CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

215431Orig1s000

OTHER REVIEW(S)

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research | Office of Surveillance and Epidemiology (OSE)
ARIA Sufficiency Memorandum for Pregnancy Safety Concerns
Version: 2024-09-13

Date:	January 21, 2025
Product Name(s):	Symbravo (meloxicam/rizatriptan)
Application Type/Number(s):	NDA 215431
Sponsor/Applicant:	Axsome Therapeutics, Inc.
NEXUS Task Tracking Tool ID #:	2024-11478
Reviewer(s):	Kieran Maroney, PhD, MPH Division of Epidemiology I
Team Lead:	Catherine Callahan, PhD, MA (Acting) Division of Epidemiology I
Division Leadership:	CAPT Sukhminder K. Sandhu, PhD, MPH, MS Division of Epidemiology I
Sub-Office Director:	Judith Zander, MD Office of Pharmacovigilance and Epidemiology
Sentinel Program Lead:	Patricia Bright, PhD, MSPH Office of Surveillance and Epidemiology

Expedited ARIA Sufficiency Template for Pregnancy Safety Concerns

1. BACKGROUND INFORMATION

1.1. Medical Product

Symbravo (20 mg meloxicam-10 mg rizatriptan), is a fixed-dose combination tablet of the nonsteroidal anti-inflammatory drug (NSAID) meloxicam and 5-HT$1_{B/D}$ agonist (triptan) drug rizatriptan.[1] The proposed indication for this new drug application (NDA) is for the acute treatment of migraine with or without aura in adults.[2]

Current FDA approved prescription oral therapies in the same classification as Symbravo include NSAIDs (diclofenac[3], celecoxib[4]), triptans (eletriptan[5], frovatriptan[6], naratriptan[7], etc.), and a triptan/NSAID combination (sumatriptan/naproxen[8]). Nonprescription oral therapies FDA approved for migraine treatment in the same classification include the NSAID ibuprofen.[9] NSAIDs inhibit cyclooxygenase-1 and cyclooxygenase-2 catalysis of prostaglandin synthesis, mediating inflammation, and pain. (1, 2) Triptans similarly prevent inflammation and pain by binding to 5-HT$1_{B/D}$ receptors, which control vasodilation. (1, 2)

The recommended dose of Symbravo is a single tablet at the onset of a migraine.[10] The maximum dose in a 24-hour period is one tablet, with safety established for up to (b) (4) doses per month; the safety of higher usage has not been evaluated.[11] The half-life of meloxicam and rizatriptan in Symbravo is (b) (4) hours and (b) (4) hours respectively.[12] Adverse events reported in at least 2% of patients treated with Symbravo include nausea, vomiting, dizziness, somnolence, diarrhea, and upper respiratory tract infection.[13]

1.2. Describe the Safety Concern

The Division of Neurology 2 (DN2) requested that the Division of Epidemiology I (DEPI-I)

---

[1] Draft Symbravo labeling dated September 27, 2021.; Livezey V. NDA 215431 Symbravo (meloxicam/rizatriptan). Clinical Review dated April 29, 2022. Silver Spring (MD), U.S. Food and Drug Administration. DARRTS Reference ID: 4972718.

[2] Draft Symbravo labeling dated September 27, 2021.

[3] NDA 0222165 Label. April 23, 2024. Silver Spring (MD), U.S. Food and Drug Administration. Accessed on November 20, 2024, at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/022165Orig1s006lbl.pdf .

[4] NDA 212157 Label. April 28, 2021. Silver Spring (MD), U.S. Food and Drug Administration. Accessed on November 20, 2024, at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/212157s002lbl.pdf.

[5] NDA 021016 Label. March 24, 2020. Silver Spring (MD), U.S. Food and Drug Administration. Accessed on November 20, 2024, at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/21016s029lbl.pdf.

[6] NDA 021006 Label. August 20, 2018. Silver Spring (MD), U.S. Food and Drug Administration. Accessed on November 20, 2024, at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/021006s022lbl.pdf.

[7] ANDA 090381 Letter. July 7, 2010. Silver Spring (MD), U.S. Food and Drug Administration. Accessed on November 20, 2024, at: https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2010/090381s000ltr.pdf.

[8] NDA 021926 Label. April 28, 2021. Silver Spring (MD), U.S. Food and Drug Administration. Accessed on November 20, 2024, at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/021926s017s018lbl.pdf.

[9] NDA 020402 Label. March 16, 2000. Silver Spring (MD), U.S. Food and Drug Administration. Accessed on November 20, 2024, at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2000/20402S5LBL.PDF.

[10] See footnote 2.

[11] See footnote 1.

[12] Summary of Clinical Pharmacology Studies dated June 30, 2021.

(b) (4)

assess the sufficiency of Active Risk Identification and Analysis (ARIA) to evaluate the safety of Symbravo exposure during pregnancy.

The prevalence of migraine varies by sex and age. (3, 4) The prevalence of migraine is higher among females compared to males. (3, 4) The prevalence of migraines among females is highest during childbearing years. (5) Evidence regarding migraine prevalence during pregnancy is mixed. While many women report a decrease in migraine frequency, others experience no improvement or even a worsening of symptoms. (6-8) For those who do not experience improvement, migraine may negatively impact pregnancy outcomes such as pregnancy induced hypertension disorders and preeclampsia/eclampsia. (9) Migraine during pregnancy can also increase low birth weight, preterm birth, and negative infant outcomes in the first year of life. (10, 11) For treatment of migraine during pregnancy, non-pharmacological treatment of migraine is preferred, however pharmacological treatments are frequently used. (12, 13) Thus, fetal exposure to pharmacological migraine treatment may occur.

Symbravo is a combination tablet of meloxicam and rizatriptan and both drugs include warnings for pregnancy in the labeling based on non-clinical and clinical studies. Non-clinical studies demonstrate meloxicam administration to pregnant rabbits throughout embryogenesis produced increased incidence of septal defects of the heart after oral dose of 60 mg/kg/day.[14] In rats and rabbits, embryolethality occurred at oral meloxicam doses (1 mg/kg/day and 5 mg/kg/day) when administered throughout organogenesis. Oral administration of rizatriptan (0, 2, 10 or 100 mg/kg/day) in pregnant rats was associated with decreased fetal body weight at the highest dose tested.[15] No adverse fetal effects were observed when rizatriptan (0, 5, 10 or 50 mg/kg/day) was administered to pregnant rabbits throughout organogenesis.[16] Placental transfer of rizatriptan to the fetus was observed in rats and rabbits.[17]

The individual components of Symbravo, meloxicam and rizatriptan, have been studied during pregnancy in published studies and postmarketing reports. Data from observational studies on meloxicam use during the first and second trimester are inconclusive.[18] NSAIDs, including meloxicam, at 20 weeks or later gestation may cause fetal renal dysfunction leading to oligohydramnios, and in some cases neonatal renal impairment and use at 30 weeks or later gestation can cause premature closure of the fetal ductus arteriosus.[19] Available data of rizatriptan from postmarketing data are not sufficient to draw conclusions about drug-associated risk for major birth defects or miscarriage.[20]

There are limited data on the safety of Symbravo in pregnant women.[21] Based on the summary on clinical safety[22], there were five pregnancies reported among patients who received at least one dose of Symbravo. One Symbravo-exposed patient experienced spontaneous abortion at 5 weeks gestation, which occurred 12 days after dosing with the study drug. The four remaining pregnancies with Symbravo exposure were live, full-term births without congenital anomalies

[14] Draft Symbravo labeling dated September 27, 2021.
[15] Ibid.
[16] Ibid.
[17] Ibid.
[18] Ibid.
[19] Ibid.
[20] Ibid.
[21] Ibid.
[22] Livezey V. NDA 215431 Symbravo (meloxicam/rizatriptan). Clinical Review dated April 29, 2022. Silver Spring (MD), U.S. Food and Drug Administration. DARRTS Reference ID: 4972718.

or pregnancy complications.

The proposed draft labeling for Symbravo submitted on September 9, 2021, includes the following warnings and precautions and information regarding use during pregnancy:[23]

5.18 Fetal Toxicity

Premature Closure of Fetal Ductus Arteriosus
Avoid use of NSAIDs, including SYMBRAVO, in pregnant women at about 30 weeks gestation and later. NSAIDs, including SYMBRAVO, increase the risk of premature closure of the fetal ductus arteriosus at approximately this gestational age.

Oligohydramnios/Neonatal Renal Impairment

Use of NSAIDs, including SYMBRAVO, at about 20 weeks gestation or later in pregnancy may cause fetal renal dysfunction leading to oligohydramnios and, in some cases, neonatal renal impairment. These adverse outcomes are seen, on average, after days to weeks of treatment, although oligohydramnios has been infrequently reported as soon as 48 hours after NSAID initiation. Oligohydramnios is often, but not always, reversible with treatment discontinuation. Complications of prolonged oligohydramnios may, for example, include limb contractures and delayed lung maturation. In some postmarketing cases of impaired neonatal renal function, invasive procedures such as exchange transfusion or dialysis were required.

If NSAID treatment is necessary between about 20 weeks and 30 weeks gestation, limit SYMBRAVO use to the lowest effective dose and shortest duration possible.

Consider ultrasound monitoring of amniotic fluid if SYMBRAVO treatment extends beyond 48 hours. Discontinue SYMBRAVO if oligohydramnios occurs and follow up according to clinical practice [see Use in Specific Populations (8.1)].

8.1 Pregnancy

SYMBRAVO has not been studied in pregnant women. However, the individual components, meloxicam and rizatriptan, have been studied and the results of these studies are described below.

Risk Summary

Meloxicam

(b) (4) *Data from observational studies regarding potential embryofetal risks of NSAID use in women in the first or second trimesters of pregnancy are inconclusive. Use of NSAIDs, including SYMBRAVO, can cause premature closure of the fetal ductus arteriosus and fetal renal dysfunction leading to oligohydramnios and, in some cases, neonatal renal impairment. Because of these risks, limit dose and duration of SYMBRAVO use between about 20 and 30 weeks of gestation, and avoid SYMBRAVO use at about 30 weeks of gestation and later in pregnancy [see Clinical*

[23] Draft Symbravo labeling dated September 27, 2021.

Considerations, Data].

Premature Closure of Fetal Ductus Arteriosus

Use of NSAIDs, including SYMBRAVO, at about 30 weeks gestation or later in pregnancy increases the risk of premature closure of the fetal ductus arteriosus.

Oligohydramnios/Neonatal Renal Impairment

Use of NSAIDs at about 20 weeks gestation or later in pregnancy has been associated with cases of fetal renal dysfunction leading to oligohydramnios, and in some cases, neonatal renal impairment.

Data from observational studies regarding other potential embryofetal risks of NSAID use in women in the first or second trimesters of pregnancy are inconclusive.

In animal reproduction studies, embryofetal death was observed in rats and rabbits treated during the period of organogenesis with meloxicam at oral doses equivalent to 0.5- and 4.9-times the maximum recommended human dose (MRHD) of 20 mg of meloxicam, based on body surface area (BSA). Increased incidence of septal heart defects were observed in rabbits treated throughout embryogenesis with meloxicam at an oral dose equivalent to 59-times the MRHD of 20 mg of meloxicam. In pre- and post-natal reproduction studies, there was an increased incidence of dystocia, delayed parturition, and decreased offspring survival at 0.06-times the MRHD of 20 mg of meloxicam. No teratogenic effects were observed in rats and rabbits treated with meloxicam during organogenesis at an oral dose equivalent to 2 and 20-times the MRHD of 20 mg of meloxicam [see Data].
Based on animal data, prostaglandins have been shown to have an important role in endometrial vascular permeability, blastocyst implantation, and decidualization. In animal studies, administration of prostaglandin synthesis inhibitors, such as meloxicam, resulted in increased pre- and post-implantation loss. Prostaglandins also have been shown to have an important role in fetal kidney development. In published animal studies, prostaglandin synthesis inhibitors have been reported to impair kidney development when administered at clinically relevant doses.

Rizatriptan

Available human data on the use of rizatriptan in pregnant women are not sufficient to draw conclusions about drug-associated risk for major birth defects and miscarriage.

In animal studies, developmental toxicity was observed following oral administration of rizatriptan during pregnancy (decreased fetal body weight in rats) or throughout pregnancy and lactation (increased mortality, decreased body weight, and neurobehavioral impairment in rat offspring) at maternal plasma exposures greater than that expected at therapeutic doses in humans [see Animal Data].

In the general U.S. population, all clinically recognized pregnancies, regardless of drug exposure, have a background rate of 2-4% for major malformations, and 15-20% for pregnancy loss. The reported rate of major birth defects among deliveries to women with migraine range from 2.2% to 2.9% and the reported rate of miscarriage was 17%, which are similar to rates reported in women without migraine.

Additional clinical considerations and data regarding use in specific populations is provided in the Appendix.

1.3. FDAAA Purpose (per Section 505(o)(3)(B))

Ensure that the selected purpose(s) is consistent with the other PMR documents in DARRTS. More than one purpose may be chosen.

- ☐ Assess a known serious risk
- ☐ Assess signals of serious risk
- ☒ Identify unexpected serious risk when available data indicate potential for serious risk

2. REVIEW QUESTIONS

2.1. Why is pregnancy safety a safety concern for this product? Check all that apply.

- ☐ Specific FDA-approved indication in pregnant individuals exists and exposure is expected
- ☐ No approved indication in pregnant individuals, but practitioners may use product off-label in pregnant individuals
- ☒ No approved indication in pregnant individuals, but there is the potential for inadvertent exposure before a pregnancy is recognized
- ☒ No approved indication in pregnant individuals, but use in individuals of childbearing age is a general concern

2.2. Regulatory Goal[24]

- ☐ Signal evaluation of specific outcome(s) – *implementation of a full epidemiological analysis to thoroughly evaluate the causal relationship between exposure to the medical product and the health outcome of interest.*
- ☐ Signal refinement of specific outcome(s) – *further investigation of an identified potential safety signal to determine whether evidence exists to support a relationship between the medical product exposure and the health outcome.*
- ☒ Signal identification – *detection of new and unexpected potential medical product safety concerns and may be for a **targeted or multiple** safety concern(s)/health outcome(s).*
  - ☐ Targeted evaluation of specific safety concern
  - ☒ Simultaneous identification of multiple unspecified adverse outcomes

2.3. What type of analysis or study design is being considered or requested along with ARIA? Check all that apply.

- ☒ Pregnancy registry with internal comparison group
- ☒ Pregnancy registry with external comparison group
- ☐ Enhanced pharmacovigilance (i.e., passive surveillance enhanced by with additional

[24] Definitions adapted from: Robb MA, Racoosin JA, Sherman RE, Gross TP, Ball R, Reichman ME, Midthun K, Woodcock J. The US Food and Drug Administration's Sentinel Initiative: expanding the horizons of medical product safety. Pharmacoepidemiol Drug Saf. 2012 Jan;21 Suppl 1:9-11. doi: 10.1002/pds.2311. PMID: 22262587.

actions)

- ☒ Electronic database study with chart review
- ☐ Electronic database study without chart review
- ☒ Other, please specify: Alternative study designs would be considered: e.g., retrospective cohort study using claims or electronic medical record data with outcome validation or a case-control study.

