CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

215431Orig1s000

NON-CLINICAL REVIEW(S)

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

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number:	215431
Supporting document/s:	24, 25
Applicant's letter date:	June 28, 2024; July 31, 2024
CDER stamp date:	June 28, 2024; July 31, 2024
Product:	AXS-07
Indication:	Acute migraine with or without aura
Applicant:	Axsome Therapeutics
Clinical Review Division:	Division of Neurology II
Reviewer:	Elizabeth Khoury, PhD
Team Leader:	David Carbone, PhD
Supervisor:	Lois Freed, PhD
Clinical Division Director:	Paul Lee, MD, PhD
Project Manager:	Lana Chen, RPh

TABLE OF CONTENTS

1 Executive Summary

1.1 Introduction

AXS-07 is a fixed-dose combination of 10 mg rizatriptan and 20 mg meloxicam submitted under Section 505(b)(2). The intended indication is acute treatment of migraine with or without aura. The sponsor is relying on Mobic (NDA 20938) and Anjeso (NDA 210583) to support meloxicam and Maxalt (NDA 20864) to support rizatriptan. This application is a resubmission of NDA 215431 for AXS-07 (Symbravo), which received a complete response on April 29, 2022.

The nonclinical deficiencies that precluded approval consisted of inadequate support for chronic administration of meloxicam and inadequate support for the proposed level of (b) (4)% for the rizatriptan impurity, rizatriptan n-oxide. In addition, according to the CMC team, the sponsor had not addressed the potential for (b) (4) impurities, (b) (4) and (b) (4) to be present in the drug product at higher than acceptable levels.

After the complete response letter was issued, the sponsor submitted a meeting request (April 22, 2024) to obtain the division's feedback on a proposed specification limit of (b) (4)% for impurity, (b) (4) which had been recently detected at levels above the qualification threshold in subsequent production batches.

The sponsor included information to address these nonclinical and CMC deficiencies in the NDA resubmission.

1.2 Brief Discussion of Nonclinical Findings

To support chronic administration of meloxicam, the sponsor is now also relying on Mobic, which is approved for the treatment of osteoarthritis and juvenile rheumatoid arthritis, as a listed drug.

The sponsor provided additional data to support the proposed specification limits for rizatriptan n-oxide and (b) (4) For assessment of genotoxic potential, the sponsor provided data demonstrating that rizatriptan n-oxide is formed by rat liver S9 fraction and would, therefore, have been assessed in the genetic toxicity studies submitted to support the approval of rizatriptan. For (b) (4) the sponsor conducted a QSAR assessment which was negative for alerting structures. To address general toxicity, the sponsor reanalyzed plasma samples from the GLP 13-week toxicity study in minipig to demonstrate that both impurities were present at sufficient levels, due to metabolism of rizatriptan and meloxicam, to support the proposed specification limits. Regarding the potential (b) (4) impurities, the sponsor provided additional information. The CMC team agrees that the data provided by the sponsor are adequate to support the specification limits proposed for these impurities. Therefore, there are no nonclinical concerns regarding these potential (b) (4) impurities.

1.3 Recommendations

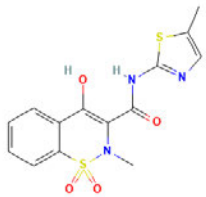
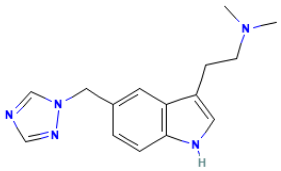
The nonclinical deficiencies described in the complete response, as well as concerns regarding the impurity (b) (4) and the potential (b) (4) impurities were adequately addressed in the resubmission. From a nonclinical perspective, the NDA is approvable.

1.3.3 Labeling

The sponsor's proposed labeling is consistent with the approved labeling for meloxicam and rizatriptan. The safety margins in the labeling, which are based on comparisons to doses normalized to body surface area (mg/m^2), are acceptable.

2 Drug Information

2.1 Drug

CAS Registry Number	71125-38-7	145202-66-0
Generic name	Meloxicam	Rizatriptan benzoate
Code name	AXS-07	
Chemical Name	4-hydroxy-2-methyl-N-(5-methylthiazol-2-yl)-2H-1,2-benzothiazine-3-carboxamide 1,1dioxide	1H-indole-3-ethanamine, N,N-dimethyl-5-(1H-1,2,4-triazol-1-ylmethyl)-, monobenzoate
Molecular Formula/Weight	$C_{14}H_{13}N_3O_4S_2$/351.4 g/mol	$C_{22}H_{25}N_5O_2$/391.5 g/mol
Structure or Biochemical Description (from PubChem)		
Pharmacological Class	NSAID	5-HT$_{1B/1D}$ receptor agonist or triptan

2.2 Relevant INDs, NDAs, BLAs and DMFs

This is a 505(b)(2) application referencing Mobic meloxicam tablets (NDA 020938), Anjeso (NDA 210583), and Maxalt rizatriptan benzoate tablets (NDA 020864).

2.3 Drug Formulation

AXS-07 is formulated as an oral tablet using conventional excipients (see table below).

