CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

211210Orig1s000

CLINICAL REVIEW(S)

CLINICAL REVIEW

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Priority or Standard	Standard
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Division/Office	DAAAP/CDER/OND/ODE II
Reviewer Name(s)	Christina Fang, M.D., M.P.H.
Review Completion Date	October 1, 2018
Established/Proper Name	Meloxicam Orally Disintegrating Tablet (ODT) 7.5 and 15 mg
(Proposed) Trade Name	Qmiiz ODT
Applicant	TerSera Therapeutics LLC
Dosage Form(s)	Orally Disintegrating Tablet
Applicant Proposed Dosing Regimen(s)	7.5 mg or 15 mg once daily for OA and RA 7.5 mg once daily for JRA
Applicant Proposed Indication(s)/Population(s)	Osteoarthritis (OA), Rheumatoid Arthritis (RA) Juvenile Rheumatoid Arthritis (JRA)
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Same as proposed above

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Glossary

AC	advisory committee
AE	adverse event
AR	adverse reaction
BE	bioequivalence
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DARRTS	
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
ICH	International Council for Harmonization
IND	Investigational New Drug Application
iPSP	initial Pediatric Study Plan
ISE	integrated summary of effectiveness

ISS	integrated summary of safety
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
NSIADs	nonsteroidal anti-inflammatory drugs
OA	osteoarthritis
OCS	Office of Computational Science
ODT	orally disintegrating tablet
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information or package insert
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
RA	rheumatoid arthritis
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event

1. Executive Summary

1.1. Product Introduction

The orally disintegrating tablet (ODT) dosage form of meloxicam was designed for drug disintegration in mouth shortly after oral administration to allow drug administration with or without liquid beverage.

The NDA was planned to rely on the FDA's prior findings of safety and efficacy of meloxicam based on human bioavailability pharmacokinetic data showing bioequivalence (BE) between meloxicam ODT and Mobic, as well as updates on relevant post-marketing safety information on meloxicam from the published literature.

1.2. Conclusions on the Substantial Evidence of Effectiveness

Efficacy was established for meloxicam ODT based on bioavailability data that demonstrated bioequivalence to the referenced product Mobic. As such, efficacy data were not required to be included in the NDA.

1.3. Benefit-Risk Assessment

Safety data in the application were limited to single-dose exposure in healthy volunteers in the four pharmacokinetic (PK) studies and are not considered sufficient for evaluation of long-term safety of meloxicam ODT or comparative safety between meloxicam ODT and Mobic. The demonstration of bioequivalence between the test product meloxicam ODT and reference product Mobic allow the application to rely on the FDA's prior findings of safety and efficacy of meloxicam. Benefit-Risk Assessments for meloxicam ODT are expected to be consistent with that of Mobic (refer to the NDA reviews of NDA 20938 for Benefit-Risk Assessments).

Meloxicam ODT formulation contains aspartame, and thus phenylalanine. Although the amount of phenylalanine contained in the meloxicam ODT formulation is relatively small, elevated phenylalanine levels may lead to serious complications including severe damage to the central nervous system in patients with phenylketonuria. Because there are not any situations where the benefits of meloxicam ODT in patients with phenylketonuria would be expected to outweigh the risks associated with phenylalanine intake, particularly in the setting of other possible sources of dietary phenylalanine and given the available therapeutic alternatives, the use of the drug should be contraindicated in patients with phenylketonuria.

Benefit-Risk Integrated Assessment

Benefits and risks of using meloxicam ODT are expected to be the same as that of Mobic® based on establishment of bioequivalence between the two products.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Osteoarthritis (OA) • Rheumatoid Arthritis (RA) • Juvenile Rheumatoid Arthritis (JRA) Pauciarticular and Polyarticular Course, in pediatric patients who weigh greater than or equal to 60 kg	Refer to the approval of Mobic® NDA-20938 dated April13, 2000 and Mobic® labeling.
Current Treatment Options	• Nonsteroidal anti-inflammatory drugs (NSAIDs) • Analgesics such as opioids and acetaminophen • Steroids • Disease-modifying anti-rheumatic drugs (DMARDs) for RA	
Benefit	• Reduce inflammation • Reduce pain • relief of the signs and symptoms of OA and RA	Refer to the approval of Mobic® NDA-20938 dated April13, 2000 and Mobic® labeling.
Risk and Risk Management	• Known risks associated with NSAIDs in general and with Mobic® in particular as stated in Mobic® labeling	Refer to the approval of Mobic® NDA-20938 dated April13, 2000 and Mobic® labeling.

