the levels of any potential (b) (4) (b) (4) including those provided in FDA Comment 1 dated January 21, 2022, will not exceed the acceptable safety levels, and analyze the registration and process validation batches of AXS-07 drug product using these methods, and to continue to monitor such (b) (4) to the end of the stability studies for these batches.

2. An acceptance criterion of not more than (NMT) (b) (4) % for rizatriptan N-oxide in your release and stability specification of drug product is not acceptable. Tighten it to NMT 0.5% consistent with the ICH Q3B (R) qualification threshold and USP Rizatriptan Benzoate Tablet monograph. Alternatively, submit adequate safety data to qualify a higher limit for the N-oxide impurity. If such data are not available, perform the appropriate nonclinical studies to support your proposed limit; for a chronic indication, the general toxicity study should be of 3 months' duration.

3. Since you have failed in accelerated studies and intermediate stability studies for the drug product, perform statistical analysis to determine the shelf-life of the product per ICH Q1E.

4. Provide tabulated stability protocols for validation batches (manufactured at commercial scale and in commercial packaging), post-approval batches and annual batches. The stability protocol for the first commercial batches should include testing under ICH intermediate and accelerated conditions.

5. We acknowledge that you provided the ASTM statistics data for (b) (4) (b) (4) for the 3 registration batches in the response dated February 23, 2022 (Seq 0012). We notice that for Meloxicam, 2 of 3 batches failed (b) (4) (b) (4) ASTM statistics test, whereas for the 3rd batch the number of sampling points was not enough to perform the statistics test due to (b) (4) (b) (4) Therefore, none of the 3 batches would be considered passing (b) (4) ASTM statistics test. Since the registration batches failed (b) (4) test, they cannot simulate a viable commercial process. We also observe the (b) (4) varies between the registration batches. We recommend you manufacture three (3) new registration batches with acceptable (b) (4) and repeat the primary stability studies. (b) (4)

6. Include (b) (4) in both release and stability specification to show that there is no (b) (4) for meloxicam (b) (4) and rizatriptan benzoate during storage of drug product or provide justification for not including this test.

Process

1. In the amendment submitted on February 23, 2022, the commercial batch size for meloxicam (b) (4) was proposed to increase from (b) (4) kg to (b) (4) kg. We acknowledge you updated the batch formula for meloxicam (b) (4) in Section 1.11. Include the batch formula for meloxicam (b) (4) in Module 3.2.P.3.2. In addition, update the commercial batch record for meloxicam (b) (4) manufacturing to reflect the increased commercial batch size, in-process tests performed at (b) (4) site and proposed hold times for all process intermediates and final meloxicam (b) (4)

2. Address the following comments for meloxicam (b) (4) process and update Module 3.2.P.3.3 and Module 3.2.P.3.4 accordingly.
   a. (b) (4)

b. [redacted]

c. [redacted]

3. We acknowledge you agreed to [redacted]

4. We acknowledge you provided the dissolution profiles for both feasibility batch CDTCN and scale-up feasibility batch CFGBW to support your proposed upper limit of tablet hardness ([redacted]kp). However, the dissolution medium [redacted] used for supporting the upper limit of the hardness is different from the proposed dissolution medium [redacted] for drug product release testing. We recommend you provide the dissolution study data obtained using the same dissolution method as that proposed for DP release testing to support your proposed hardness range ([redacted]kp with target [redacted]kp). Note that the data from failed registration batches cannot be used to support your proposed hardness range.

5. In the amendment submitted on February 23, 2022, you proposed mitigation strategy to [redacted]

[redacted] (b) (4) Update the commercial batch records accordingly and address the following comments.

a. [redacted] (b) (4)

b.

c.

d.

6. We acknowledge you [redacted] (b) (4) (b) (4)

7. We acknowledge you established the [redacted] (b) (4) (b) (4)

(b) (4)
.

8. We acknowledge you confirmed there is no change for the proposed (b) (4)
(b) (4)

Biopharmaceutics

1. For the fixed-dose combinational (FDC) drug products, the Agency typically recommends the development of separate/different dissolution methods for each of the two drug substances (or API) unless a single method can be satisfactorily demonstrated to be suitable and discriminating for the drug substances. Given that, we do not consider that you have adequately justified the selection of (b) (4)
(b) (4)
(b) (4) for the proposed single dissolution method. Specifically,

   - While we acknowledge the demonstrated improvement in (b) (4)
(b) (4)

   - Based on the provided information and data, we do not believe that the use of (b) (4) for dissolution testing is justified. Please note that in principle, the Agency does not recommend the use of (b) (4) without appropriate justifications and supporting evidence. In addition, you reported that (b) (4)
Based on the provided information and data/figures in your responses to the

Information Request (dated 02/18/2022), you should explore the utility of (b) (4) (b) (4)

- We do not consider the reported investigation of discriminating ability of the proposed dissolution method being appropriately performed. While the Agency typically recommends ±10% range for the study, you should provide adequately justifications for the relevant or meaningful ranges of the critical material attributes (CMA) or critical process parameters (CPP) in the aberrant formulations tested.