2.4. Identify the epidemiologic domain(s) where ARIA is not sufficient and provide a rationale on ARIA insufficiency for those epidemiologic domain(s). Then, provide an assessment of the overall ARIA sufficiency.

Epidemiologic Domain for registry study	**Explanation on ARIA insufficiency for registry study**	**Explanation on ARIA insufficiency for database study or alternative study design**
☐ Study Population		
☐ Exposures (and Comparators)		
☒ Outcomes	ARIA lacks access to medical records. The pregnancy registry being considered requires that an expert clinical geneticist or dysmorphologist review and classify medical records of all major congenital malformations.	The complementary database or alternative study design (retrospective cohort or case control) would require chart validation of outcomes.
☒ Covariates	ARIA does not provide sufficient information on potential confounders (e.g., body mass index, smoking status, illicit drug use, alcohol intake, socioeconomic status) which may be captured in a registry.	ARIA does not provide sufficient information on potential confounders (e.g., body mass index, smoking status, illicit drug use, alcohol intake, socioeconomic status) which may be captured in a database study with medical chart review to assess some of these potential confounders.
☐ Analytic Tools		

Overall ARIA sufficiency		
	☒ Insufficient ☐ Sufficient	☒ Insufficient ☐ Sufficient

2.5. If ARIA is deemed insufficient, include the PMR language to be included in the approval letter.

• 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 or 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.

• A pregnancy outcomes study using a different study design than provided for in the study above (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, and small-for-gestational-age births in women exposed to Symbravo during pregnancy compared to an unexposed control population.

2.6. References:

1. Ong JJY, De Felice M. Migraine Treatment: Current Acute Medications and Their Potential Mechanisms of Action. Neurotherapeutics. 2018;15(2):274-90.
2. Mitsikostas DD, Ward TN. Chapter 13 - Evidence-based symptomatic treatment of migraine. In: Swanson JW, Matharu M, editors. Handbook of Clinical Neurology. 199: Elsevier; 2024. p. 203-18.
3. Lebedeva ER. Chapter Nine - Sex and age differences in migraine treatment and management strategies. In: Moro E, Arabia G, Tartaglia MC, Ferretti MT, editors. International Review of Neurobiology. 164: Academic Press; 2022. p. 309-47.
4. Chalmer MA, Kogelman LJA, Callesen I, Christensen CG, Techlo TR, Møller PL, et al. Sex differences in clinical characteristics of migraine and its burden: a population-based study. European Journal of Neurology. 2023;30(6):1774-84.
5. Burch R, Rizzoli P, Loder E. The Prevalence and Impact of Migraine and Severe Headache in the United States: Figures and Trends From Government Health Studies. Headache: The Journal of Head and Face Pain. 2018;58(4):496-505.
6. Granella F, Sances G, Pucci E, Nappi RE, Ghiotto N, Nappi G. Migraine with Aura and Reproductive Life Events: A Case Control Study. Cephalalgia. 2000;20(8):701-7.

7. Kvisvik EV, Stovner LJ, Helde G, Bovim G, Linde M. Headache and migraine during pregnancy and puerperium: the MIGRA-study. J Headache Pain. 2011;12(4):443-51.
8. Holdridge A, Donnelly M, Kuruvilla DE. Integrative, Interventional, and Non-invasive Approaches for the Treatment for Migraine During Pregnancy. Current Pain and Headache Reports. 2022;26(4):323-30.
9. Phillips K, Koonalintip P, Wakerley BR. Migraine and Pregnancy. Life (Basel). 2024;14(10).
10. Skajaa N, Szépligeti SK, Xue F, Sørensen HT, Ehrenstein V, Eisele O, et al. Pregnancy, Birth, Neonatal, and Postnatal Neurological Outcomes After Pregnancy With Migraine. Headache. 2019;59(6):869-79.
11. Burch R. Epidemiology and Treatment of Menstrual Migraine and Migraine During Pregnancy and Lactation: A Narrative Review. Headache. 2020;60(1):200-16.
12. Ibrahim MO, Sarmini D. Abortive and Prophylactic Therapies to Treat Migraine in Pregnancy: A Review. Cureus. 2024;16(10):e70807.
13. Nezvalová-Henriksen K, Spigset O, Nordeng H. Maternal Characteristics and Migraine Pharmacotherapy During Pregnancy: Cross-Sectional Analysis of Data from a Large Cohort Study. Cephalalgia. 2009;29(12):1267-76.

2.7. Appendix

Clinical Considerations and Data regarding use in specific populations included in the proposed draft labeling for Symbravo submitted on September 9, 2021.[25]

8.1 Pregnancy

Clinical Considerations

Disease-Associated Maternal and/or Embryo/Fetal Risk

In women with migraine, there is an increased risk of adverse perinatal outcomes in the mother, including pre-eclampsia and gestational hypertension.

Fetal/Neonatal Adverse Reactions

Premature Closure of Fetal Ductus Arteriosus:

Avoid use of NSAIDs in women at about 30 weeks gestation and later in pregnancy, because NSAIDs, including SYMBRAVO, can cause premature closure of the fetal ductus arteriosus [see Data].

Oligohydramnios/Neonatal Renal Impairment

If an NSAID is necessary at about 20 weeks gestation or later in pregnancy, limit the use to the lowest effective dose and shortest duration possible. If SYMBRAVO treatment extends beyond 48 hours, consider monitoring with ultrasound for oligohydramnios. If oligohydramnios

[25] Draft Symbravo labeling dated September 27, 2021.

occurs, discontinue SYMBRAVO and follow up according to clinical practice [see Data].

Labor or delivery

There are no studies on the effects of meloxicam during labor or delivery. In animal studies, NSAIDs, including meloxicam, inhibit prostaglandin synthesis, cause delayed parturition, and increase the incidence of stillbirth.

Data

Human Data for Meloxicam

Premature Closure of Fetal Ductus Arteriosus:

Published literature reports that the use of NSAIDs at about 30 weeks of gestation and later in pregnancy may cause premature closure of the fetal ductus arteriosus.

Oligohydramnios/Neonatal Renal Impairment:

Published studies and postmarketing reports describe maternal NSAID use at about 20 weeks gestation or later in pregnancy associated with fetal renal dysfunction leading to oligohydramnios, and in some cases, neonatal renal impairment. These adverse outcomes are seen, on average, after days to weeks of treatment, although oligohydramnios has been infrequently reported as soon as 48 hours after NSAID initiation. In many cases, but not all, the decrease in amniotic fluid was transient and reversible with cessation of the drug. There have been a limited number of case reports of maternal NSAID use and neonatal renal dysfunction without oligohydramnios, some of which were irreversible. Some cases of neonatal renal dysfunction required treatment with invasive procedures, such as exchange transfusion or dialysis.

Methodological limitations of these postmarketing studies and reports include lack of a control group; limited information regarding dose, duration, and timing of drug exposure; and concomitant use of other medications. These limitations preclude establishing a reliable estimate of the risk of adverse fetal and neonatal outcomes with maternal NSAID use.

Because the published safety data on neonatal outcomes involved mostly preterm infants, the generalizability of certain reported risks to the full-term infant exposed to NSAIDs through maternal use is uncertain.

Human Data for Rizatriptan

In a pregnancy registry for rizatriptan users, no pattern of congenital anomalies or other adverse birth outcomes was identified over the period of 1998 to 2018. However, the lack of identification of any pattern should be viewed with caution, as the number of prospective reports with outcome information was low and did not provide sufficient power to detect an increased risk of individual birth defects associated with the use of rizatriptan. Additionally, there was significant loss to follow-up in the prospective pregnancy reports, further complicating this assessment of an association between rizatriptan and any pattern of congenital anomalies or other adverse birth outcomes.

In a study using data from the Swedish Medical Birth Register, live births to women who reported using triptans or ergots during pregnancy were compared with those of women who did not. Of the 157 births with first-trimester exposure to rizatriptan, 7 infants were born with malformations (relative risk 1.01 [95% CI: 0.40 to 2.08]). A study using linked data from the Medical Birth Registry of Norway to the Norwegian Prescription Database compared pregnancy outcomes in women who redeemed prescriptions for triptans during pregnancy, as well as a migraine disease comparison group who redeemed prescriptions for triptans before pregnancy only, compared with a population control group. Of the 310 women who redeemed prescriptions for rizatriptan during the first trimester, 10 had infants with major congenital malformations (OR 1.03 [95% CI: 0.55 to 1.93]), while for the 271 women who redeemed prescriptions for rizatriptan before, but not during, pregnancy, 12 had infants with major congenital malformations (OR 1.48 [95% CI: 0.83 to 2.64]), each compared with the population comparison group.

Animal Data for Meloxicam

Meloxicam was not teratogenic when administered to pregnant rats during fetal organogenesis at oral doses up to 4 mg/kg/day (2-fold greater than the MRHD of 20 mg of meloxicam based on BSA comparison). Administration of meloxicam to pregnant rabbits throughout embryogenesis produced an increased incidence of septal defects of the heart at an oral dose of 60 mg/kg/day (59-fold greater than the MRHD of 20 mg of meloxicam based on BSA comparison). The no effect level was 20 mg/kg/day (20-fold greater than the MRHD of 20 mg of meloxicam based on BSA conversion). In rats and rabbits embryolethality occurred at oral meloxicam doses of 1 mg/kg/day and 5 mg/kg/day, respectively (0.5 and 4.9-fold greater, respectively, than the MRHD of 20 mg of meloxicam based on BSA comparison) when administered throughout organogenesis.

Oral administration of meloxicam to pregnant rats during late gestation through lactation increased the incidence of dystocia, delayed parturition, and decreased offspring survival at meloxicam doses of 0.125 mg/kg/day or greater (0.06-times the MRHD of 20 mg of meloxicam based on BSA comparison).

Animal Data for Rizatriptan

When rizatriptan (0, 2, 10, or 100 mg/kg/day) was administered orally to pregnant rats throughout organogenesis, a decrease in fetal body weight was observed at the highest doses tested. The no-effect dose for adverse effects on embryofetal development was 10 mg/kg/day (10-times the MRHD of 10 mg of rizatriptan based on BSA comparison). When rizatriptan (0, 5, 10, or 50 mg/kg/day) was administered orally to pregnant rabbits throughout organogenesis, no adverse fetal effects were observed. The highest dose tested of 50 mg/kg/day was 97-times the MRHD of 10 mg of rizatriptan based on BSA comparison. Placental transfer of drug to the fetus was demonstrated in both species.

Oral administration of rizatriptan (0, 2, 10, or 100 mg/kg/day) to female rats prior to and during mating and continuing throughout gestation and lactation resulted in reduced body weight in offspring from birth and throughout lactation at all but the lowest dose tested (2 mg/kg/day). The no-effect dose (2 mg/kg/day) for adverse effects on postnatal development was 2-times the MRHD of 10 mg rizatriptan based on BSA comparison.

Oral administration of rizatriptan (0, 5, 100, or 250 mg/kg/day) throughout organogenesis

and lactation resulted in neonatal mortality, reduced body weight (which persisted into adulthood), and impaired neurobehavioral function in offspring at all but the lowest dose tested. The no-effect dose for adverse effects on postnatal development (5 mg/kg/day) was 5-times the MRHD of 10 mg rizatriptan based on BSA comparison.

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/

KIERAN J MARONEY
01/21/2025 10:44:20 AM

CATHERINE L CALLAHAN
01/21/2025 10:47:58 AM

SUKHMINDER K SANDHU
01/21/2025 10:50:40 AM

JUDITH W ZANDER
01/21/2025 10:52:54 AM

PATRICIA L BRIGHT
01/21/2025 11:01:28 AM

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	January 21, 2025
To:	Lana Chen Senior Regulatory Project Manager **Division of Neurology II (DN2)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Marcia Williams, PhD Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Kelly Jackson, PharmD Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Lindsay McCann, PharmD, BCCCP Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Medication Guide (MG)
Drug Name (established name):	SYMBRAVO (meloxicam and rizatriptan)
Dosage Form and Route:	tablets, for oral use
Application Type/Number:	NDA 215431
Applicant:	Axsome Therapeutics, Inc.

1 INTRODUCTION

On July 31, 2024, Axsome Therapeutics, Inc. submitted for the Agency's review a 505(b)(2) resubmission for New Drug Application (NDA) 215431 for SYMBRAVO (meloxicam and rizatriptan) tablets, for oral use. This resubmission is in response to the Complete Response Letter dated April 29, 2024. The applicant is seeking approval for SYMBRAVO (meloxicam and rizatriptan) for the acute treatment of migraine with or without aura in adults.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Neurology II (DN2) on August 29, 2024, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) for SYMBRAVO (meloxicam and rizatriptan) tablets, for oral use.

3 MATERIAL REVIEWED

- Draft SYMBRAVO (meloxicam and rizatriptan) MG received on July 31, 2024, and received by DMPP and OPDP on January 7, 2025.
- Draft SYMBRAVO (meloxicam and rizatriptan) Prescribing Information (PI) received on July 31, 2024, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on January 7, 2025.

4 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the MG the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss.

In our collaborative review of the MG we:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the PI
- removed unnecessary or redundant information
- ensured that the MG is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

5 CONCLUSIONS

The MG is acceptable with our recommended changes.