Table 1: Composition of AXS-07 Drug Product

Component	Function	Amount per Tablet	
		mg	%w/w
(b) (4)			
Meloxicam, USP	Active	20	(b) (4)
Rizatriptan benzoate (equivalent to 10 mg freebase), USP	Active	14.53	
(b) (4)	(b) (4)	(b) (4)	
Sulfobutyl-ether-β-cyclodextrin sodium (SBECD),			
Microcrystalline Cellulose (b) (4) NF/Ph. Eur./JP.			
Pregelatinized Starch, NF/Ph. Eur.			
Colloidal Silicon Dioxide, USP/NF/Ph. Eur./JP			
Povidone, USP/Ph. Eur./JP			
Crospovidone (b) (4) NF/Ph. Eur./JP			
Magnesium Stearate, NF/Ph. Eur./JP			
Sodium Bicarbonate, USP			
(b) (4)			(b) (4)

JP = Japanese Pharmacopoeia, NF = National Formulary; Ph. Eur. = European Pharmacopeia; USP = United States Pharmacopeia; NA = Not Applicable

(b) (4)

(Sponsor's Table)

2.4 Comments on Novel Excipients

No concerns.

2.5 Comments on Impurities/Degradants of Concern

New data were submitted that support the proposed acceptance criteria of NMT (b) (4)% and (b) (4)% for rizatriptan-N-oxide and (b) (4), respectively. Rizatriptan-N-oxide and (b) (4) are also metabolites of rizatriptan and meloxicam, respectively, in both human and minipig; however, according to the Clinical Pharmacology team, neither is considered a major circulating human metabolite. Additionally, the CMC team identified the potential for the formation of the (b) (4) impurities (b) (4)

(b) (4) The CMC team has concluded that the analytical data provided by the sponsor are adequate.

2.6 Proposed Clinical Population and Dosing Regimen

Adults with migraine with or without aura. One AXS-07 tablet (20 mg meloxicam/10 mg rizatriptan) by mouth at the onset of a migraine.

2.7 Regulatory Background

IND submission date: June 28, 2017
NDA submission date: June 30, 2021
Complete Response letter: April 29, 2022
NDA resubmission date: July 31, 2024

3 Studies Submitted

3.1 Studies Reviewed

- TP-002 updated toxicokinetic report
- TP-003: Pharmacokinetic study of AXS-07 after single and repeat oral doses in minipig
- TP-004: 2-week repeat oral dosing study of (b) (4) in minipig

3.3 Previous Reviews Referenced

Nonclinical Review (NDA 215431) by Edmund Nesti, PhD (April 29, 2022)

5 Pharmacokinetics/ADME/Toxicokinetics

5.1 PK/ADME

A Pharmacokinetic Study of AXS-07 and Rizatriptan Benzoate after Single and Repeat Oral Doses in Minipigs

Study TP003 (non-GLP): Gottingen minipigs (2/sex/group) were administered daily oral doses of 3 mg/kg meloxicam in combination with 1.5 mg/kg rizatriptan benzoate or 1.5 mg/kg rizatriptan alone. It was unclear from the study report whether the meloxicam/rizatriptan combination was the actual drug product, but the 2:1 meloxicam/rizatriptan ratio is consistent with that for AXS-07. The meloxicam/rizatriptan dose used in this study was selected because it was the high dose in a 13-week repeat dose toxicity study in minipig (Study 220615). There was no control. Plasma TK parameters for meloxicam, rizatriptan, (b) (4) were assessed on Days 1, 7, and 14 (see table below). There were no sex differences in C_{max} and AUC or signs of accumulation following repeat dosing for any of the analytes.

Selected Oral AXS-07 PK Parameters[a]

Analyte	Day	C_{max} (ng/mL)	T_{max} (h)	AUC_{0-24} (ng*h/mL)	Percent Parent AUC (%)
Meloxicam	1	1680	8	18500	NC
	7	2530	8.75	26500	NC
	14	1930	1.75	21200	NC
(b) (4)	1	(b) (4)			
	7				
	14				
Rizatriptan	1	51400	2.25	145000	NC
	7	18600	4	107000	NC
	14	33900	3.13	122000	NC
(b) (4)	1	(b) (4)			
	7				
	14				

[a] 3.0 mg/kg meloxicam/ 1.5 mg/kg rizatriptan dose daily for 14 days
[b] Parent drug: meloxicam
[c] Parent drug: rizatriptan
NC: not calculated

TP-002 Toxicokinetic Reanalysis of Plasma Samples

Plasma samples collected in study AXS007-TP002, which was submitted with the original NDA application and was previously reviewed by Dr. Edmund Nesti, were reanalyzed to assess TK parameters for rizatriptan and the metabolites rizatriptan n-

oxide, which is also an impurity in the clinical drug product. A comparison of rizatriptan TK parameters from the original submission and the reanalysis indicated general similarity. Additionally, the new analysis indicated the AUC for rizatriptan n-oxide ranged from 178% to 280% of parent (i.e., rizatriptan) on Day 90.