2. The originally proposed acceptance criterion of (b) (4) (b) (4) as quality control for both meloxicam and rizatriptan is permissive based on the submitted dissolution profile data from the (b) (4) batches. Note that all the batches of the proposed product exhibited rapidly dissolving profiles with (b) (4) In your resubmission, you should submit study report for the method development and generate complete dissolution profile data (n=12) of biobatch/registration batches and stability batches using the final selected dissolution method(s) for both drug substances. In addition, you should propose a new set of acceptance criterion for each drug substance based on the biobatch/registration batches. The acceptance criterion should be set based on the time-point where (b) (4)% of the dissolution occurs.

NONCLINICAL

1. To support the safety of meloxicam in AXS-07, you rely on FDA's finding of safety for Anjeso (meloxicam injection) and a completed 13-week oral toxicity study in minipig (AXS007-TP002). You propose AXS-07 for chronic use; however, Anjeso is not approved for chronic use. Therefore, you will need to provide information to support the safety of meloxicam for chronic use. Approaches for providing such information include relying on FDA's findings of safety for a listed drug that contains meloxicam for chronic use, providing the information by right-of-reference, or by submitting 6- and 9-month oral toxicity studies of meloxicam in rodent and nonrodent, respectively.

PRESCRIBING INFORMATION

We reserve comment on the proposed labeling until the application is otherwise adequate. We encourage you to review the labeling review resources on the Prescription Drug Labeling Resources[1] and Pregnancy and Lactation Labeling Final Rule[2] websites, including regulations and related guidance documents and the Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances.

CARTON AND CONTAINER LABELING

The following are draft carton and container labeling comments which should be addressed in any subsequent application:

Identified Issues and Recommendations for Axsome Therapeutics, Inc.			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Container Labels (Trade and Professional Sample)			
1.	We note a hyphen "-" is used between the two active ingredients.	This format is not in alignment with the USP nomenclature guidelines available from https://www.usp.org/sites/default/files/usp/document/usp-nomenclature-guidelines.pdf The hyphen mark "-" in "meloxicam and rizatriptan" could lead to misinterpretation of the tablet contents.	We recommend replacing the hyphen symbol between the two ingredients with the word "and" throughout the labels as follows: "meloxicam and rizatriptan"
2.	The finished dosage form "tablet" is stated after the strength statement on the same line.	The layout of the finished dosage form is not consistent with the presentation of the proprietary name, established name, dosage	We recommend relocating the dosage form on the same line or directly below the established name. For example: Symbravo

Appears this way on original

[1] https://www.fda.gov/drugs/laws-acts-and-rules/prescription-drug-labeling-resources
[2] https://www.fda.gov/drugs/labeling-information-drug-products/pregnancy-and-lactation-labeling-drugs-final-rule

		form, and strength for drug products. See *Draft Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors* (lines 336-342) available from: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf.	(meloxicam and rizatriptan) tablet 20 mg/10mg OR **Symbravo** (meloxicam and rizatriptan) tablet 20 mg/10mg Also refer to comment number one directly above.
3.	The prominence of the product strength expression can be improved to increase readability.	Product strength is critical information and should be prominent on the principal display panel per our *Draft Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors* available from: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf.	Ensure the product strength is prominent, taking into account all pertinent factors, including typography, layout, contrast, and other printing features. For example, you may consider increasing the font size, using a bolder font or different font color or background color or by other means to increase the prominence and readability of the strength.
4.	The recommended dosage statement can be improved.	To ensure consistency with the prescribing information and across the container labels.	We recommend revising the statement, (b) (4) to read "Recommended Dosage: See prescribing information."
5.	The Medication Guide statement can be improved.	The Medication Guide provides information that is necessary to patients' safe and effective use of the product. Per 21 CFR	We recommend revising the Medication Guide statement (b) (4) (b) (4) to "Attention: Dispense