6 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

10 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

---

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/

KELLY D JACKSON
01/21/2025 01:13:19 PM

LINDSAY M MCCANN
01/21/2025 01:52:32 PM

MARCIA B WILLIAMS
01/21/2025 02:05:19 PM

LASHAWN M GRIFFITHS
01/21/2025 02:36:55 PM

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: January 21, 2024

To: Lana Chen, Regulatory Project Manager, Division of Neurology Products, DN2

Heather Fitter, DN2

Tracy Peters, Associate Director for Labeling, DN

From: Lindsay McCann, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Taylor Burnett Mmagu, Team Leader, OPDP

Subject: OPDP Labeling Comments for SYMBRAVO (rizatriptan and meloxicam) tablets, for oral use

NDA/BLA: 215431

Background: In response to DN2's consult request dated August 29, 2024, OPDP has reviewed the proposed Prescribing Information (PI), Medication Guide (MG), and carton and container labeling for the NDA 215431 resubmission for SYMBRAVO (rizatriptan and meloxicam) tablets, for oral use.

PI:
OPDP's review of the proposed PI is based on the draft labeling emailed to OPDP on January 7, 2025 and our comments are provided below.

MG:
A combined OPDP and Division of Medical Policy Programs (DMPP) has been completed for the proposed PPI, and comments were sent under separate cover.

Carton and Container Labeling:
OPDP's review of the proposed carton and container labeling is based on the draft labeling submitted by the sponsor to the electronic document room on October 21, 2024 and our comments are provided below.

Thank you for your consult. If you have any questions, please contact Lindsay McCann at 301-796-3719 or Lindsay.McCann@fda.hhs.gov.

25 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

---

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/

LINDSAY M MCCANN
01/21/2025 02:20:30 PM

MEMORANDUM
REVIEW OF REVISED LABELS

Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	November 29, 2024
Requesting Office or Division:	Division of Neurology 2 (DN 2)
Application Type and Number:	NDA 215431
Product Name, Dosage Form, and Strength:	Symbravo (meloxicam and rizatriptan) tablets, 20 mg/10 mg
Applicant Name:	Axsome Therapeutics, Inc. (Axsome)
FDA Received Date:	November 27, 2024
TTT ID #:	2024-10002-2
DMEPA 2 Safety Evaluator:	Beverly Weitzman, PharmD
DMEPA 2 Team Leader:	Stephanie DeGraw, PharmD

1 PURPOSE OF MEMORANDUM

Axsome Therapeutics, Inc. submitted revised container labels (trade and professional sample) received on November 27, 2024, for Symbravo (meloxicam and rizatriptan) tablets. The Division of Neurology 2 (DN 2) requested that we review the revised container labels (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review[a] and in response to our November 26, 2024 information request, which recommended Axsome increase the prominence of the strength statement.[b]

2 CONCLUSION

Axsome implemented all of our recommendations. Thus, we find the container labels acceptable from a medication error perspective and we do not have any additional recommendations at this time.

1 Page(s) of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

[a] Weitzman, B. Label and Labeling Review for Symbravo (NDA 215431). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2024 OCT 28. TTT ID No.: 2024-10002-1.

[b] Ngembus, D. on behalf of Chen, L. Information Request: Carton & Container Labeling Comments for NDA 215431. 2024 NOV 26. Available from: https://darrts.fda.gov/darrts/ViewDocument?documentId=090140af80784942&showAsPdf=true.

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/

STEPHANIE L DEGRAW on behalf of BEVERLY WEITZMAN
11/29/2024 12:27:10 PM

STEPHANIE L DEGRAW
11/29/2024 12:28:02 PM

MEMORANDUM
REVIEW OF REVISED LABELS

Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	October 28, 2024
Requesting Office or Division:	Division of Neurology 2 (DN 2)
Application Type and Number:	NDA 215431
Product Name, Dosage Form, and Strength:	Symbravo (meloxicam and rizatriptan) tablets, 20 mg/10 mg
Applicant Name:	Axsome Therapeutics, Inc.
FDA Received Date:	October 21, 2024
TTT ID #:	2024-10002-1
DMEPA 2 Safety Evaluator:	Beverly Weitzman, PharmD
DMEPA 2 Associate Director for Nomenclature and Labeling:	Hina Mehta, PharmD

1 PURPOSE OF MEMORANDUM

Axsome Therapeutics, Inc. submitted revised container labels (trade and professional sample) received on October 21, 2024 for Symbravo (meloxicam and rizatriptan) tablets. The Division of Neurology 2 (DN 2) requested that we review the revised container labels for Symbravo (meloxicam and rizatriptan) tablets (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

Our review of the container labels determined Axsome Therapeutics, Inc. implemented most of our container label recommendations made in our previous labeling review; however, we note that the presentation of the established name does not appear to be at least half the size of the proprietary name. We further note, the Applicant revised the styling of the proprietary name to an artistic presentation of the letter "V".

As such, we provide a new recommendation based on the revised container labels regarding the artistic presentation of the letter "V" of the proprietary name as well as reiterating our previous recommendation to ensure the established name is at least half the size of the proprietary name to be accordance with 21 CFR 201.10(g)(2). We provide the identified medication error issues, our rationale for concern, and our proposed recommendations to minimize the risk for medication error in Section 3 (Table 1) for Axsome Therapeutics, Inc.

3 RECOMMENDATIONS FOR AXSOME THERAPEUTICS, INC.

Table 1. Identified Issues and Recommendations for Axsome Therapeutics, Inc. (entire table to be conveyed to Applicant)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Container Labels (Trade and Professional Sample)			
1.	The established name is not at least half the size of the proprietary name and is difficult to read as previously noted.	We refer you to 21 CFR 201.10(g)(2) which states that the established name shall be printed in letters that are at least half as large as the letters comprising the proprietary name, and the established name shall have a prominence commensurate with the prominence with	Revise the established name so that the established name is presented in accordance with 21 CFR 201.10(g)(2).

[a] Weitzman, B. Label and Labeling Review for Symbravo (NDA 215431). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2024 SEP 23. TTT ID No.: 2024-10002.

Table 1. Identified Issues and Recommendations for Axsome Therapeutics, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
		which such proprietary name appears, taking into account all pertinent factors, including typography, layout, contrast, and other printing features.	
2.	The presentation of the letter "V" in the proprietary name, Symbravo, can be improved for readability.	The artistic presentation of the letter "V" may detract from the readability and may distort the interpretation of the proprietary name.	We recommend you consider different styling for the letter "V" in the proprietary name as well as utilizing a single font color for the entire proprietary name to improve readability and avoid misinterpretation of the proprietary name. We also recommend you consider the presentation of the "V" on your proposed container labels in your previous labeling submission.

1 Page(s) of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

---

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/

BEVERLY WEITZMAN
10/28/2024 02:54:47 PM

HINA S MEHTA
10/29/2024 10:34:29 AM

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis 2 (DMEPA 2)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	September 23, 2024
Requesting Office or Division:	Division of Neurology 2 (DN 2)
Application Type and Number:	NDA 215431
Product Name, Dosage Form, and Strength:	Symbravo[a] (meloxicam and rizatriptan) tablet, 20 mg/10 mg
Product Type:	Multi-Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Axsome Therapeutics, Inc.
FDA Received Date:	June 28, 2024 and July 31, 2024
TTT ID #:	2024-10002 (previous review OSE # 2021-1315)
DMEPA 2 Safety Evaluator:	Beverly Weitzman, PharmD
DMEPA 2 Team Leader	Stephanie DeGraw, PharmD

[a] The proposed proprietary name, Symbravo was found conditionally acceptable on March 10, 2022, under the previous review cycle. Our evaluation of the proposed proprietary name Symbravo under the Class 2 resubmission is ongoing at the time of this review.

1 REASON FOR REVIEW

On July 31, 2024, Axsome Therapeutics, Inc. (Axsome) submitted a Class 2 resubmission for NDA 215431 for Symbravo (meloxicam and rizatriptan) tablets in response to the Agency's Complete Response (CR) letter, issued April 29, 2022.[b]

The Division of Neurology 2 (DN 2) requested that we review the proposed prescribing information, medication guide, and container labels (trade and professional sample) for areas of vulnerability that may lead to medication errors.

2 REGULATORY HISTORY

NDA 215431 is a 505(b)(2) NDA, and the listed drug products are Maxalt (NDA 020864), Anjeso (NDA 210583), and Mobic (NDA 020938).

NDA 215431 was originally submitted on June 30, 2021. During that review cycle we completed a review of the prescribing information (PI), medication guide (MG), and container labels on March 16, 2022.[c] However, the application received a complete response (CR) letter on April 29, 2022, due to product quality and nonclinical issues. Our recommendations for the container labels were sent to the Applicant as part of the CR letter; however, the CR letter noted that the FDA reserved comment on the proposed labeling (i.e., PI and MG) until the application is otherwise adequate. Therefore, our recommendations for the PI and MG were not communicated to the Applicant.

In response to the CR letter issued April 29, 2022, Axsome submitted a Class 2 resubmission for NDA 215431 on June 28, 2024. Under this submission, the Applicant submitted container labels, which were revised in response to our recommendations sent to the Applicant in the April 29, 2022 CR letter, as well as referenced the PI and MG submitted during the previous review cycle on September 27, 2024, and July 30, 2024, under sequence numbers 0005 and 0001, respectively.[d] We further note the Applicant stated, "no changes are proposed to the most recent version of the draft PI and MG submitted in sequence numbers 0005 and 0001."

On July 26, 2024, the Agency notified Axsome that June 28, 2024 submission was not considered a complete response. Subsequently, Axsome submitted a new Class 2 resubmission on July 31, 2024. No new labels or labeling were submitted; therefore, this review evaluates the container labels submitted on June 28, 2024, and the PI and MG submitted on September 27, 2024, and July 30, 2024.

---

[b] Kozauer, N. Complete Response Letter for NDA 215431. Issued 2022 APR 29. Available from: https://darrts.fda.gov/darrts/ViewDocument?documentId=090140af8065c478

[c] Weitzman, B. Label and Labeling Review for Symbravo (NDA 215431). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2022 MAR 16, 2024. OSE RCM.: 2021-1315.

[d] Cover Letter – NDA Resubmission for NDA 215431. New York (NY). Axsome Therapeutics, Inc. 2024 JUN 28. Available from: \\CDSESUB1\EVSPROD\nda215431\0024\m1\us\cover-letter.pdf

3 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Review	
Material Reviewed	Appendix Section
Relevant Product Information	A
Labels and Labeling	B
Recommendations for the Container Labels from Previous Review Completed March 16, 2022	C

4 CONCLUSION & RECOMMENDATIONS

Our review of the container labels determined that the Applicant implemented all previously communicated container label recommendations (see Appendix C) made in our previous labeling review (OSE # 2021-1315 dated March 16, 2022). However, we identified new issues with the proposed labels. For example, the established name does not appear to be at least half the size of the proprietary name, and in the strength statement, there is no space between the numbers and the mg unit of measure on the principal display panel. Therefore, we have new recommendations based on the revised container labels, submitted June 28, 2024, in Section 6 (Table 3) below for the Axsome Therapeutics, Inc.

Our review of the proposed prescribing information (PI) and medication guide (MG) determined we maintain most of our PI and MG recommendations from the previous review. These recommendations are provided below in Section 5 (Table 2) for the Division of Neurology 2.

We further note the Applicant changed the package size configuration from a (b) (4) bottle to 9-count bottle. However, because a new PI was not submitted, the (b) (4) bottle and NDC are still listed in Section 16 of the PI, but the new 9-count bottle package size and NDC are not listed. Therefore, we provide a new recommendation based on the new package size configuration in Section 5 (Table 2) below for the Division of Neurology 2.

5 RECOMMENDATIONS FOR DIVISION OF NEUROLOGY 2 (DN 2)

Table 1. Identified Issues and Recommendations for Division of Neurology 2 (DN 2)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Prescribing Information (PI) and Medication Guide (MG)– General Issues			
1.	In the product title of the PI and throughout the labeling, we note that the rizatriptan portion of the established name is presented as the salt form (i.e., rizatriptan benzoate) instead of the active moiety (i.e., rizatriptan).	This is not in accordance 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.	Revise the active ingredient from "rizatriptan benzoate" to read "rizatriptan" in the product title of the PI and throughout the PI and MG labeling where applicable. Additionally, include the salt equivalency statement "(equivalent to 14.5 mg rizatriptan benzoate)" where applicable as determined by OPQ (e.g., Dosage Forms and Strengths and Description sections).
Highlights of Prescribing Information			
1.	We note a hyphen "-" is used between the two active ingredients in the Dosage Forms and Strengths section of the HL.	This format is not in alignment the USP nomenclature guidelines available from https://www.usp.org/sites/default/files/usp/document/usp-nomenclature-guidelines.pdf. The hyphen symbol "-" in "meloxicam and rizatriptan" could lead to misinterpretation of the tablet contents. Further, addition of the salt equivalency statement may be recommended to be in accordance 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 replacing the hyphen symbol between the two ingredients with the word "and" as well as including the salt equivalency statement as follows: "Tablets: 20 mg meloxicam and 10 mg rizatriptan (equivalent to 14.5 mg of rizatriptan benzoate)." We defer to OPQ to determine the appropriateness of including the salt equivalency statement in the Dosage Forms and Strengths section of the HL.