Rizatriptan N-oxide TK parameters from 13-week study in minipig

Day	AXS-07 Dose (mg/kg) MLX	RIZ	Sex	C_{max} (pg/mL)	T_{max} (h)	AUC_{0-t} (pg*h/mL)
1	1	0.727	M	(b) (4)		
			F			
	3	2.18	M			
			F			
	5	3.633	M			
			F			
90	1	0.727	M			
			F			
	3	2.18	M			
			F			
	5	3.633	M			
			F			

6 General Toxicology

6.2 Repeat-Dose Toxicity

Study title: A 2-Week Once Daily Oral Gavage Toxicity and Toxicokinetic Study with (b) (4) in Gottingen Minipigs

Study no.: AXS007-TP004

Study report location: EDR

Conducting laboratory and location: (b) (4)

Date of study initiation: March 7, 2024

GLP compliance: Yes

QA statement: Yes

Drug, lot #, and % purity: (b) (4), 99.9%

Methods

Doses:	0, 0.01, 0.05, 0.1 mg/kg (b) (4)
Frequency of dosing:	Daily
Route of administration:	Oral gavage
Dose volume:	10 mL/kg
Formulation/Vehicle:	Deionized water
Species/Strain:	Gottingen minipig
Number/Sex/Group:	3
Age:	13-16 weeks old
Weight:	7.4-8.6 kg (M), 6.5-8.7 kg (F)
Satellite groups:	None
Unique study design:	None
Deviation from study protocol:	No significant deviations from study protocol

Observations and Results

Mortality and Clinical Signs

Clinical observations were conducted twice daily. Detailed observations were conducted weekly. There were no mortalities or (b) (4) related clinical signs.

Body Weights

Body weights were recorded weekly. On Day 14, there were slight (<10%) increases in body weights in HDM and HDF compared to controls.

Food Consumption

Qualitative food consumption was assessed daily. There were no effects of (b) (4) on food consumption.

Ophthalmoscopy

Not assessed.

ECG

Not assessed.

Hematology, Clinical Chemistry, Urinalysis

Blood and urine samples were collected from fasted animals during the predose phase and on Day 15 of the dosing phase. There were no (b) (4) related changes in hematology, coagulation, clinical chemistry, or urinalysis parameters.

Gross Pathology

There were no (b) (4) related gross pathology findings.

Organ Weights

There were no (b) (4) related changes in organ weights.

Histopathology

Adequate Battery: Yes
Signed and Dated Pathology Report: Yes
Peer Review: No

Histological Findings:
There were no (b) (4) related microscopic observations.

Toxicokinetics

Plasma TK parameters for (b) (4) were assessed on Days 1 and 14. C_{max} increased in a less than dose-proportional manner while AUC increased in greater than dose proportional manner. No sex differences were observed in TK parameters.

Day	(b) (4) (mg/kg)	Sex	AUC_{0-t} (ng*hr/mL)	C_{max} (ng/mL)	T_{max} (h)	$T_{1/2}$ (h)
1	0.01	Female	(b) (4)			
		Male				
	0.05	Female				
		Male				
	0.1	Female				
		Male				
14	0.01	Female				
		Male				
	0.05	Female				
		Male				
	0.1	Female				
		Male				

Data source: TP003 Study Report
NC – not calculated.

Dosing Solution Analysis

All formulations were within 92.3% to 103.5% of nominal concentration.

11 Integrated Summary and Safety Evaluation

Introduction

AXS-07 is an orally administered fixed-dose combination of 20 mg meloxicam (NSAID) and 10 mg rizatriptan (triptan) that was submitted under the 505(b)(2) pathway for the acute treatment of migraine with or without aura in adults. The listed drugs are Mobic (meloxicam tablets; NDA 020938), Anjeso (meloxicam IV, NDA 210583), and Maxalt (rizatriptan tablets; NDA 020864). Upon review of the initial NDA submission in 2022, it was determined that the application was not approvable from a nonclinical perspective because the sponsor attempted to rely on the approved product Anjeso (meloxicam), which is not indicated for chronic use, and did not provide adequate data to support the proposed specification limit of (b) (4)% for the impurity rizatriptan-N-oxide.

After issuing the Complete Response, the Division was informed that, due to a change in manufacturing process, the impurity (b) (4) now exceeds the qualification limit of 0.5%, and the sponsor is now proposing a specification limit of NMT (b) (4)%. Additionally, new concerns regarding the potential formation of (b) (4) and (b) (4) impurities were raised by the CMC review team.

Chronic Administration of Meloxicam

To address the issue of support for chronic administration of meloxicam, the sponsor is now also relying on Mobic meloxicam tablets (NDA 020938), which are approved for chronic use.

Potential (b) (4) Impurities

Regarding the potential (b) (4) impurities, (b) (4) and (b) (4) the CMC team has concluded that the analytical methods provided by the sponsor support the proposed specification limits that would result in total daily doses of (b) (4) ng for (b) (4) and (b) (4) ng/day for (b) (4) and (b) (4) Therefore, there are no nonclinical concerns.