		208.24(d), the label shall instruct the authorized dispenser to provide a Medication Guide to each patient and shall state how the Medication Guide is provided.	the accompanying Medication Guide to each patient."
6.	The contents statement ("Each tablet contains…") does not include the salt equivalency statement for the active moiety, rizatriptan.	This does not align with the *Guidance for Industry Naming of Drug Products Containing Salt Drug Substances* available from: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM379753.pdf	We recommend revising the statement (b) (4) to read "Each tablet contains 20 mg meloxicam and 10 mg rizatriptan (equivalent to 14.5 mg rizatriptan benzoate)."
7.	We note container labels states that this product should be stored "in its original bottle." However, there is no statement on the container labels directing the pharmacist whether to dispense this product in the original bottle or another specific type of container.	Per 21 CFR 201.100 (b)(7), the label should bear "A statement directed to the pharmacist specifying the type of container to be used in dispensing the drug product to maintain its identity, strength, quality, and purity."	Please clarify the intent of the storage statement. If there is a specific reason this product should be dispensed (and therefore stored by the intended user [e.g., patient or caregiver]) in a specific type of container (e.g., its original container, or a tight, light-resistant container), then include this information on the labels and labeling.
Container Label (Trade)			
1.	The proposed format for the expiration date (YYYY-MM) does not specify whether the month (MM) will be displayed using numerical (for example, 06), or alphabetical (for	We are concerned that the current presentation of the expiration date on the commercial container label may cause confusion. For example, presentation of the month as 'MM' in alphabetical characters	Identify the expiration format you intend to use. FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-

	example, JU) characters.	does not clearly communicate whether 'MA' or 'JU' is for the months of March or May and the months of June or July, respectively. Therefore, we are unable to assess the expiration date format from a medication safety perspective, which may increase the risk for deteriorated drug medication errors.	MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or a space be used to separate the portions of the expiration date.
2.	The undefined placeholder (XXXXXXXXXX) may be located too close to the machine readable (2D data matrix) barcode.	The close proximity of an undefined code near the 2D data matrix barcode may lead to confusion or affect the scanability of the barcode due to lack of whitespace around the barcode.	Please provide the purpose of the undefined code (XXXXXXXXXX) located near the 2D data matrix barcode and ensure it does not affect users' ability to scan the barcode.
Container Label (Professional Sample)			
1.	The purpose of the placeholder (XXXXXXXXXX) located near the expiration date and lot number is unclear.	The close proximity of an undefined code near expiration date and lot number may lead to confusion.	Please provide the purpose of the undefined code (XXXXXXXXXX) located next to the expiration date and lot number statements.

PROPRIETARY NAME

Please refer to correspondence dated, March 10, 2022, which addresses the proposed proprietary name Symbravo. This name was found acceptable pending approval of the

application in the current review cycle. Please resubmit the proposed proprietary name when you respond to the application deficiencies.

SAFETY UPDATE

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(*b*). The safety update should include data from all nonclinical and clinical studies/trials of the drug under consideration regardless of indication, dosage form, or dose level.

(1) Describe in detail any significant changes or findings in the safety profile.

(2) When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

- Present new safety data from the studies/clinical trials for the proposed indication using the same format as in the original submission.
- Present tabulations of the new safety data combined with the original application data.
- Include tables that compare frequencies of adverse events in the original application with the retabulated frequencies described in the bullet above.
- For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

(3) Present a retabulation of the reasons for premature trial discontinuation by incorporating the drop-outs from the newly completed trials. Describe any new trends or patterns identified.

(4) Provide case report forms and narrative summaries for each subject who died during a clinical trial or who did not complete a trial because of an adverse event. In addition, provide narrative summaries for serious adverse events.

(5) Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original application data.

(6) Provide updated exposure information for the clinical studies/trials (e.g., number of subjects, person time).

(7) Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.

(8) Provide English translations of current approved foreign labeling not previously submitted.

OTHER

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 314.110. If you do not take one of these actions, we may consider your lack of response a request to withdraw the application under 21 CFR 314.65. You may also request an extension of time in which to resubmit the application.

A resubmission must fully address all the deficiencies listed in this letter and should be clearly marked with "**RESUBMISSION**" in large font, bolded type at the beginning of the cover letter of the submission. The cover letter should clearly state that you consider this resubmission a complete response to the deficiencies outlined in this letter. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

You may request a meeting or teleconference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the draft guidance for industry *Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products*

The drug product may not be legally marketed until you have been notified in writing that this application is approved.

If you have any questions, call Lana Chen, Regulatory Project Manager, at (301) 796-1056.

Sincerely,

{See appended electronic signature page}

Nick Kozauer, MD
Director
Division of Neurology 2
Office of Neuroscience
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/

NICHOLAS A KOZAUER
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