Table 1. Identified Issues and Recommendations for Division of Neurology 2 (DN 2)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
2.	The maximum daily dose is not included in the Dosage and Administration section of the HL.	Including a maximum dose may help prevent wrong dose medication errors, specifically overdose errors (i.e., HCPs and patients may erroneously assume the dose may be repeated since the dose may be repeated for rizatriptan oral tablets).	We recommend revising the recommended dosing statement to clearly identify the maximum daily dose of Symbravo as follows or something similar: "The recommended dose of Symbravo is one tablet by mouth at the onset of a migraine. The maximum daily dose is 20 mg meloxicam and 10 mg rizatriptan (1 tablet)." We defer to clinical team for final determination of the appropriate recommended dosage statement.
Full Prescribing Information – Section 2 Dosage and Administration			
1.	We note that subsection 2.1 Recommended Dose states "The safety and effectiveness of a second dose have not been established", however, the maximum daily dose is not included in the recommended dosage statement .	Including a maximum dose may help prevent wrong dose medication errors, specifically overdose errors (i.e., HCPs and patients may erroneously assume the dose may be repeated since the dose may be repeated for rizatriptan oral tablets).	We recommend revising the recommended dosing statement to clearly identify the maximum daily dose of Symbravo as follows or something similar: "The recommended dose of Symbravo is one tablet by mouth at the onset of a migraine. The maximum daily dose should not exceed 20 mg meloxicam and 10 mg rizatriptan (1 tablet). The safety and effectiveness of a second dose have not been established." We defer to clinical team for final determination of the appropriate recommended dosage statement.
Full Prescribing Information – Section 3 Dosage Forms and Strengths			
1.	The rizatriptan portion of the established name is presented as the salt form (i.e., rizatriptan	This is not in accordance with the *Guidance for Industry Naming of Drug Products Containing Salt Drug*	We recommend revising the Dosage Form and Strength statements to read "Tablets: 20 mg meloxicam and 10 mg

Table 1. Identified Issues and Recommendations for Division of Neurology 2 (DN 2)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	benzoate) instead of the active moiety (i.e., rizatriptan). Additionally, this information is not presented in the standard format as described in the OND Labeling Review Tool.	*Substances* available from: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM379753.pdf.	rizatriptan (equivalent to 14.5 mg rizatriptan benzoate), white and modified capsule-shaped, debossed with "MXRZ" on one side and "20/10" on the other." We defer to OPQ to determine the appropriateness of the salt equivalency statement.
Full Prescribing Information – Section 16 How Supplied/Storage and Handling			
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 symbol "-" 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" as follows: "meloxicam 20 mg and rizatriptan 10 mg" We defer to OPQ to determine if the salt equivalency statement should be included in Section 16.
2.	We note that the container labels include the storage statement "store in original bottle", whereas Section 16 How Supplied does not include this statement.	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." Additionally, the storage statement should be consistent across all labels and labeling.	Clarify the intent of the storage statement "store in original bottle." 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 we recommend including this information on all labels and labeling. We defer to OPQ to determine the appropriateness of the storage statement "store in original bottle."
3.	Per the container labels submitted on June 28,	This is inconsistent with the NDC and net quantity	We recommended revising the package size configuration from

Table 1. Identified Issues and Recommendations for Division of Neurology 2 (DN 2)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	2024, the package size configuration has change from a (b) (4) bottle to a 9-count bottle. However, because a new PI was not submitted, the (b) (4) bottle and NDC are still listed in Section 16, whereas the new 9-count bottle package size and NDC have not been added.	statement presented on the new 9-count trade label which may lead to confusion.	(b) (4) to "Bottles of 9 tablets" and revising the NDC from (b) (4) to "81968-020-09" to reflect the new 9-count trade bottle container label .
Medication Guide (MG)			
1.	The placeholder "TRADENAME" is used throughout the MG labeling.	The proposed proprietary name, Symbravo, was found acceptable on 3/10/2022. Our evaluation of the proposed proprietary name Symbravo under the Class 2 resubmission is ongoing at the time of this review.	The placeholder, TRADENAME, should be replaced with the proposed proprietary name, Symbravo, throughout the MG labeling, if it is again found conditionally acceptable.

6 RECOMMENDATIONS FOR AXSOME THERAPEUTICS, INC.

Table 2. Identified Issues and Recommendations for Axsome Therapeutics, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Container Labels (Trade and Professional Sample)			
1.	The established name is not at least half the size of the proprietary name.	We refer you to 21 CFR 201.10(g)(2) which states that the established name shall be printed in letters that are at least half as large as the letters comprising the proprietary name, and the established name shall have a	Revise the established name and/or the proprietary name so that the established name is presented in accordance with 21 CFR 201.10(g)(2).

Table 2. Identified Issues and Recommendations for Axsome Therapeutics, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
		prominence commensurate with the prominence with which such proprietary name appears, taking into account all pertinent factors, including typography, layout, contrast, and other printing features.	
2.	As currently presented, the strength statement does not include a space between the numbers and mg unit of measure (i.e., 20mg/10mg) on the principal display panel. Additionally, we acknowledge the strength statement was bolded; however, the prominence can be further improved.	Lack of adequate spacing and prominence may impact readability.	We recommend revising the 20mg/10mg strength statement to include adequate spacing. Revise to read: 20 mg/10 mg Additionally, consider increasing the font size of the strength statement.
3.	The manufacturer name “axsome” competes in prominence with critical product information. Specifically, it is significantly larger and more prominent than the established name and strength.	Critical product information such as the established or and product strength should appear as the most prominent information.	We recommend decreasing the font size of the “axsome” name and/or increasing the font size of critical information as noted in recommendations above.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 4 presents relevant product information for Symbravo that Axsome Therapeutics, Inc. submitted on June 30, 2021, and the listed drugs, Maxalt and Anjeso and Mobic.

Table 4. Relevant Product Information for Symbravo and Listed Drugs, Maxalt[e], Anjeso[f] and Mobic[g]

Product Name	Symbravo	Maxalt (NDA 020864)	Anjeso (NDA 210583)	Mobic (NDA 020938)
Initial Approval Date	N/A	6/29/1998	2/20/2020	4/13/2000
Active Ingredient	meloxicam and rizatriptan	rizatriptan benzoate	meloxicam	
Indication	For the acute treatment of migraine with or without aura in adults	For the acute treatment of migraine with or without aura in adults and in pediatric patients 6 to 17 years old.	For use in adults for the management of moderate-to-severe pain, alone or in combination with non-NSAID analgesics.	Osteoarthritis (OA), Rheumatoid Arthritis (RA), Juvenile Rheumatoid Arthritis (JRA) in patients who weigh ≥ 60 kg
Route of Administration	oral	oral	intravenous	oral
Dosage Form	tablet	tablet	injection	tablet
Strength	20 mg/10 mg	5 mg and 10 mg	30 mg/mL per vial	7.5 mg and 15 mg
Dose and Frequency	The recommended dose is one tablet by mouth at the onset of a migraine. The safety and effectiveness of a	Adults: 5 mg or 10 mg for the acute treatment of migraines. The 10-mg dose may provide a greater effect than the 5-	30 mg once daily, administered by intravenous bolus injection over 15 seconds.	OA and RA: Starting dose: 7.5 mg once daily Dose may be increased to 15 mg once daily

[e] Maxalt (rizatriptan benzoate) tablet [NDA 020864 Prescribing Information]. Drugs@FDA. U.S. Food and Drug Administration. OCT 2019 [cited 2024 SEP 20]. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/020864s023,020865s024lbl.pdf

[f] Anjeso (meloxicam) injection (NDA 210583) Prescribing Information. Drugs@FDA. U.S. Food and Drug Administration. JUL 2021 [cited 2024 SEP 20]. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/210583s001lbl.pdf

[g] Mobic (meloxicam) tablet (NDA 020938) Prescribing Information. Drugs@FDA. U.S. Food and Drug Administration. APR 2021 [cited 2024 SEP 20]. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/020938s028lbl.pdf

	second dose have not been established.	mg dose but may have a greater risk of adverse reactions. Redosing in Adults: If the migraine returns, a second dose may be administered 2 hours after the first dose. The maximum daily dose should not exceed 30 mg in any 24-hour period. Pediatric Patients (Age 6 to 17 years): 5 mg in patients weighing less than 40 kg (88 lb) and 10 mg in patients weighing 40 kg (88 lb) or more.		JRA: 7.5 mg once daily in children ≥ 60 kg. MOBIC Tablets are not interchangeable with approved formulations of oral meloxicam even if the total milligram strength is the same.
How Supplied	Bottles of 9 tablets: The tablets are white and modified capsule-shaped, debossed with "MXRZ" on one side and "20/10" on the other.	5 mg: pale pink, capsule-shaped, compressed tablets coded MRK on one side and 266 on the other 10 mg: pale pink, capsule-shaped, compressed tablets coded MAXALT on one side and MRK 267 on the other.	Sterile, opaque, pale yellow, non-pyrogenic, aqueous dispersion intended for intravenous use available as a clear, 2 mL, single-dose vial containing 30 mg/mL per vial.	7.5 mg tablets in bottles of 100 tablets; 15 mg tablets in bottles of 100 tablets.

Storage	Store at 20°C to 25°C (68°F to 77°F), excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature].	Store at room temperature, 15°C-30°C (59°F-86°F)	Store at 15°-25°C (59°-77°F), with excursions permitted between 4°-30°C (40°-86°F). Do not freeze. Protect from light.	Store at 20°C-25°C (68°F-77°F); excursions permitted to 15°C-30°C (59°F-86°F) [see USP Controlled Room Temperature] Keep MOBIC tablets in a dry place.
Container Closure	High-density polyethylene (HDPE) bottles with a (b) (4) closure and foil induction seal. Bottles are filled with either 3 tablets for the physician sample or 9 tablets for the commercial prescription and include a silica gel desiccant packet.	Carton of 18 tablets	Single dose vial	Aluminum blister packs

APPENDIX B. LABELS AND LABELING

B.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[h] along with postmarket medication error data, we reviewed the following Symbravo labels and labeling submitted by Axsome Therapeutics, Inc.

- Container (Trade and Professional Sample) labels received on June 28, 2024
- Prescribing Information (image not shown) received on September 27, 2021, available from \\CDSESUB1\evsprod\nda215431\0005\m1\us\1-14-1-3-draft-label-clean.doc
- Medication Guide (image not shown) received on June 30, 2021, available from \\CDSESUB1\evsprod\nda215431\0001\m1\us\1-14-1-3-draft-med-guide.docx

B.2 Label and Labeling Images

Container Labels

(b) (4)

[h] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

APPENDIX C. Container Label Recommendations from Previous DMEPA Review

Previous DMEPA Label & Labeling Review completed March 16, 2022, available from: https://darrts.fda.gov/darrts/ViewDocument?documentId=090140af8064f921.

Excerpt (container label recommendations only):

5 RECOMMENDATIONS FOR AXSOME THERAPEUTICS, INC.

Table 3. Identified Issues and Recommendations for Axsome Therapeutics, Inc. (entire table to be conveyed to Applicant)			
	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 form, and strength for drug products. See *Draft Guidance for Industry: Safety Considerations for*	We recommend relocating the dosage form on the same line or directly below the established name. For example: **Symbravo** (meloxicam and rizatriptan) tablet 20 mg/10mg OR

Table 3. Identified Issues and Recommendations for Axsome Therapeutics, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	**RATIONALE FOR CONCERN**	**RECOMMENDATION**
		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.	**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) (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 208.24(d), the label shall instruct the authorized dispenser to provide a	We recommend revising the Medication Guide statement (b) (4) (b) (4) to "Attention: Dispense the accompanying Medication Guide to each patient."

Table 3. Identified Issues and Recommendations for Axsome Therapeutics, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	**RATIONALE FOR CONCERN**	**RECOMMENDATION**
		Medication Guide to each patient and shall state how the Medication Guide is provided.	
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 "Each tablet contains: 20 mg meloxicam and 10 mg rizatriptan" 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 example, JU) characters.	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 does not clearly communicate whether 'MA' or 'JU' is for the months of	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-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if

Table 3. Identified Issues and Recommendations for Axsome Therapeutics, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	**RATIONALE FOR CONCERN**	**RECOMMENDATION**
		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.	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.

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/

BEVERLY WEITZMAN
09/23/2024 08:27:35 AM

STEPHANIE L DEGRAW
09/23/2024 09:01:35 AM

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: May 2, 2022

To: Lana Chen, Regulatory Project Manager
Division of Neurology II (DN II)

Tracy Peters, Associate Director for Labeling, DN II

From: Sapna Shah, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Aline Moukhtara, Team Leader, OPDP

Subject: OPDP Labeling Comments for SYMBRAVO (meloxicam and rizatriptan) tablets, for oral use

NDA: 215431

This memo is in response to the DN II labeling consult request dated July 21, 2021. Reference is made to a Complete Response letter that was issued on April 29, 2022. Therefore, OPDP defers comments on the proposed labeling at this time, and request that DN II submit a new consult request during the subsequent review cycle. If you have any questions, please contact Sapna Shah at (240) 402-6068 or Sapna.Shah@fda.hhs.gov.

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/

SAPNA SHAH
05/02/2022 03:17:32 PM

CLINICAL OUTCOME ASSESSMENT (COA) CONSULT REVIEW

COA Tracking ID:	C2021353
NDA#/Referenced IND for NDA:	NDA215431
Applicant:	(b) (4)
Established Name/Trade Name:	AXS-07
Indication:	Migraine ☐Rare Disease/Orphan Designation ☐Pediatrics
PDUFA Goal Date:	April 29, 2022
Review Division:	Division of Neurology (DN2)
Clinical Reviewer:	Viveca Livezey
Clinical Team Leader (TL)	Heather Fitter
Regulatory Project Manager:	Lana Chen
COA Reviewer:	Robert Fieo
COA TL:	David Reasner
Instruments reviewed:	Migraine Treatment Optimization Questionnaire (M-TOQ-4) ☒ Patient-reported outcome (PRO)

Table of Contents

1. EXECUTIVE SUMMARY

In this submission, the applicant is seeking approval of AXS-07 (a fixed-dose combination of meloxicam and rizatriptan; 20 mg meloxicam-10 mg rizatriptan) for the acute treatment of migraine (b) (4) The applicant submitted a Clinical Study Report (Study AXS-07-301) describing their multi-center, randomized, double-blind, 4-arm, parallel group, single-dose, placebo and active-controlled study. The primary objective of this review is to evaluate from a COA perspective, (b) (4) the Migraine Treatment Optimization Questionnaire (M-TOQ-4). This instrument is a 4-item PRO intended to assess 4 domains of migraine treatment efficacy, which include:1) functioning, 2) rapid relief, 3) consistency/duration of relief, 4) risk of recurrence (additionally characterized as "emotional response"& comfort level in planning daily activities). The M-TOQ-4 was not included in the endpoint hierarchy but, rather, used as a screening tool for the Sponsor's enrichment strategy. (b) (4) The main thesis of this review is that these M-TOQ-4 values (threshold & mean) may be difficult to meaningful interpret, due to insufficient evidence pertaining to content comprehensiveness and measurement properties.