Qualification of Impurities

The sponsor did not conduct a toxicity study using a drug batch that contains the impurities rizatriptan N-oxide and (b) (4) at levels that would support the proposed specification limits. Therefore, the sponsor conducted a TK analysis using samples collected in the previously conducted 13-week oral toxicity study of AXS-07 in minipig for rizatriptan N-oxide and a new 2-week PK study in minipig for (b) (4)

Rizatriptan N-oxide

The new TK analysis conducted by the sponsor demonstrated that rizatriptan N-oxide is a metabolite in minipig, resulting in C_{max} and AUC_{0-24h} of (b) (4) ng/mL and (b) (4) ng*h/mL, respectively, at the highest dose tested in the 13-week study. These levels would be expected to far exceed those in humans at the proposed specification limit of

(b) (4)% (i.e., (b) (4)mg). The proposed impurity specification limit for rizatriptan N-oxide is, therefore, supported by the nonclinical data.

(b) (4) (b) (4)however, according to the Clinical Pharmacology team, the AUC for (b) (4) in humans is anticipated to be low (approximately (b) (4)ng*h/mL) at the MRHD of AXS-07. In minipig, TK parameters for (b) (4) were not assessed in the reanalysis of the plasma samples from the 13-week study. Instead, the sponsor conducted a 2-week PK bridging study in which the dose of rizatriptan/meloxicam matched that of the high dose in the 13-week study. Based on these bridging data, it is estimated that the C_{max} and AUC for (b) (4) in the 13-week study were (b) (4) ng/mL and (b) (4)ng*h/mL, respectively. An additional study was conducted in minipigs in which (b) (4) was directly administered at oral doses of up to 0.1 mg/kg, a dose approximately ``` times that at the proposed specification limit of (b) (4)% for (b) (4) Plasma (b) (4) exposures at 0.1 mg/kg were similar to those estimated to have been achieved at the highest dose of AXS-07 tested in the 13-week study. which is approximately (b) (4) times, on a mg/m^2 basis, that in humans at the proposed specification limit of (b) (4)%. The additional analyses conducted by the sponsor demonstrate that the circulating levels of (b) (4) (b) (4) due to metabolism in the 13-week study in minipig are adequate to qualify (b) (4) at the proposed specification limit of (b) (4)% (b) (4)

Recommendations

The nonclinical deficiencies in the original submission, as well as new concerns regarding the (b) (4) and potential (b) (4)impurities, were adequately addressed by the sponsor. From a nonclinical perspective, this application is considered approvable.

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/

ELIZABETH S KHOURY
01/27/2025 10:27:22 AM

DAVID L CARBONE
01/27/2025 10:40:44 AM

LOIS M FREED
01/27/2025 11:07:59 AM

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

PHARMACOLOGY/TOXICOLOGY NDA/BLA REVIEW AND EVALUATION

Application number:	215431
Supporting document/s:	1
Applicant's letter date:	June 30, 2021
CDER stamp date:	June 30, 2021
Product:	SYMBRAVO; AXS-07; meloxicam-rizatriptan
Indication:	Acute Treatment of Migraine With or Without Aura
Applicant:	Axsome Therapeutics
Review Division:	Division of Neurology 2
Reviewer:	Edmund Nesti, PhD
Supervisor:	Lois Freed, PhD
DN2 Division Director:	Nick Kozauer, MD
DPT-N Division Director:	Lois Freed, PhD
Project Manager:	Lana Chen, PharmD

Disclaimer

Except as specifically identified, all data and information discussed below and necessary for approval of 215431 are owned by Axsome Therapeutics or are data for which Axsome Therapeutics has obtained a written right of reference. Any information or data necessary for approval of 215431 that Axsome Therapeutics does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as reflected in the drug's approved labeling. Any data or information described or referenced below from reviews or publicly available summaries of a previously approved application is for descriptive purposes only and is not relied upon for approval of 215431.

TABLE OF CONTENTS

1 Executive Summary

1.1 Introduction

AXS-07 (meloxicam (MLX)/rizatriptan (RIZ)) is indicated for the acute treatment of migraine with or without aura in adults. This is a 505(b)(2) NDA referencing Anjeso meloxicam injection and Maxalt tablets. The maximum recommended human dose is one tablet (20 mg meloxicam - 10 mg rizatriptan) by mouth at the onset of a migraine.

1.2 Brief Discussion of Nonclinical Findings

The pivotal 13-week general toxicology study + 28-day recovery period in minipig assessed oral doses of AXS-07 (MLX/RIZ: 1/0.7, 3/2.2, or 5/3.6 mg/kg, QD), MLX (5 mg/kg), and RIZ (3.6 mg/kg) administered daily. The NOAEL for AXS-07 was the MD, based on one HDM (MLX/RIZ) that was euthanized on Day 75 due to poor health (reduced appetite, body weight loss, bloody stool, and decreased activity). In the gastrointestinal tract there was mild to marked erosion of the mucosa in the stomach, cecum, and colon. The remaining HD animals had minimal to mild erosion in the stomach, jejunum, cecum, and colon, which resolved during the recovery period. The AUC at the NOAEL was similar to that at the maximum recommended human dose of AXS-07 (20 mg meloxicam -10 mg rizatriptan). There were no adverse findings in the MLX (5 mg/kg) or RIZ (3.6 mg/kg) groups.