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

□	The patient experience data that was submitted as part of the application include:	Section where discussed, if applicable
	□ Clinical outcome assessment (COA) data, such as	[e.g., Sec 6.1 Study endpoints]
	□ Patient reported outcome (PRO)	
	□ Observer reported outcome (ObsRO)	
	□ Clinician reported outcome (ClinRO)	
	□ Performance outcome (PerfO)	
	□ Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)	
	□ Patient-focused drug development or other stakeholder meeting summary reports	[e.g., Sec 2.1 Analysis of Condition]
	□ Observational survey studies designed to capture patient experience data	
	□ Natural history studies	
	□ Patient preference studies (e.g., submitted studies or scientific publications)	
	□ Other: (Please specify)	
□	Patient experience data that were not submitted in the application, but were considered in this review:	
	□ Input informed from participation in meetings with patient stakeholders	
	□ Patient-focused drug development or other stakeholder meeting summary reports	[e.g., Current Treatment Options]
	□ Observational survey studies designed to capture patient experience data	
	□ Other: (Please specify)	
■	Patient experience data was not submitted as part of this application.	

2. Therapeutic Context

2.1. Analysis of Condition

The common symptoms and signs associated with rheumatoid arthritis (RA) include joint pain and stiffness and tender, warm, and swollen joints. The common symptoms and signs associated with osteoarthritis (OA) include joint pain, tenderness, and stiffness with loss of flexibility.

2.2. Analysis of Current Treatment Options

NSIADs, steroids, and analgesics such as acetaminophen and opioid have been used for treatment of RA and OA. Additional RA treatments include disease-modifying anti-rheumatic drugs (DMARDs) and chelators and additional OA treatments include duloxetine, muscle relaxants, and nutraceuticals (e.g., glucosamine/chondroitin sulfate).

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Meloxicam ODT has not been marketed in the US or foreign countries.

3.2. Summary of Presubmission/Submission Regulatory Activity

The protocols for the four pharmacokinetic (PK) studies were included in the initial IND (104140) submission dated November 20, 2009. The Division agreed with the Sponsor that clinical efficacy or safety trials would not be required if meloxicam ODT could be bioequivalent to the referenced Meloxicam product. The Division provided specific recommendations for the Sponsor to obtain a biowaiver for in vivo testing of the 7.5 mg dose strength (refer to the letter sent to the Sponsor dated May 27, 2010).

At the preNDA meeting held on July 12, 2017 (refer to the meeting minutes in DARRTS dated August 8, 2017) the Division accepted the Sponsor's proposal to use results of PK studies and literature support for submission of NDA in general, based on the review of preliminary information provided by the Sponsor.

The Division informed the Sponsor that we would review information on relative bioavailability between meloxicam ODT and Mobic® at dose strength of 15 mg and review biowaiver request for the 7.5 mg strength at the time of NDA submission to determine if the data would be adequate.

The Division expressed concerns about more delayed Tmax under fed versus fasted conditions tested, in comparison to the extent of delay of Tmax by food described in Mobic® labeling and recommended direct comparison of the two products in a BE study under fed condition. In response to the Sponsor's argument about irrelevance of delayed Tmax due to chronic use of their product with intended long-term therapeutic effect at steady state, the Division requested the Sponsor to show comparable systemic exposures between meloxicam ODT and Mobic® at steady state and under fed conditions and to provide clinical justification for delayed Tmax with food.

The Division also provided some specific advice on how to use literature information and suggested literature search to cover the time period starting from the year of Mobic® approval in 2000 to the year of the most recent NSAID class safety labeling update and how to use Module 2 and 5 to present Integrated Summary of Efficacy (ISE) and Integrated Summary of Safety (ISS), agreed that case narratives and related case report forms (CRFs) would not be required because there were no deaths, serious adverse events (AEs), discontinuations due to an AE, or other significant AEs, and reminded the Sponsor about having an agreed initial Pediatric Study Plan (iPSP) before NDA submission.

3.3. Foreign Regulatory Actions and Marketing History

None.

4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

The Division of New Drug Bioequivalence Evaluation (DNDBE) within the Office of Study Integrity and Surveillance (OSIS) recommends accepting data without an on-site inspection because OSIS recently inspected the sites for clinical trials and data analysis and with the inspectional outcome classified as No Action Indicated (NAI) (refer to the memo dated March 19, 2018 filed in DARRTS).

4.2. Product Quality

Based on the OPQ (Office of Pharmaceutical Quality) discipline reviews for drug substance, drug product, process including microbiology, facilities and biopharmaceutics, the information submitted in the initial submission with clarifications in the subsequent submissions is considered acceptable with no outstanding request for further information (refer to the CMC review for detail).

4.3. Clinical Microbiology

Refer to review section 4.2 above.

4.4. Nonclinical Pharmacology/Toxicology

Nonclinical studies were not required because there are no novel excipients in the drug product or impurities or degradation products in the meloxicam drug substance and drug product that exceed ICH regulatory thresholds according to Dr. Armaghan Emami's review of Pharmacology/Toxicology. The non-clinical program of this NDA relied on the known safety

profile of Mobic® and on the published pharmacology, PK, and toxicology literature (refer to her review in DARRTS dated September 20, 2018 for detail).

4.5. Clinical Pharmacology

According to Dr. Deep Kwatra's review of clinical pharmacology (refer to the PK review filed in DARRTS on September 17, 2018 for detail) the results of the relative bioavailability study 10943701 revealed that meloxicam ODT was bioequivalent to Mobic® tested at 15 mg level under fasted condition as measured by Cmax (the maximal plasma concentration) and AUC0-t and AUC0-∞ (area under the plasma concentration time curve), and that were no significant differences in t1/2 (elimination half-life) and Tmax (time to maximum plasma concentration) between the two products.