(b) (4)

Reviewer comment(s): *DCOA met with Clinical (Clinical Reviewer & MO) to determine the value of an IR covering qualitative evidence meant to support the content validity and quantitative evidence supporting proposed M-TOQ-4 cut scores.; no IR was issued.* (b) (4)

This New Drug Application (NDA) is based on positive results from the Phase 3 MOMENTUM trial in acute migraine (Study AXS-07-301), which was conducted pursuant to a Special Protocol Assessment, and the Phase 3 INTERCEPT trial (Study AXS-07-303). As per the sponsor, AXS-07 rapidly, substantially, and statistically significantly improves migraine pain and associated symptoms as compared to placebo, meloxicam, and rizatriptan. The efficacy of AXS-07 was demonstrated on the co-primary and key secondary endpoints, and across a broad range of clinically relevant measures.

Summary of Efficacy Endpoint Results (Clinical Study Report AXS-07-301–Synopsis)

	AXS-07 (N=428)	Placebo (N=209)	Meloxicam (N=421)	Rizatriptan (N=419)
Co-Primary Endpoints (vs. Placebo)				
2-hour Pain Freedom	85 (19.9%)	14 (6.7%)	49 (11.6%)	73 (17.4%)
p-value vs. AXS-07		<0.001	0.001	NS
2-hour MBS Freedom	158 (36.9%)	51 (24.4%)	137 (32.5%)	150 (35.8%)
p-value vs. AXS-07		0.002	NS	NS
Onset of Efficacy				
Time to Pain Relief (median)	1.5 hours	12.0 hours	4.0 hours	4.0 hours
p-value vs. AXS-07		<0.001	<0.001	<0.001
Sustained Efficacy				
24-hour Sustained Pain Freedom (**Key Secondary**)	69 (16.1%)	11 (5.3%)	37 (8.8%)	47 (11.2%)
p-value vs. AXS-07		<0.001	0.001	0.038
48-hour Sustained Pain Freedom	66 (15.4%)	11 (5.3%)	34 (8.1%)	37 (8.8%)
p-value vs. AXS-07		<0.001	<0.001	0.003
24-hour Sustained Pain Relief	228 (53.3%)	70 (33.5%)	177 (42.0%)	184 (43.9%)
p-value vs. AXS-07		<0.001	0.001	0.006
48-hour Sustained Pain Relief	199 (46.5%)	65 (31.1%)	159 (37.8%)	153 (36.5%)
p-value vs. AXS-07		<0.001	0.010	0.003

Notes on Table: Percent reflects, patients experiencing efficacy across several trial timeframe endpoints (i.e., 2-hour, 24 & 48-hours); for sustained pain freedom endpoints, the denominator is the percent of patients with pain freedom at Hour 2. Likewise, for sustained pain relief endpoints, the denominator is the percent of patients with pain relief at Hour 2."

(b) (4)

2 REVIEW CONCLUSIONS

Review conclusions are based on the following supportive documentation:

1) Clinical Study Report AXS-07-301 (*Synopsis*; Report date, 09 June 2021)
2) Original Protocol Phase 3 AXS-07-301 trial (Version 1.0, 16 Jan 2019)
3) Clinical Study Report AXS-07-301 (*body*; Version date, 16 Jan 2019)
4) Reference literature provided in support of M-TOQ-4 validation:
   Lipton et al., 2017; Lipton et al., 2016; Lipton et al, 2015; Lipton et al, 2013; Lipton et al, 2009; Lipton et al, 2008; Lipton et al., 1999

The M-TOQ-4 was reviewed for content validity, as well as measurement properties: The primary conclusion of this review is that M-TOQ-4 values (b) (4)) may be difficult to meaningful interpret, due to insufficient evidence pertaining to content comprehensiveness and measurement properties.

Issue 1: Data interpretability.

- The Sponsor's scoring algorithm entails summing the 4-items to generate a total score. The developer considered the 15-item M-TOQ version (M-TOQ-15) too long for use in **primary care settings** (Lipton et al., 2009). Thus, to create a short form, domains were reviewed to identify the single item that best represented the entire domain by examination of the item-to-total correlations within each domain. Previously, the developer had noted only modest correlations among the **five treatment optimization** domains in the M-TOQ-15 and, therefore, it is unlikely that the abbreviated scale, derived from the most distinctive items from each domain, strengthened the relationship among domains. The currently available evidence also does not support a single concept and, consequently, employing the total score may not be warranted, depending on the application. Thus, it is particularly important to determine if all domains in the M-TOQ-4 are contributing information in a balanced manner or whether total score values are overly influenced by a subset of the four treatment optimization domains.
- The scoring methodology issue (i.e., whether subdomains can be effectively aggregated into a single score) limits confidence in the treatment proposed optimization thresholds (i.e., *maximum*= score of 8, *moderate*= 4-7, *poor*= 1-3, and *very poor*= 0). Nonetheless, measurement weaknesses aside, when the protocol-specified, **enrichment threshold** (total score ≤ 7) was used to dichotomize patients into those with an inadequate response to prior acute migraine therapy (i.e., those patients who report experiencing migraine relief, less than half the time on any M-TOQ-4 item), the enrolled patients were adequately symptomatic at baseline, and the alpha-controlled endpoints were sensitive to apparent treatment benefit.

  Reviewer Comment(s): *Further, the key concern is whether the M-TOQ-4 measures what the sponsor says it measures, i.e., the inclusion criterion selects adequate/inadequate response to the prior therapy. In this case, two related but distinct COA suitability criteria appear relevant:*

  1) *Scoring and structure of the total score–the domains encompass four apparently meaningful endorsements of migraine relieve.*
  2) *Whether the proposed enrichment cut score is the optimal screening threshold, and the manner in which it outperforms alternative thresholds.*

Issue 2: Content relevancy.

- The initial M-TOQ validation work (Lipton et al., 2009) began with 19 items (item pool), based on a review of existing migraine scales from the literature and **input from clinical experts**. The final M-TOQ-15 scale (15-items) was grouped into 5 domains of migraine treatment optimization, which included: 1) functioning, 2) rapid relief, 3) consistency of relief, 4) risk of recurrence and 5) tolerability. It is unclear whether:
  a. The abbreviated scale (i.e., M-TOQ-4) assesses domains that are most relevant to patients in the context of adequate response to treatment. For example, it is unclear as to whether the tolerability domain was least relevant in this context and, thus, most appropriate to exclude.
  b. A single item per domain is sufficient to accurately represent the patient experience. For instance, perhaps certain domains are more complex than others and those

domains might benefit from additional items while still employing far fewer items than the M-TOQ-15.

Reviewer Comment(s): The M-TOQ-4 response scale includes four frequency-based options (never [0], rarely [0], <half the time [1], and ≥ half the time [2]). Given the currently available evidence, it is unclear whether patients understand the response options as intended, or the degree to which response options correctly convey the patient experience for a given item/domain.

Issue 3: Recall.
There exists some commentary from the literature for this indication related to the suitability of an extended recall period for headache questionnaires (i.e., one-month). For example, Kawata et al. noted the limits in assessing migraine symptoms with extended recall due to day-to-day fluctuations that can occur during the various phases of a migraine episode *(Headache* 2019;59:1253-1269).

From a COA perspective, (b) (4) there is not sufficient evidence to support the M-TOQ-4 as a measurement tool. The paucity of information pertains to measurement properties, but also to content validity (e.g., patient acceptance of item response options). Additional analyses would increase the clarity and interpretability of M-TOQ-4 score values and benefit the sponsor's future drug development efforts. These might include the following:

- The Sponsor provided several references from the literature (authored by the scale developer) in support of M-TOQ-4 validity and measurement properties. However, a majority of the referenced studies include alternative M-TOQ versions, differing in item content and response options than the M-TOQ-4. Validation of the original version, M-TOQ-15, reported a "treatment optimization" concept that was comprised of five distinct domains or subdomains. There was evidence from the literature (Lipton et al., 2009) indicating that the statistically derived factors of the M-TOQ, identified by factor analysis, are modestly correlated which raises concerns over aggregating domains into a single construct (i.e., total score). Thus, the Sponsor should examine statistical association between each M-TOQ-4 domain and their associations with the total score in the target population.
- The Sponsor proposed several thresholds, which included: M-TOQ-4 total score of 8, designating **maximum** migraine treatment efficacy; a range of total scores (4 to 7) defined as **moderate** treatment efficacy; a rating of **poor** efficacy for patients presenting with scores in the range of 1 to 3 ; and a **very poor** classification for patients who received a score of zero. Finally, a cut-score of ≤7 (i.e., all patients not presenting with a history of maximum efficacy) was employed as the threshold for study enrichment. Evidence in support of the proposed thresholds was not presented. Therefore, future evidence, in support of threshold suitability, should include sensitivity/specificity (e.g., ROC curves).

- Patient input (qualitative concept elicitation) confirming whether the M-TOQ-4 effectively captures concepts of treatment efficacy that are most relevant and meaningful to patients in the context of adequate response to treatment.
- Additional patient input (qualitative cognitive interviews) confirming whether the response options are functioning as intended, as well as subsequent quantitative findings (e.g., floor or ceiling effects at the item level).

(b) (4)

Reviewer Comment(s): *Lipton et al. (2015 [scale developer]) indicated, "Cut scores were defined based on clinical judgment and psychometric analysis. After selecting these cut scores, we performed sensitivity analyses with various cut scores and obtained fundamentally similar results (data available upon request)." This evidence should be provided for FDA review.*

(b) (4)

3 BACKGROUND AND CORRESPONDENCE ON CLINICAL OUTCOME ASSESSMENT(S)

Regulatory Background:

- Pre-IND Written Responses Only meeting minutes dated August 25, 2017, confirmed the following:
  - One Phase 3 study would be sufficient to support an NDA (Question 5f).
  - The long-term safety database for AXS-07 should include at least 300 patients treated for 6 months, and 100 patients treated for 1 year, treating a minimum of 2 migraines/month.

Reviewer Comment(s): *These values reflect ICH recommended minimums and, thus, it appears that there are no special considerations for the proposed patient population.*

- The Sponsor submitted Study AXS-07-301 for a Special Protocol Assessment (SPA), and an initial No Agreement Letter, sent December 12, 2018, confirmed the following:
  a. No objection to the inclusion of patients who have a history of inadequate response to prior acute migraine treatments as a type of enrichment strategy.
  b. Agreement on the use of sustained headache pain freedom between Hour 2 and Hour 24 to establish component contribution to overall drug effect for the individual components of AXS-07.
- The Sponsor revised Study AXS-07-301 as requested in the No Agreement Letter and a SPA agreement was reached on January 31, 2019, which confirmed that the agreed

design and planned analysis adequately address the objectives necessary to support a regulatory submission.

Reviewer Comment(s): *The protocol synopsis (dated 09 June 2021) suggests that the Phase 3 study (AXS-07-301) SAP accounted for a history of inadequate response to prior acute migraine treatments, i.e., assessed using the 4-item Migraine Treatment Optimization Questionnaire (M-TOQ-4).*

The study was conducted pursuant to the agreed SPA, and the statistical analysis was performed according to the agreed SAP. The SAP was finalized and submitted to the Investigational New Drug Application (IND) prior to database lock and study unblinding.

- At the pre-NDA meeting, held on July 16, 2020, the following agreements were reached:
  – The text portion of the integrated summaries of the safety and efficacy will be presented as the Clinical Summaries of Efficacy (Module 2.7.3) and Safety.

Previous COA Reviews:
NA

Disease Background:
Migraine is a common neurologic disorder that presents with attacks of **head pain** and associated symptoms **such as nausea, vomiting, photophobia, and phonophobia**, and in most patients (53-79%), **cutaneous allodynia**. Allodynic patients experience ordinarily non-painful stimuli as painful (e.g., brushing hair, wearing glasses). Allodynia most often develops during the first few hours of an attack, although patients with chronic migraine are sometimes allodynic between attacks (Lipton et al., 2017).

The presence of allodynia can influence the treatment of acute migraine attacks. Cutaneous allodynia has been shown to be strongly predictive of poor pain-free (PF) response rates at 2 hours through 24 hours after triptan therapy; in the absence of allodynia, overall PF response rates nearly doubled (from 48 to 93% [Lipton et al., 2017]).

Other factors associated with acute treatment response include the **intensity of pain** at the time of treatment and the **interval** from headache onset to treatment (Lipton et al., 2017).

Reviewer Comment(s): *On the topic of aura symptoms, it was indicated (see protocol synopsis dated 09 June 2021) that, to qualify for the study, patients were required to have an established diagnosis of migraine (history indicating the presence of migraine for at least 1 year)* ***with or without aura*** *as defined by the International Classification of Headache Disorder, 3rd Edition (ICHD-3).*

Investigational Product
Rizatriptan is a 5-HT1B/D agonist (triptan) currently approved for the acute treatment of migraine (Maxalt product label), and meloxicam is a nonsteroidal anti-inflammatory drug (NSAID) currently approved for the relief of the signs and symptoms of osteoarthritis and rheumatoid arthritis, and for the management of moderate-to-severe pain (Mobic product label; Anjeso product

label). AXS-07 (20 mg meloxicam-10 mg rizatriptan) is a fixed-dose combination of meloxicam and rizatriptan being developed for the acute treatment of migraine with or without aura in adults.

4 CLINICAL OUTCOME ASSESSMENT REVIEW

4.1 Clinical Trial Population

To qualify for the study, patients were required to have:

- An established diagnosis of migraine (history indicating the presence of migraine for at least 1 year) with or without aura as defined by the International Classification of Headache Disorders, 3rd Edition (ICHD-3).
- Experiencing an average of 2 to 8 moderate or severe migraine attacks per month (no more than 10 migraine days per month) over the past three months and, importantly, have a history of inadequate response to prior acute migraine treatments.
- An inadequate response was defined as the following: a score of ≤7 on the M-TOQ-4 which corresponds to less than maximal migraine treatment efficacy in response to prior treatments (timeframe/recall equal to **preceding four weeks at screening**).

A complete list of the inclusion and exclusion criteria is summarized in section 9.3. "Selection of Study Population" of Clinical Study Report AXS-07-301.