Clinical development was allowed to proceed without chronic toxicology studies because under the IND the sponsor had expressed plans to rely on Mobic (mexloxicam) tablets, which are approved for chronic administration. However, Mobic was not given as a listed drug in the NDA.

The sponsor did not provide adequate data to support the proposed limit (b) (4)%) for the impurity, rizatriptan-N-oxide; therefore, the limit should be lowered to 0.5%.

1.3 Recommendations

1.3.1 Approvability

The nonclinical NDA package does not support approval of AXS-07, because 1) the sponsor has not provided data to support chronic oral administration of meloxicam, 2) data were not provided to qualify the proposed limit (b) (4)%) for the impurity, rizatriptan-N-oxide.

1.3.3 Labeling

(b) (4)

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

2 Drug Information

2.1 Drug

CAS Registry Number
71125-38-7; 145202-66-0

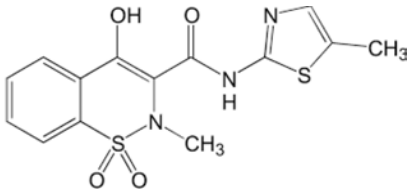
Generic Name
Meloxicam; rizatriptan benzoate

Code Name
AXS-07

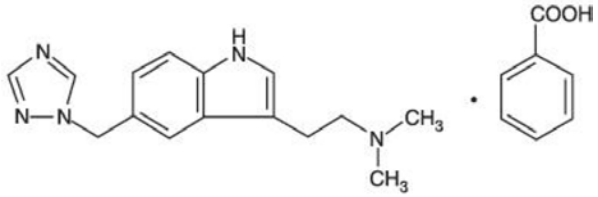
Chemical Name
4-hydroxy-2-methyl-N-(5-methylthiazol-2-yl)-2H-1,2-benzothiazine-3-carboxamide 1,1-dioxide; 1*H*-indole-3-ethanamine, *N*,*N*-dimethyl-5-(1*H*-1,2,4-triazol-1-ylmethyl)-, monobenzoate

Molecular Formula/Molecular Weight
Meloxicam: $C_{14}H_{13}N_3O_4S_2$/351.4 g/mol
Rizatriptan: $C_{22}H_{25}N_5O_2$/391.5 g/mol

Structure or Biochemical Description
Meloxicam:



Rizatriptan:



Pharmacologic Class
Anti-migraine pain relief (an NSAID + a serotonin 5-$HT_{1B/1D}$ receptor agonist or triptan).

2.2 Relevant INDs, NDAs, BLAs and DMFs

This is a 505(b)(2) application referencing Anjeso meloxicam injection (NDA 210583) and Maxalt rizatriptan benzoate tablets (NDA 020864).

2.3 Drug Formulation

See sponsor's table below.

Table 1: Composition of AXS-07 Drug Product

Component	Function	Amount per Tablet	
		mg	% (w/w)
(b) (4)			
Meloxicam, USP	Active	20	(b) (4)
Rizatriptan benzoate (equivalent to 10 mg freebase), USP	Active	14.53	
(b) (4)	(b) (4)	(b) (4)	
Sulfobutyl-ether-β-cyclodextrin sodium (SBECD), USP/Ph. Eur.			
Microcrystalline Cellulose (b) (4) NF/Ph. Eur./JP			
Pregelatinized Starch, NF/Ph. Eur.			
Colloidal Silicon Dioxide, USP/NF/Ph. Eur./JP			
Povidone, USP/Ph. Eur./JP			
Crospovidone (b) (4) NF/Ph. Eur./JP			
Magnesium Stearate, NF/Ph. Eur./JP			
Sodium Bicarbonate, USP			
(b) (4)			
			(b) (4)

JP = Japanese Pharmacopoeia, NF = National Formulary; Ph. Eur. = European Pharmacopeia; USP = United States Pharmacopeia

(b) (4)

2.4 Comments on Novel Excipients

None

2.5 Comments on Impurities/Degradants of Concern

Data were not provided to support the proposed specification of (b) (4)% for the rizatriptan-N-oxide impurity.

2.6 Proposed Clinical Population and Dosing Regimen

Adults with migraine with or without aura. One AXS-07 tablet (20 mg meloxicam -10 mg rizatriptan) by mouth at the onset of a migraine. The safety and effectiveness of a second dose have not been established.

2.7 Regulatory Background

IND submission date: June 28, 2017
NDA submission date: June 30, 2021

3 Studies Submitted

3.1 Studies Reviewed

- Validation of a LC/MS-MS detection methods for meloxicam, rizatriptan, and (b) (4) (b) (4) in minipig.
- A Rising-Dose and Multiple Dose Study of AXS-07 by Oral Administration in Minipigs
- A GLP 13-Week Study of AXS-07 by Oral Administration in Minipigs with a 28-Day Recovery Period.