4.2 Clinical Trial Design

Table 1. Clinical Trial Design for Study AXS-07-301

Trial Phase	Trial Design	Trial Duration	Registration Intent
Phase 3	☐ Single arm ☐ Open label ☒ Double-blind ☒ Randomized ☐ Placebo-/Vehicle-controlled ☒ Active comparator-controlled ☐ Cross-over ☐ Multinational ☐ Non-inferiority	12 weeks to complete; 14-day screening; 10 weeks to complete	Yes

The Sponsor conducted a Phase 3, multicenter, randomized, double-blind, 4-arm, parallel group, single-dose, placebo- and active-controlled study to evaluate the efficacy and safety of AXS-07 in patients with a history of inadequate response to prior acute migraine treatments as assessed by the M-TOQ-4. Patients who successfully completed the screening visit (Visit 1) and continued to meet all entry criteria were randomly assigned to treatment at Visit 2 (randomization). Patients received, in a 2:2:2:1 ratio, AXS-07, rizatriptan 10 mg, meloxicam 20 mg, or placebo, all dispensed for at-home study treatment of a single migraine attack. A total of 1477 patients were included in the Intent-to-Treat (ITT) population (efficacy analyses): 428 patients in the AXS-07 group, 419 patients in the rizatriptan group, 421 patients in the meloxicam group, and 209 patients in the placebo group.

4.3 Endpoint Position, Definition, and Assessment Schedule

Table 2 describes the placement of the COAs in the endpoint hierarchy, including the endpoint definition and assessment schedule.

Table 2. Endpoint Position, Definition, and Assessment Schedule for Study AXS-07-301

Endpoint Position	Assessment (If COA, specify Name and Type)	Endpoint Definition	Assessment Frequency
Co-Primary	4-point rating scale from the Headache Diary: migraine pain intensity;	Percentage of subjects with headache pain freedom at Hour 2, with headache pain freedom defined as a reduction in headache severity from moderate or severe pain to no pain	Day 1
Co-Primary	Presence or absence of Most Bothersome Symptom (MBS; nausea, photophobia, or phonophobia) from the Headache Diary	Percentage of subjects with absence of the MBS (nausea, photophobia, or phonophobia) at Hour 2, with the MBS defined at the onset of migraine, prior to drug administration	Day 1
Key Secondary ☒ Multiplicity adjusted	headache pain freedom; pain freedom between Hours 2 and Hours 24	Sustained headache pain freedom between Hours 2 and 24, defined as having no headache pain at Hour 2	Day 1
Secondary ☒ Multiplicity adjusted	functional disability; daily activities; 4-point rating scale from the Headache Diary	Percent of subjects able to perform normal daily activities at Hour 2	Day 1

Reviewer Comment(s): *For 48 hours after study drug dosing, subjects were to use the Headache Diary to record the* ***intensity*** *of the migraine headache (1-mild, 2-moderate, 3-severe or 0-none),* ***presence or absence migraine*** *symptoms (photophobia, phonophobia, nausea), functional disability, and Patient Global Impression of Change (PGI-C). Headache Diary data were to be collected at the following times: Baseline (at onset of moderate to severe migraine pain, [pre-dose]) and 15, 30 and 45 minutes, and 1, 2, 4, 12, 16, 24, and 48 hours after dosing.*

4.5 Clinical Outcome Assessment(s)

4.5.1 Clinical Outcome Assessment Description(s)

Migraine Treatment Optimization Questionnaire (M-TOQ-4)

As per the sponsor, M-TOQ-4 is a validated, reliable, self-reported, easy-to-use, 4-item questionnaire that assesses the adequacy of treatment efficacy for the purpose of optimizing treatment (Lipton et al, 2015; Lipton et al, 2013; Lipton et al, 2009; Lipton et al, 2008). For each of the 4 questions of the M-TOQ-4, the response scale includes 4 frequency-based options (never [0], rarely [0], <half the time [1], and ≥ half the time [2]). The maximum total score is 8, representing maximal treatment efficacy. The M-TOQ-4 was administered at screening to determine eligibility.

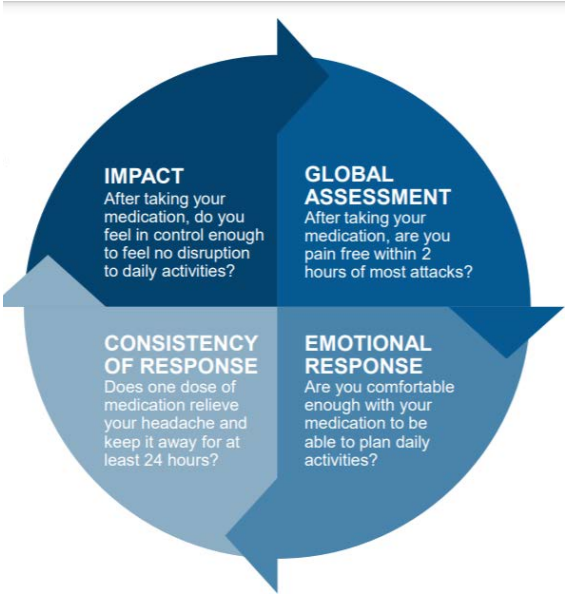
4.5.2 Conceptual Framework(s)

The M-TOQ-4 is a PRO developed to:

- Identify patients with an inadequate treatment response
- Identify patients who require a change of their current acute treatment

The conceptual framework for the M-TOQ-4 (Lipton et al., 2016) is presented below:

Figure 1. M-TOQ-4 Conceptual Framework



Reviewer Comment(s): *The initial validation work on the* M-TOQ-15 *(Lipton et al., 2009) identified 5 domains of migraine treatment efficacy, which included: 1) functioning, 2) rapid relief, 3) consistency of relief, 4) risk of recurrence and 5) tolerability.*

4.5.3 Scoring Algorithm

Each item is rated on a 4-category, frequency-based, response scale (never [0], rarely [0], <half the time [1], and ≥ half the time [2]). Each item response is summed to derive the M-TOQ-4 total score, with a range from 0 to 8. The developer identified four "treatment efficacy" thresholds, which include:

- *Maximum*, based on a sum score of 8
- *Moderate*, including a range of scores from 4-7
- *Poor*, including a range of scores, from 1-3
- *Very poor*, to characterize a score of 0

The sponsor performed a pivotal study in which patients were required to have a score of ≤ 7 on the M-TOQ-4 for inclusion – corresponding to moderate or worse response to prior treatments over the preceding 4 weeks.

Reviewer comment(s): *In a sample of 5,681 eligible respondents with episodic migraine (EM) who completed the M-TOQ-4, the developer observed the following frequencies for the four groupings noted above (Lipton et al., 2015):*

- *1,648 respondents (29.0%) had **maximum** treatment efficacy*
- *2,657 (46.8%) had **moderate** treatment efficacy*
- *1,007 (17.7%) had **poor** treatment efficacy*
- *369 (6.5%) had **very poor** treatment efficacy*

4.5.4 Content Validity

Literature Review:

The item pool for the long-form version of the M-TOQ was developed through an iterative process.

- Two study authors reviewed published questionnaires focusing on treatment needs, disability and quality of life in migraine as well as patient preference and satisfaction.
- Questions from the published literature were organized according to candidate domains shown by previous research to be important for assessing the benefit of acute treatments for migraine headaches.
- These domains included: ability to function, rapid relief of headache pain, consistency of response, improvement in associated symptoms, prevention of headache recurrence, side-effects and global response.

Expert Input:

An Expert Panel including neurologists, headache specialists, primary care doctors, epidemiologists, psychiatrists and methodologists prioritized the domains and the candidate questions in each domain.

The developer considered the M-TOQ-15 version (15-items over 5 domains) too long for use in **primary care settings** (Lipton et al., 2009). Thus, to create a short form, domains were reviewed to identify the single item that best represented the entire domain; this was undertaken by examining item-to-total correlations within each domain. The result was a five-item scale (M-TOQ-5) with the following items for each factor:

- consistency (item 8)
- functioning (item 3)
- recurrence (item 14)
- side-effects (item 16)
- rapid relief (item 6); later replaced with a **global item** (#18)

Although item 6 (pain-free) and item 8 (pain relief) loaded on different factors in a psychometric analysis employing common factor analyses, they are very similar. Therefore, item 6 (pain-free) was later omitted from the five items and replaced with item 18.

Patient Input
Cognitive interviews to establish **cultural or linguistic equivalence**.
Sample (Lipton et al., 2009): The sample included 50 patients per language group (five languages), with an age range of 40–71. Patients were typically women (90.1%), with chronic migraine headaches of moderate-to-severe intensity (92.7%).

Reviewer Comment(s): *It's unclear how well the qualitative reporting noted above will align with patient experience for the currently proposed indication–* (b) (4)

Methodology: Ease of comprehension of the questionnaires was evaluated by focus groups conducted in each country. Based on the results of the focus groups, the language of individual questions was modified, as needed.

Reviewer Comment(s): *Seemingly, the primary of objective of the conducting cognitive interviews was to establish language equivalence. Any future FDA review of the M-TOQ-4 should inquire as to the availability of qualitative study materials (e.g., cognitive interview guides).*

4.5.5 Other Measurement Properties

The original validation work was conducted on the 19-item pool using dichotomous yes/no response options (Lipton et al., 2009). The developer subsequently modified the response scale to four frequency-based response options (never, rarely, less than half the time, and more than or equal to half the time) and selected 6 key questions. A 6-item version was included in the AMPP Study survey in 2006 and 2007, but the developer notes that additional validation work was done on the 6-item version after those surveys (Lipton et al., 2012). In a later study, the 6-item version was reduced to 4-items (the currently proposed PRO) "that best assessed treatment efficacy" (Lipton et al., 2015), but the developer acknowledges that the **M-TOQ-4 has not been validated as a stand-alone measure**. Finally, the developer noted recall bias as a potential limitation of the measure due to the extended recall period (i.e., how often patients achieved certain effects with their "usual" acute headache treatment(s) over the preceding month [Lipton et al., 2016]).

Construct validity
Structural validity (factor structure)
The developer reported a 5-factor model for the M-TOQ-15. Five treatment optimization domains/factors were identified: 1) functioning, 2) rapid relief, 3) consistency of relief, 4) risk of recurrence and 5) tolerability. It was further indicated that the inter-factor correlations were low to moderate (***r* = 0.04–0.52**), suggesting that some factors may measure distinct clinical dimensions of treatment optimization (Lipton RB et al., 2009).

Convergent validity
Pearson correlation coefficients were used to assesses M-TOQ associations with headache-related disability (MIADS; 3-month look-back), functional status & quality of life (HIT-6; relationship with domains of pain, social functioning, energy level, and cognitive/mental health), and perceived quality of life (MSQoL). Results for both M-TOQ-15 and M-TOQ-5 correlations were modest and ranged from 0.30 to 0.44.

Reliability

Internal consistency

The M-TOQ-4 had a Cronbach's α of **0.59**, which was increased to 0.66 with the addition of the **global item**, represented in the M-TOQ-5 version.

Reviewer Comment(s): *In addressing the lower than generally accepted internal consistency, the developer notes the following: "Since we selected the single items that are most representative of different domains, and as we chose these domains as they represent different dimensions of a broader concept, it is not surprising that the alphas for the M-TOQ-4 and M-TOQ-5 are modest" (Lipton et al., 2009).The degree of divergence between domains appears to warrant further consideration. It may be, for example, that a smaller set of domains are sufficiently uni dimensional.*

Test–retest reliability

Test-retest reliability was established in a sub-sample of sixty-four patients who completed the M-TOQ-15 twice (mean number of days between administrations was 10.5 [SD 4.7]). The developer reported intraclass correlation coefficients for three M-TOQ versions (19/15/5 items), ranging from .87-.89. Lastly, item level test–retest reliability revealed *k* values ranging from 0.61 to 0.87 (Lipton et al., 2009).

Reviewer Comment(s): *The scale developer indicated good test-retest reliability at the domain and item level. However, it appears that these findings were based on an older version of the M-TOQ, which employed a simpler "yes/no" item response format.*

5 Page(s) have been Withheld in Full as B4 (CCI/TS) immediately following this page

---

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/

ROBERT A FIEO
04/22/2022 03:02:29 PM

DAVID S REASNER
04/22/2022 04:50:40 PM

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy Initiatives
Division of Medical Policy Programs

REVIEW DEFERRAL MEMORANDUM

Date:	April 19, 2022
To:	Lana Chen Regulatory Project Manager **Division of Neurology II (DN2)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Sharon Williams, MSN, BSN, RN Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
From:	Kelly Jackson, PharmD Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
Subject:	Review Deferred: Medication Guide (MG)
Drug Name (established name):	SYMBRAVO (meloxicam and rizatriptan)
Dosage Form and Route:	tablets, for oral use
Application Type/Number:	NDA 215431
Applicant:	Axsome Therapeutics, Inc.

1 INTRODUCTION

On June 30, 2021, Axsome Therapeutics, Inc. submitted for the Agency's review a 505(b)(2) New Drug Application (NDA) 215431 for SYMBRAVO (meloxicam and rizatriptan) tablets, for oral use. The Reference Listed Drugs are ANJESO (meloxicam) Injection, NDA 210583 and MAXALT (rizatriptan benzoate) tablets, NDA 020864. The proposed indication for SYMBRAVO is the acute treatment of migraine with or without aura in adults. On July 21, 2021, the Division of Neurology II (DN2) requested that the Division of Medical Policy Programs (DMPP) review the Applicant's proposed Medication Guide (MG), for SYMBRAVO (meloxicam and rizatriptan).

This memorandum documents the DMPP review deferral of the Applicant's proposed MG for SYMBRAVO (meloxicam and rizatriptan).

2 CONCLUSIONS

Due to outstanding clinical deficiencies, DN2 plans to issue a Complete Response (CR) letter. Therefore, DMPP defers comment on the Applicant's patient labeling at this time. A final review will be performed after the Applicant submits a complete response to the Complete Response (CR) letter. Please send us a new consult request at such time.

Please notify us if you have any questions.

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/

KELLY D JACKSON
04/19/2022 07:59:52 AM

SHARON W WILLIAMS
04/19/2022 08:38:01 AM

LASHAWN M GRIFFITHS
04/19/2022 12:38:07 PM

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis 2 (DMEPA 2)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	March 16, 2022
Requesting Office or Division:	Division of Neurology 2 (DN 2)
Application Type and Number:	NDA 215431
Product Name, Dosage Form, and Strength:	Symbravo[a] (meloxicam and rizatriptan) tablet, 20 mg/10 mg
Product Type:	Multi-Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Axsome Therapeutics, Inc.
FDA Received Date:	June 30, 2021 and September 27, 2021
OSE RCM #:	2021-1315
DMEPA 2 Safety Evaluator:	Beverly Weitzman, PharmD
DMEPA 2 Acting Team Leader	Stephanie DeGraw, PharmD

[a] The proposed proprietary name, Symbravo was found conditionally acceptable on March 7, 2022.

1 REASON FOR REVIEW

As part of the approval process for Symbravo (meloxicam and rizatriptan) tablet, the Division of Neurology 2 (DN 2) requested that we review the proposed Symbravo prescribing information (PI), medication guide (MG) and container labels for areas of vulnerability that may lead to medication errors.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B – N/A
Human Factors Study	C – N/A
ISMP Newsletters*	D – N/A
FDA Adverse Event Reporting System (FAERS)*	E – N/A
Other	F – N/A
Labels and Labeling	G

N/A=not applicable for this review
*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 CONCLUSION & RECOMMENDATIONS

The proposed prescribing information (PI), medication guide (MG) and container labels may be improved to promote the safe use of this product from a medication error perspective. We provide the identified medication error issues, our rationale for concern, and our proposed recommendations to minimize the risk for medication error in Section 4 (Table 2) for the Division and in Section 5 (Table 3) for Axsome Therapeutics, Inc.

4 RECOMMENDATIONS FOR DIVISION OF NEUROLOGY 2 (DN 2)

Table 1. Identified Issues and Recommendations for Division of Neurology 2 (DN 2)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Prescribing Information (PI) and Medication Guide (MG)– General Issues			
1.	In the product title of the PI and throughout the labeling, we note that the established name is presented as the salt form (i.e., rizatriptan benzoate) instead of the active moiety (i.e., rizatriptan).	This is not in accordance 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.	Revise the active ingredient from "rizatriptan benzoate" to read "rizatriptan" in the product title of the PI and throughout the PI and MG labeling where applicable. Additionally, include the salt equivalency statement "(equivalent to 14.5 mg rizatriptan benzoate)" where applicable (e.g., Dosage forms and strengths and Description sections).
Highlights of Prescribing Information			
1.	We note a hyphen "-" is used between the two active ingredients in the Dosage Forms and Strengths section of the HL. Additionally, we note that the salt equivalency statement "equivalent to 14.5 mg of rizatriptan benzoate" is not present in the Dosage Forms and Strengths section of the HL.	This format is not in alignment the USP nomenclature guidelines available from https://www.usp.org/sites/default/files/usp/document/usp-nomenclature-guidelines.pdf. The hyphen symbol "-" in "meloxicam and rizatriptan" could lead to misinterpretation of the tablet contents. Further, addition of the salt equivalency statement may be recommended to be in accordance with the *Guidance for Industry Naming of Drug Products Containing Salt Drug Substances* available from: http://www.fda.gov/downl	We recommend replacing the hyphen symbol between the two ingredients with the word "and" as well as including the salt equivalency statement as follows: "Tablets: 20 mg meloxicam and 10 mg rizatriptan (equivalent to 14.5 mg of rizatriptan benzoate)." We defer to OPQ to determine the appropriateness of including the salt equivalency statement in the Dosage Forms and Strengths section of the HL.

Table 1. Identified Issues and Recommendations for Division of Neurology 2 (DN 2)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
		oads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM379753.pdf.	
2.	The maximum daily dose is not included in the Dosage and Administration section of the HL.	Including a maximum dose may help prevent wrong dose medication errors, specifically overdose errors (i.e., HCPs and patients may erroneously assume the dose may be repeated since the dose may be repeated for rizatriptan oral tablets).	We recommend revising the recommended dosing statement to clearly identify the maximum daily dose of Symbravo as follows or something similar: "The recommended dose of Symbravo is one tablet by mouth at the onset of a migraine in a 24-hour period. The maximum daily dose is 20 mg meloxicam and 10 mg rizatriptan (1 tablet)." We defer to clinical team for final determination of the appropriate recommended dosage statement.
Full Prescribing Information – Section 2 Dosage and Administration			
1.	We note that subsection 2.1 Recommended Dose states "The safety and effectiveness of a second dose have not been established", however, the maximum daily dose is not included in the recommended dosage statement .	Including a maximum dose may help prevent wrong dose medication errors, specifically overdose errors (i.e., HCPs and patients may erroneously assume the dose may be repeated since the dose may be repeated for rizatriptan oral tablets).	We recommend revising the recommended dosing statement to clearly identify the maximum daily dose of Symbravo as follows or something similar: "The recommended dose of Symbravo is one tablet by mouth at the onset of a migraine. The maximum daily dose should not exceed 20 mg meloxicam and 10 mg rizatriptan (1 tablet). The safety and effectiveness of a second dose have not been established."

Table 1. Identified Issues and Recommendations for Division of Neurology 2 (DN 2)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
			We defer to clinical team for final determination of the appropriate recommended dosage statement.
Full Prescribing Information – Section 3 Dosage Forms and Strengths			
1.	The established name is presented as the salt form (i.e., rizatriptan benzoate) instead of the active moiety (i.e., rizatriptan).	This is not in accordance 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 Dosage Form and Strength statement (b) (4) to read "Symbravo tablets contain 20 mg meloxicam and 10 mg rizatriptan (equivalent to 14.5 mg rizatriptan benzoate)." We defer to OPQ to determine the appropriateness of the salt equivalency statement.
Full Prescribing Information – Section 16 How Supplied/Storage and Handling			
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 symbol "-" 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" as follows: "Meloxicam 20 mg and rizatriptan 10 mg"
2.	The salt equivalency statement is not included in Section 16 How Supplied.	Addition of the salt equivalency statement may be recommended to be in accordance with the	We defer to OPQ to determine the appropriateness of including the salt equivalency statement in Section 16.

Table 1. Identified Issues and Recommendations for Division of Neurology 2 (DN 2)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
		Guidance for Industry Naming of Drug Products Containing Salt Drug Substances available from: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM379753.pdf.	
3.	We note that the container labels include the storage statement "store in original bottle", whereas Section 16 How Supplied does not include this statement. Additionally, there is no statement on the container labels directing the pharmacist whether to dispense the 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." Additionally, the storage statement should be consistent across all labels and labeling.	Clarify the intent of the storage statement "store in original bottle." 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. We defer to OPQ to determine the appropriateness of the storage statement "store in original bottle." Ensure the storage statement is consistent across all labels and labeling. Also, refer to recommendation number eight under the heading *"Container Labels (Trade and Professional Sample)"* below for discussion of the storage statement "store in original bottle" on the container labels.

Medication Guide (MG)			
1.	The placeholder "TRADENAME" is used throughout the MG labeling.	The proposed proprietary name, Symbravo was found acceptable on 3/7/2022.[b]	The placeholder, TRADENAME, should be replaced with the conditionally acceptable name, Symbravo, throughout the MG labeling.

5 RECOMMENDATIONS FOR AXSOME THERAPEUTICS, INC.

Table 2. Identified Issues and Recommendations for Axsome Therapeutics, Inc. (entire table to be conveyed to Applicant)			
	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 form, and strength for drug products. See *Draft Guidance for Industry: Safety Considerations for*	We recommend relocating the dosage form on the same line or directly below the established name. For example: Symbravo (meloxicam and rizatriptan) tablet 20 mg/10mg OR

[b] Weitzman, B. Proprietary Name Review for Symbravo (NDA 215431). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2022 MAR 7. PNR ID No. 2022-1044724401.

Table 2. Identified Issues and Recommendations for Axsome Therapeutics, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	**RATIONALE FOR CONCERN**	**RECOMMENDATION**
		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.	**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 208.24(d), the label shall instruct the authorized dispenser to provide a	We recommend revising the Medication Guide statement (b) (4) (b) (4) to "Attention: Dispense the accompanying Medication Guide to each patient."

Table 2. Identified Issues and Recommendations for Axsome Therapeutics, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
		Medication Guide to each patient and shall state how the Medication Guide is provided.	
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 "Each tablet contains: 20 mg meloxicam and 10 mg rizatriptan" 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 example, JU) characters.	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 does not clearly communicate whether 'MA' or 'JU' is for the months of	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-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if

Table 2. Identified Issues and Recommendations for Axsome Therapeutics, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
		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.	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.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 4 presents relevant product information for Symbravo that Axsome Therapeutics, Inc. submitted on June 30, 2021, and the listed drugs, Maxalt and Anjeso.

Table 4. Relevant Product Information for Symbravo and Listed Drugs, Maxalt[c] and Anjeso[d]

Product Name	Symbravo	Maxalt (NDA 020864)	Anjeso (NDA 210583)
Initial Approval Date	N/A	6/29/1998	2/20/2020
Active Ingredient	meloxicam and rizatriptan	rizatriptan benzoate	meloxicam
Indication	For the acute treatment of migraine with or without aura in adults	For the acute treatment of migraine with or without aura in adults and in pediatric patients 6 to 17 years old.	For use in adults for the management of moderate-to-severe pain, alone or in combination with non-NSAID analgesics.
Route of Administration	oral	oral	Intravenous
Dosage Form	tablet	tablet	Injection
Strength	20 mg/10 mg	5 mg and 10 mg	30 mg/mL per vial
Dose and Frequency	The recommended dose is one tablet by mouth at the onset of a migraine. The safety and effectiveness of a second dose have not been established.	Adults: The recommended starting dose of MAXALT is either 5 mg or 10 mg for the acute treatment of migraines in adults. The 10-mg dose may provide a greater	The recommended dose of ANJESO is 30 mg once daily, administered by intravenous bolus injection over 15 seconds.

[c] Maxalt (rizatriptan benzoate) tablet (NDA 020864) Prescribing Information. Available in Drugs@FDA under NDA 020864/S-023: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/020864s023,020865s024lbl.pdf

[d] Anjeso (meloxicam) injection (NDA 210583) Prescribing Information. Available in Drugs@FDA under NDA 210583/S-001: https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/210583s001lbl.pdf

		effect than the 5-mg dose, but may have a greater risk of adverse reactions. Redosing in Adults: If the migraine returns, a second dose may be administered 2 hours after the first dose. The maximum daily dose should not exceed 30 mg in any 24-hour period. <u>Pediatric Patients (Age 6 to 17 years)</u> Dosing in pediatric patients is based on the patient's body weight. The recommended dose of MAXALT is 5 mg in patients weighing less than 40 kg (88 lb), and 10 mg in patients weighing 40 kg (88 lb) or more. Dosage Adjustment for Patients on Propranolol: <u>Adult Patients</u> In adult patients taking propranolol, only the 5-mg dose of MAXALT is recommended, up to a maximum of 3 doses in any 24-hour period (15 mg)	

		<u>Pediatric Patients</u> For pediatric patients weighing 40 kg (88 lb) or more, taking propranolol, only a single 5-mg dose of MAXALT is recommended (maximum dose of 5 mg in a 24-hour period). MAXALT should not be prescribed to propranolol-treated pediatric patients who weigh less than 40 kg (88 lb)	
How Supplied	Bottles of (b)(4) tablets: The tablets are white and modified capsule-shaped, debossed with "MXRZ" on one side and "20/10" on the other.	5 mg: pale pink, capsule-shaped, compressed tablets coded MRK on one side and 266 on the other 10 mg: pale pink, capsule-shaped, compressed tablets coded MAXALT on one side and MRK 267 on the other	ANJESO (meloxicam) injection is a sterile, opaque, pale yellow, non-pyrogenic, aqueous dispersion intended for intravenous use available as a clear, 2 mL, single-dose vial containing 30 mg/mL per vial.
Storage	Store at 20°C to 25°C (68°F to 77°F), excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature].	Store MAXALT Tablets at room temperature, 15°C-30°C (59°F-86°F)	Store at 15-25°C (59 to 77°F), with excursions permitted between 4-30°C (40 to 86°F) Do not freeze. Protect from light. Not made with natural rubber latex.
Container Closure	Bottles of (b)(4) tablets	Carton of 18 tablets	Single dose vial

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[e] along with postmarket medication error data, we reviewed the following Symbravo labels and labeling submitted by Axsome Therapeutics, Inc. (Axsome).

- Container (Trade and Professional Sample) labels received on June 30, 2021.
- Prescribing Information (Image not shown) received on September 27, 2021, available from
  \\CDSESUB1\evsprod\nda215431\0005\m1\us\1-14-1-3-draft-label-clean.doc
- Medication Guide received on June 30, 2021, available from
  \\CDSESUB1\evsprod\nda215431\0001\m1\us\1-14-1-3-draft-med-guide.docx

G.2 Label and Labeling Images

(b) (4)

[e] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/

BEVERLY WEITZMAN
03/16/2022 10:53:25 PM

STEPHANIE L DEGRAW
03/17/2022 10:50:16 AM

Clinical Inspection Summary

Date	1/25/2022
From	Cara Alfaro, Pharm.D., Clinical Analyst Phillip Kronstein, M.D., Team Leader Kassa Ayalew, M.D., M.P.H., Division Director/(Acting) Branch Chief Good Clinical Practice Assessment Branch Division of Clinical Compliance Evaluation Office of Scientific Investigations
To	Lana Chen, Regulatory Project Manager Viveca Livezey, M.D., Medical Officer Heather Fitter, M.D., Team Leader Division of Neurology 2 Office of Neuroscience
NDA #	215431
Applicant	Axsome Therapeutics, Inc.
Drug	Meloxicam/rizatriptan oral tablets
NME	No
Proposed Indication	Acute treatment of migraine with or without aura in adults
Consultation Request Date	8/26/2021
Summary Goal Date	1/28/2022
Priority/Standard Review	Standard
Action Goal Date	4/29/2022
PDUFA Date	4/29/2022

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Drs. Hudson, Nadkarni, and Padala were inspected in support of this NDA, covering Protocols AXS-07-301 and AXS-07-303. Despite some protocol deviations, the studies appear to have been conducted adequately, and the data generated by these sites appear acceptable in support of the respective indication.

At Dr. Nadkarni's site, for Protocol AXS-07-303, seven of sixteen randomized subjects had missing electronic diary (eDiary) efficacy data for timepoints after administration of investigational product for a migraine attack, including the 2-hour primary efficacy timepoint. Five of these subjects were randomized to AXS-07 (meloxicam/rizatriptan), and two were randomized to placebo. During the inspection, it was noted that five of these seven subjects with missing data had eDiary compliance rates <80% during the screening period and were, per protocol, not eligible for randomization. There was no evidence that the missing data were due to any reason other than subject noncompliance. We defer to the statistical reviewers on how to handle the missing data from this site.