3.2 Studies Not Reviewed

None

3.3 Previous Reviews Referenced

None

5 Pharmacokinetics/ADME/Toxicokinetics

5.1 PK/ADME

AXS-07 and [redacted] (b) (4) was detected in minipig plasma using validated LC-MS/MS methods.

6 General Toxicology

6.1 Single-Dose Toxicity

A single ascending oral dose study assessed AXS-07 (MLX/RIZ) in minipig (1/sex) at the following doses: 2/1, 4/2, 8/4, and 16/8 mg/kg. Clinical signs, body weight, hematology, and gross pathology were assessed. There were no drug-related findings.

6.2 Repeat-Dose Toxicity

A 14-day daily oral AXS-07 (MLX/RIZ: 10/5 mg/kg) dose study in minipig (2/sex/day) assessed clinical signs, body weight, hematology, coagulation, urinalysis, clinical chemistry, and gross pathology. Red blood cell count and hematocrit were decreased approximately 30%, compared to control, in one drug-treated male on Day 14.

Study title: A GLP 13-Week Study of AXS-07 by Oral Administration in Minipigs with a 28-Day Recovery Period

Study no.: AXS007-TP002

Study report location: EDR

Conducting laboratory and location: [redacted] (b) (4)

Date of study initiation: November 6, 2019

GLP compliance: Yes

QA statement: Yes

Drug, lot #, and % purity:

AXS-07	Lot #	Purity
Meloxicam	A-19-0100 (269001Y02F)	100%
Rizatriptan	1076764	100%

Key Study Findings

The NOAEL was the MD ($AUC_{0\text{-}inf}$: 36 h*µg/mL (MLX) and 0.3 h*µg/mL (RIZ)) based on one HDM that was euthanized due to poor health (reduced appetite, body weight loss, bloody stool, and decreased activity). In the gastrointestinal tract, there was erosion of the mucosa in the stomach, cecum, and colon. In the remaining HD animals, there was minimal to mild erosion in the gastrointestinal tract (stomach, jejunum, cecum, and colon), which resolved during the recovery period.

Methods

Doses:	MLX/RIZ: 0/0, 1/0.7, 3/2.2, or 5/3.6; MLX: 5 mg/kg; RIZ: 3.6 mg/kg
Frequency of dosing:	Daily
Route of administration:	Oral capsule
Dose volume:	N/A
Formulation/Vehicle:	Empty Capsule
Species/Strain:	Gottingen minipig
Number/Sex/Group:	Main study: 3/sex/group; Recovery: 2/sex/group (C, MD, and HD)
Age:	At dosing initiation: 15 weeks
Weight:	At dosing initiation: 7 to 10 kg
Satellite groups:	None
Unique study design:	None
Deviation from study protocol:	There were minor deviations that did not affect study validity.

Observations and Results

Mortality

One HDM was euthanized on Day 75. Dosing in this one animal was stopped on Day 72.

Clinical Signs

The euthanized HDM had liquid feces on Day 47 and decreased activity beginning on Day 73 until death. Blood was detected in a fecal sample taken on the day of euthanasia.

Body Weights

The euthanized HDM lost 9% of its body weight between Day 64 and 71.

Food Consumption

The euthanized HDM had reduced appetite beginning on Day 72.

Ophthalmoscopy

There were no drug-related findings.

ECG

There were no drug-related findings.

Hematology, Coagulation, and Clinical Chemistry

The euthanized HDM had increased neutrophil (NEUT), monocyte (MONO), large unstained cells (LUC), and platelet (PLT) counts on Day 58. On the day of euthanasia (Day 75), there were increases in NEUT, LUC, PLT, urea nitrogen (UREAN), troponin (TROPON), globulin (GLOB), and fibrinogen (FIB), and shortened activated partial thromboplastin time (APTT) and decreased albumin (ALB).

Hematology, Clinical Chemistry, Coagulation, and Troponin Findings in Males

Day	52					75	91			
Animal #	1001-4005				4002	4002	1001-4005			
mg/kg	0/0	1/0.7	3/2.2	5/3.6	5/3.6	5/3.6	0/0	1/0.7	3/2.2	5/3.6
NEUT 10^3 µL	4.8	3.7	5.2	5.2	6.5	6.6	1.7	3.1	1.8	1.5
MONO 10^3 µL	0.4	0.42	0.5	0.6	1.1	0.5	0.3	0.3	0.3	0.3
LUC 10^3 µL	0.1	0.1	0.2	0.2	0.5	0.6	0.1	0.1	0.1	0.2
PLT 10^3 µL	428	498	497	637	1036	1448	453	524	484	586
UREAN mg/dL	-	-	-	-	-	16	6.2	6.7	4.8	7
GLOB g/dL	-	-	-	-	-	3.5	0.9	1.6	1.0	1.1
ALB g/dL	-	-	-	-	-	3	5.6	5.0	5.2	5.4
APTT sec	-	-	-	-	-	8.9	16	12	15	16
FIB mg/dL	-	-	-	-	-	844	324	347	294	267
Day	-3					75	91			
TROPON ng/mL	0.03	0.03	0.03	0.03	0.03	0.16	-	-	-	-
Hematology	Clinical chemistry				Coagulation		4002: HDM sacrificed on Day 75			

Urinalysis

There were no drug-related findings.

Gross Pathology

There were no drug-related findings.

Organ Weights

There were no drug-related findings.

Histopathology

Adequate Battery
Yes

Signed pathologist report
Yes

Peer Review
No

Histological Findings
In the euthanized HDM, there was: erosion of the mucosa in the stomach, cecum, and colon, and neutrophilic inflammation.

Males in the AXS-07 groups were observed with minimal to mild erosion in the gastrointestinal tract (stomach, jejunum, cecum, and colon), which resolved following the recovery period. There were no drug-related findings in females.

Summary of Microscopic Findings – Terminal Euthanasia (Day 92/93) - Males

	Males					
Group	**1**	**2**	**3**	**4**	**5**	**6**
MLX/RIZ Dose (mg/kg/dose)	**0**	**1.0/0.727**	**3.0/2.180**	**5.0/3.633**	**5.0/-**	**-/3.633**
No. Animals Examined	**3**	**3**	**3**	**2**	**3**	**3**
Cecum (No. Examined)	3	3	3	2	3	3
Erosion	(0)[a]	(1)	(0)	(1)	(0)	(1)
Minimal	0	1	0	1	0	1
Colon (No. Examined)	3	3	3	2	3	3
Erosion	(0)	(0)	(0)	(0)	(0)	(1)
Minimal	0	0	0	0	0	1
Jejunum (No. Examined)	3	3	3	2	3	3
Erosion	(0)	(0)	(0)	(0)	(1)	(0)
Minimal	0	0	0	0	1	0
Stomach (No. Examined)	3	3	3	2	3	3
Erosion	(1)	(0)	(1)	(1)	(2)	(1)
Minimal	1	0	0	0	2	1
Mild	0	0	1	1	0	0

[a] Numbers in parentheses represent the number of animals with the finding.

Sponsor's table

Special Evaluation

None

Toxicokinetics

Repeat dosing with AXS-07, MLX, and RIZ increased exposure ($AUC_{0\text{-}inf}$). Generally, AXS-07 exposure increased dose proportionally. MLX alone produced similar exposure to MLX in AXS-07. MLX exposure was similar between sexes when administered alone or in AXS-07. RIZ exposure was greater in LDF and MDF, compared to LDM and MDM. At the HD and alone, RIZ exposure was similar between sexes. Exposure to (b) (4) was less than (b) (4) of RIZ.

Toxicokinetic data on Day 90

Dose (mg/kg)		Sex	$AUC_{0\text{-}inf}$ (h*µg/mL)			C_{max} (µg/mL)		
MLX	RIZ		MLX	RIZ	(b) (4)	MLX	RIZ	(b) (4)
1	0.7	M	9	0.1		2	0.02	
		F	10	0.1		2	0.04	
3	2.2	M	36	0.3		4	0.1	
		F	37	0.4		4	0.1	
5	3.6	M	84	0.6		7	0.2	
		F	78	0.5		6	0.1	
5	-	M	88	-	-	10	-	-
		F	92	-	-	11	-	-

-	3.6	M	-	0.6	(b) (4)	-	0.2	(b) (4)
		F	-	0.7		-	0.1	

Table 10.135: Accumulation Ratios (Day 90/Day 1) of Plasma TK Parameters in Minipigs

Analyte	Sex	Treatment	AR AUC_{0-t}	AR AUC_{0-inf}	AR C_{max}
Meloxicam	Female	AXS-07 1.0-0.727 mg/kg	2.19	2.16	2.95
		AXS-07 3.0-2.180 mg/kg	1.42	1.63	1.35
		AXS-07 5.0-3.633 mg/kg	2.07	1.68	1.61
		Meloxicam 5 mg/kg	1.88	1.85	1.86
	Male	AXS-07 1.0-0.727 mg/kg	1.62	1.10	1.33
		AXS-07 3.0-2.180 mg/kg	3.51	NC	2.73
		AXS-07 5.0-3.633 mg/kg	2.70	2.08	3.13
		Meloxicam 5 mg/kg	2.82	1.72	5.11
Rizatriptan	Female	AXS-07 1.0-0.727 mg/kg	2.23	2.30	1.69
		AXS-07 3.0-2.180 mg/kg	1.56	1.61	0.937
		AXS-07 5.0-3.633 mg/kg	1.80	1.93	3.15
		Rizatriptan 3.633 mg/kg	1.78	1.77	0.868
	Male	AXS-07 1.0-0.727 mg/kg	1.59	1.69	0.845
		AXS-07 3.0-2.180 mg/kg	2.17	1.75	2.70
		AXS-07 5.0-3.633 mg/kg	2.03	2.02	1.98
		Rizatriptan 3.633 mg/kg	1.85	1.84	0.694
(b) (4)	Female	AXS-07 1.0-0.727 mg/kg	(b) (4)		
		AXS-07 3.0-2.180 mg/kg			
		AXS-07 5.0-3.633 mg/kg			
		Rizatriptan 3.633 mg/kg			
	Male	AXS-07 1.0-0.727 mg/kg			
		AXS-07 3.0-2.180 mg/kg			
		AXS-07 5.0-3.633 mg/kg			
		Rizatriptan 3.633 mg/kg			

NC = Not Calculated; AR=Accumulation ratio.