II. BACKGROUND

Meloxicam/rizatriptan (AXS-07) oral tablets are being developed under NDA 215431 (IND 135972) for the acute treatment of migraine with or without aura in adults. Both medications are available as separate entities, meloxicam as Mobic® and others (including generics) and rizatriptan as Maxalt® (as well as generics). For this NDA submission, the sponsor has combined both entities into one single oral tablet. The sponsor has submitted two Phase 3 studies to support the efficacy and safety of meloxicam/rizatriptan for the acute treatment of migraine with or without aura in adults.

Protocol AXS-07-301 (MOMENTUM)

Title: "A randomized, double-blind, single-dose, placebo-controlled study to assess the efficacy and safety of AXS-07 (meloxicam and rizatriptan) for the acute treatment of migraine in adults"

Subjects: 1526

Sites: 80 sites in the United States

Study Initiation and Completion Dates: 3/1/2019 to 12/1/2019

This was a Phase 3, randomized, double-blind, 4-arm, parallel group, single-dose, placebo-controlled trial in subjects with migraine attacks. Included were males or females 18 to 65 years of age; established diagnosis of migraine with or without aura as defined by the International Classification of Headache Disorder, 3rd Edition (ICHD-3); an average of 2 to 8 moderate or severe migraine attacks per month (no more than 10 migraine days/month) over the past 3 months; history of usual migraine duration of >3 hours untreated for the 3 months prior to screening; if taking concomitant selective serotonin or norepinephrine reuptake inhibitor (SSRI/SNRI), dose has been stable for at least 8 weeks prior to randomization; and history of inadequate response to prior acute migraine treatments. An inadequate response was defined as a score ≤7 on the Migraine Treatment Optimization Questionnaire (m-TOQ-4), corresponding to moderate or worse response to prior treatments over the preceding 4 weeks. Excluded were subjects with >8 monthly migraine attacks during either of the 2 months before screening; chronic daily headache (≥15 days per month of non-migraine headaches during each of the 3 months before screening); or uncontrolled hypertension.

The study was comprised of three phases:

Screening (up to 14-days)

Double-blind Treatment
Subjects were randomized (2:2:2:1) to one of the following study arms (no stratification):

- AXS-07 (20 mg meloxicam/10 mg rizatriptan) oral tablet
- Rizatriptan 10 mg oral tablet
- Meloxicam 20 mg oral tablet
- Placebo oral tablet

At Visit 2 (Day 1, randomization), an electronic diary (eDiary) was provided to subjects and subjects were trained on diary completion. Subjects used the eDiary to record migraine data. Subjects were instructed to complete the diary for 48 hours after the first migraine that occurred after randomization and investigational product (IP) dosing.

IP was dispensed for at-home treatment of a single migraine attack. Subjects had 10 weeks to complete treatment with IP. After randomization, subjects were to take IP after the onset of moderate or severe pain intensity.

No rescue medication was allowed within 2 hours after the start of the migraine attack. After the 2-hour time point data was recorded, if subjects had inadequate relief from IP, they could take an allowable rescue medication such as triptans, NSAIDS, antiemetics, non-NSAID analgesics (e.g., acetaminophen, gabapentin), and/or sedatives.

Follow-up Visit
A follow-up visit occurred within 7 days after treating one migraine attack or within 10 weeks of randomization if IP was not used.

The co-primary efficacy endpoints were the percentage of subjects with headache pain freedom and absence of most bothersome symptom (MBS) at 2 hours after dosing. The key secondary endpoint was the percentage of subjects with sustained freedom from headache pain between 2 and 24 hours after dosing.

Protocol AXS-07-303 (INTERCEPT)

Title: "A randomized, double-blind, single-dose, placebo-controlled study to assess the efficacy and safety of AXS-07 (meloxicam and rizatriptan) for the acute treatment of migraine in adults"

Subjects: 283

Sites: 41 sites in the United States

Study Initiation and Completion Dates: 10/8/2019 to 3/16/2020

This was a Phase 3, randomized, double-blind, single-dose, placebo-controlled trial in subjects with migraine attacks. The eligibility criteria were similar to Protocol AXS-07-301 (see above) with the exception that subjects must have 2 to 8 migraine attacks per month

(no severity criteria) over the past 3 months, and there were no criteria for inadequate response to prior acute migraine treatments.

The study was comprised of three phases:

Screening (up to 28 days)
Subjects completing the screening visit (Visit 1) entered a 28-day screening period during which they recorded the details (baseline characteristics, headache pain intensity, associated migraine symptoms, and treatments used) of all migraines. The subject must have reported at least 1 and no more than 8 migraines during this 28-day period to be eligible for randomization.

Double-blind Treatment
Subjects were randomized (1:1) to one of the following study arms (no stratification):

- AXS-07 (meloxicam 20 mg/rizatriptan 10 mg) oral tablet
- Placebo oral tablet

At Visit 2 (Day 1, randomization), the eDiary was provided and subjects were trained on diary completion. Subjects used the eDiary to record migraine data. Subjects were instructed to complete the diary for 48 hours after the first migraine occurs after randomization and IP dosing.

IP was dispensed for at-home treatment of a single migraine attack. Subjects had 6 weeks to complete treatment with IP. After randomization, subjects were to take IP after the onset of mild pain intensity.

No rescue medication was allowed within 2 hours after the start of the migraine attack. After the 2-hour time point data was recorded, if subjects had inadequate relief from IP, they could take an allowable rescue medication (same as Protocol AXS-07-301).

Follow-up Visit
A follow-up visit occurred within 7 days after treating one migraine attack or within 6 weeks of randomization if IP was not used.

The co-primary efficacy endpoints were the percentage of subjects with headache pain freedom and absence of MBS at 2 hours after dosing. The key secondary endpoints were the time to headache pain freedom and functional disability at 2 hours after dosing.

Rationale for Site Selection

The clinical sites were chosen primarily based on risk ranking in the site selection tool, numbers of enrolled subjects, randomization imbalances, missing eDiary data, and prior inspectional history.

III. RESULTS

1. **John Hudson, M.D.**
   Site #764
   FutureSearch Trials
   5508 Parkcrest Drive, Ste. 300 & 301
   Austin, TX 78731
   Inspection Dates: 9/27/2021 – 9/29/2021

   At this site for Protocol AXS-07-301, 40 subjects were screened and 35 subjects were randomized, all of whom completed the study.

   Signed informed consent forms, dated prior to participation in the study, were present for all subjects who were screened. An audit of the study records of all randomized subjects was conducted. Records reviewed included, but were not limited to, source documents, monitoring documents, IRB/sponsor communications, financial disclosure, test article accountability, inclusion/exclusion criteria, adverse event reports, laboratory results, concomitant medications, protocol deviations, and primary efficacy endpoint data (headache, most bothersome symptom [MBS]).

   A certified CD containing site-specific raw eDiary data, audit trails, and any associated data clarification requests was available at the site for data verification. Headache data and MBS data on the certified CD were verified against the sponsor data line listings; no discrepancies were noted. There was no evidence of underreporting of adverse events.

2. **Salil Nadkarni, D.O.**
   Site #850
   Downtown L.A. Research Center, Inc.
   1125 W. 6th Street, Suite 307
   Los Angeles, CA 90017
   Inspection Dates: 9/20/2021 – 9/24/2021

   At this site for Protocol AXS-07-303, 17 subjects were screened and 16 subjects were randomized, all of whom completed the study.

   Signed informed consent forms, dated prior to participation in the study, were present for all subjects who were screened. An audit of the study records of all randomized subjects was conducted. Records reviewed included, but were not limited to, source documents, monitoring documents, IRB/sponsor communications, financial disclosure, test article accountability, inclusion/exclusion criteria, adverse event reports, laboratory results, concomitant medications, protocol deviations, and primary efficacy endpoint data (headache, most bothersome symptom [MBS]).

A certified CD containing site-specific raw eDiary data, audit trails, and any associated data clarification requests was available at the site for data verification. Headache data and MBS data on the certified CD were verified against the sponsor data line listings; no discrepancies were noted. There was no evidence of underreporting of adverse events.

Missing eDiary data for timepoints after administration of investigational product (IP) for a migraine attack, including the 2-hour primary efficacy timepoint, were noted in the sponsor's protocol deviation line listings for 7 of 16 randomized subjects at this site. Five of these subjects were randomized to AXS-07 (meloxicam/rizatriptan), and two were randomized to placebo. Source documents at the site noted reasons for missing data, including that subjects had fallen asleep or that subjects believed they had entered the data although there was no record in the device or portal.

For five of these seven subjects with missing eDiary data, there was evidence of eDiary noncompliance during the screening period. Protocol inclusion criteria include only a statement that subjects must be willing and able to complete the eDiary. Elsewhere in the protocol (Section 9.1.2 Screening Period), it is stated that subjects must have at least 80% compliance with the timepoints in the eDiary during the 28-day screening period in order to be eligible for the study. Five of the seven subjects with missing eDiary data after IP administration had compliance rates of 45 to 66% during the screening period and were therefore not eligible for the study. A sponsor protocol newsletter available at the site provided instructions to the sites for calculation of eDiary compliance in the ERT portal before randomization (Visit 2).

Reviewer's comment: Missing eDiary data for timepoints after administration of IP was noted for 7 of 16 randomized subjects at this site. Five of these seven subjects had eDiary compliance <80% during the screening period and therefore should not have been randomized. The missing data occurred for 5 subjects randomized to AXS-07 and 2 subjects randomized to placebo. There was no evidence that the missing data were due to any reason other than subject noncompliance. We defer to the statistical reviewers on how to handle the missing data from this site.

3. Prasad Padala, M.D
Site #778
Atria Clinical Research Management, LLC
11321 I-30, Suite 308
Little Rock, AR 72209
Inspection Dates: 11/15/2021 – 11/18/2021

At this site for Protocol AXS-07-301, 41 subjects were screened, 30 were randomized, and 28 subjects completed the study. Two subjects discontinued the study due to withdrawal of consent and eDiary noncompliance.

Signed informed consent forms, dated prior to participation in the study, were present for all subjects who were screened. An audit of the study records of all randomized subjects was conducted. Records reviewed included, but were not limited to, source documents, monitoring documents, IRB/sponsor communications, financial disclosure, test article accountability, inclusion/exclusion criteria, adverse event reports, laboratory results, concomitant medications, protocol deviations, and primary efficacy endpoint data (headache, most bothersome symptom [MBS]).

A certified CD containing site-specific raw eDiary data, audit trails, and any associated data clarification requests was available at the site for data verification. Headache data and MBS data on the certified CD were verified against the sponsor data line listings; no discrepancies were noted. There was no evidence of underreporting of adverse events.

During the inspection, missing eDiary data for Subject (b) (6) randomized to rizatriptan 10mg, was noted. After administration of IP for a migraine, Subject (b) (6) entered data into the eDiary for the 2- and 4-hour postdose timepoints only. The missing data was not noted in the sponsor's protocol deviation line listings but was reflected in the primary efficacy endpoint data listing. A contemporaneous note-to-file documenting this deviation was available at the site. The site noted that the sponsor was inadvertently not notified of the protocol deviation.

Reviewer's comment: Although some eDiary data for Subject (b) (6) *was missing, the 2-hour timepoint (primary efficacy endpoint) was not missing. Therefore, there is no impact of this inspectional finding on the statistical analysis of the primary efficacy endpoint.*

{See appended electronic signature page}

Cara Alfaro, Pharm.D.
Clinical Analyst
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Phillip Kronstein, M.D.
Team Leader and Acting Branch Chief
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

cc:

Central Document Room/NDA #215431
Division of Neurology 2/Division Director/Nicholas Kozauer
Division of Neurology 2/Deputy Division Director/Paul Lee
Division of Neurology 2/Medical Team Leader/Heather Fitter
Division of Neurology 2/Medical Officer/Viveca Livezey
Division of Neurology 2/Project Manager/Lana Chen
OTS/OB/DBI/Statistics Reviewer/Jinnan Liu
OTS/OB/DBI/Statistics Team Leader/Kun Jin
OSI/Office Director/David Burrow
OSI/Office Deputy Director/Laurie Muldowney
OSI/DCCE/ Division Director/Kassa Ayalew
OSI/DCCE/GCPAB/(Acting) Branch Chief/Kassa Ayalew
OSI/DCCE/GCPAB/Team Leader/Phillip Kronstein
OSI/DCCE/GCPAB/Reviewer/Cara Alfaro
OSI/GCPAB Program Analyst/Yolanda Patague

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/

CARA L ALFARO
01/25/2022 09:48:20 AM

PHILLIP D KRONSTEIN
01/25/2022 10:06:20 AM

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: 11/15/2021

TO: Division of Neurology II (DN II)
Office of Neuroscience (ON)

FROM: Division of New Drug Study Integrity (DNDSI)
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: **Decline to conduct an on-site inspection**

RE: NDA 215431

The Division of New Drug Study Integrity (DNDSI) within the Office of Study Integrity and Surveillance (OSIS) determined that inspections are not warranted at this time for the sites listed below. The rationale for this decision is noted below.

Rationale

Syneos, Toronto: The Office of Regulatory Affairs (ORA) inspected the site in December 2019, which falls within the surveillance interval. The inspection was conducted under the following submissions: NON-RESPONSIVE. Please note that this site is now permanently closed.

Altasciences, Overland Park: ORA inspected the site in June 2019, which falls within the surveillance interval. The inspection was conducted under the following submissions: NON-RESPONSIVE and NON-RESPONSIVE

(b) (4) OSIS inspected the site in (b) (4), which falls within the surveillance interval. The inspection was conducted under the following submissions: NON-RESPONSIVE NON-RESPONSIVE

The final classification for the inspections was No Action Indicated (NAI).

Therefore, based on the rationale described above, inspections are not warranted at this time.

Inspection Sites

Facility Type	Facility Name	Facility Address
Clinical	Syneos Health Clinique	720 King Street West, Suite 700, Toronto, Ontario, Canada
Clinical	Altasciences Clinical Research, Inc.	10103, 10203, and 10183 Metcalf Avenue, Overland Park, KS
Analytical	(b) (4)	

James J. Lumalcuri -S

Digitally signed by James J. Lumalcuri -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2002349361, cn=James J. Lumalcuri -S
Date: 2021.11.15 09:44:33 -05'00'

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/

JAMES J LUMALCURI
11/15/2021 09:54:33 AM