Sponsor's table

Dosing Solution Analysis

Doses were prepared by placing weighed amounts of each test article into capsules. "Records of dose preparation were used to document the accuracy of dose preparation." Dose preparation records could not be located in the study report.

11 Integrated Summary and Safety Evaluation

AXS-07 is a combination of meloxicam (NSAID) and rizatriptan (triptan) indicated for the acute treatment of migraine with or without aura in adults. This is a 505(b)(2) NDA referencing Anjeso meloxicam injection (NDA 210583), and Maxalt (rizatriptan) tablets (NDA 020864). Under the IND, the sponsor had expressed plans to rely on reference Mobic (meloxicam) tablets; however, Mobic was not a given as a listed drug in the NDA. The recommended dose is one tablet (20 mg meloxicam (MLX) - 10 mg rizatriptan (RIZ)) by mouth at the onset of a migraine.

The sponsor submitted single-dose, 14-day, and 13-week oral toxicity studies assessing AXS-07 in minipig. The single-dose (MLX/RIZ: 2/1, 4/2, 8/4, or 16/8 mg/kg; 2/sex/group) study assessed clinical signs, body weight, hematology, and gross pathology. There were no drug-related findings.

The 14-day study (10/5 mg/kg; 1/sex/group) assessed clinical signs, body weight, hematology, coagulation, urinalysis, clinical chemistry, and gross pathology. There was an approximate a 30% decrease in red blood cell count and hematocrit in one drug-related male on Day 14. The sponsor attributed this finding to gastrointestinal blood loss, based on a published study showing that 3.5 mg/kg meloxicam administered for 13 weeks caused gastric ulceration (Lehmann et al., 1996). The gross pathology assessment showed no evidence of GI toxicity.

The pivotal 13-week (+ 28-day recovery period) study (MLX/RIZ: 1/0.7, 3/2.2, or 5/3.6 mg/kg; MLX: 5 mg/kg; RIZ: 3.6 mg/kg; main: 3/sex/group; recovery: 2/sex/group-C, MD, & HD) assessed a standard battery of parameters. The NOAEL was the MD, based on one HDM (MLX/RIZ) that had to be euthanized on Day 75 due to poor health (reduced appetite, body weight loss (9%), bloody stool, and decreased activity [beginning on Day 73]). On the day of death (Day 75), there were increases in neutrophils (4x), monocytes (2x), large unstained cells (6x), platelet counts (3x), urea nitrogen (3x), globulin (4x), fibrinogen (3x), and troponin (5x), and decreased albumin (2x) and shortened activated partial thromboplastin time (2x), compared to controls. Histological findings showed erosion of the mucosa in the stomach, cecum, and colon, and neutrophilic inflammation in the cecum and colon. In the remaining HD animals, there was minimal to mild erosion in the gastrointestinal tract (stomach, jejunum, cecum, and colon), which resolved during the recovery period. There were no adverse findings in the MLX alone or RIZ alone groups.

Generally, plasma AXS-07 exposure increased dose proportionally. The AUC at the NOAEL was approximately equivalent to that at the maximum recommended human dose of AXS-07 (20 mg meloxicam -10 mg rizatriptan).

Species	Drug	Dose		$AUC_{0\text{-inf}}$ (h*µg/mL)	Margin
Minipig 13-week	Meloxicam	NOAEL	3 mg/kg	36	1
	Rizatriptan	NOAEL	2.2 mg/kg	0.3	3
Human (AXS-07-102-CSR)	Meloxicam	Max	20 mg	48	-
	Rizatriptan	Max	10 mg	0.1	-

The nonclinical NDA package does not support approval of AXS-07, because 1) data were not provided to support chronic oral administration of meloxicam. The sponsor will need to provide support for the safety of chronic administration of meloxicam to humans, e.g., reference a meloxicam product that is approved for chronic oral administration or conduct a chronic toxicology study in a nonrodent species. 2) Data were not provided to qualify the proposed (b) (4)% limit for the impurity/metabolite rizatriptan-N-oxide; therefore, the limit for rizatriptan-N-oxide in the drug product should be lowered to the 0.5% qualification threshold.

References

Lehmann HA, Baumeister M, Lützen L, Wiegleb J. Meloxicam: A Toxicology Overview. *Inflammopharmacology* 1996; 4:105-123.

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/

EDMUND D NESTI
04/29/2022 05:13:14 AM

LOIS M FREED
04/29/2022 12:14:30 PM
I concur that the lack of nonclinical support for the proposed specification limit for the impurity, rizatriptan-N-oxide, and for chronic administration of meloxicam are deficiencies that should be adequately addressed prior to approval of the NDA.