The findings from the food effect study 10943702 showed bioequivalence between meloxicam ODT products tested under fed condition versus fasted condition and a longer delay of Tmax by high fat meal from 4 to 13 hours than food effects on delay of Tmax by only 1-2 hours (b) (4)

In comparison of steady-state PK profiles between meloxicam ODT and Mobic® based on exposure prediction through PK modeling, meloxicam ODT given at 15 mg once daily (QD) produced a meloxicam PK profile within the range of Mobic® 15 mg QD under both fed and fasted conditions.

The biowaiver request for conducting dose proportionality studies between 7.5 mg and 15 mg strengths is considered acceptable based on the review by the Division of Biopharmaceutics.

Based on the review of the literature reports of three studies investigating the impact of CYP2C9 polymorphisms on meloxicam pharmacokinetics and consideration of data limitation from lack of patient level raw PK data and of details about bioanalytical methods used, the pharmacogenomics reviewer Dr. Oluseyi Adeniyi has the following labeling recommendations:

- CYP2C9 activity is reduced in individuals with genetic variants such as the CYP2C9*2 and CYP2C9*3 alleles. Limited data from three published reports showed that meloxicam AUC was substantially higher in individuals with reduced CYP2C9 activity, particularly in poor metabolizers (e.g., *3/*3), compared to normal metabolizers (*1/*1). The frequency of CYP2C9 poor metabolizer genotypes varies based on racial/ethnic background but is generally present in <5% of the population (for Section 12.5 Pharmacogenomics).

- Poor Metabolizers of CYP2C9 Substrates: In patients who are known or suspected to be poor CYP2C9 metabolizers based on genotype or previous history/experience with other CYP2C9 substrates (such as warfarin and phenytoin) consider dose reduction as they may have abnormally high plasma levels due to reduced metabolic clearance (for Section 8 Use in Specific Populations).

4.6. Devices and Companion Diagnostic Issues

None.

4.7. Consumer Study Reviews

None.

5. Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

Table 1 List of Clinical Studies

Type	Study#, site, date	Section	Design	Treatment	N	Population
PK Relative bioavailability	**10943701** Houston, TX 3/2/10-3/12/10	5.3.3.1.2 (S-1)	Single-center Single-dose Open-label Randomized 2-way crossover (fasted)	A: Meloxicam ODT 15 mg* B: Mobic® tablets 15 mg	32	Adult healthy volunteers
PK Food effect	**10943702** Houston, TX 3/6/10-3/16/10	5.3.3.1.1 (S-2)	Single-center Single-dose Open-label Randomized 2-way crossover (fed vs fasted)	A: Meloxicam ODT 15 mg* (fed) B: Meloxicam ODT 15 mg* (fasted)	32	Adult healthy volunteers
PK Relative bioavailability	C09173 India 1/7/10-1/31/10	5.3.3.1.4 (S-4)	Single-center Single-dose Open-label Randomized 3-way crossover (fasted)	A: Meloxicam ODT 15 mg* B: Meloxicam ODT 15 mg** C: Mobic® tablets 15 mg	18	Male adult healthy volunteers
PK Relative bioavailability	CB081206 India 8/28/09-9/8/09	5.3.3.1.3 (S-3)	Single-center Single-dose Open-label Randomized 2-way crossover (fasted)	A: Meloxicam ODT 15 mg*** B: Mobic® tablets 15 mg	18	Male adult healthy volunteers

5.2. Review Strategy

The review of the NDA is focused on the safety data from the four PK studies and updates of safety profile on Mobic® reported in literature.

6. Review of Relevant Individual Trials Used to Support Efficacy

Efficacy studies were not required or submitted for this NDA.

7. Integrated Review of Effectiveness

The effectiveness of meloxicam ODT in the proposed indications is based on relative bioavailability data that established bioequivalence between the proposed product and the reference product.

8. Review of Safety

8.1. Safety Review Approach

The safety database consisted of four single-dose PK studies of meloxicam ODT as summarized in the Study Inventory Table in the review section 5.2. Safety data were pooled from these four studies and AEs were categorized by body systems and grouped under two treatments: meloxicam ODT versus Mobic®.

8.2. Review of the Safety Database

8.2.1. Overall Exposure

Study drug exposure was limited to exposure to a single dose in 100 healthy volunteers in four PK studies, including exposure to the to-be-marketed formulation of meloxicam ODT 15 mg in 82 subjects (52 exposed to a single dose and 30 to two doses given as a single dose in different study period), 35 subjects to a single dose of an older formulation of meloxicam ODT 15 mg used in PK studies at the Indian study site, and 68 subjects to a single dose of Mobic® 15 mg tablet.

Table 2 Exposure Summary

Study number	**N**	**Demographics (Male/Female; Age Range)**	**Meloxicam ODT 15 mg**			**Mobic® 15 mg**
US studies			To-be marketed		Other	
			One dose	Two doses a week apart	One dose	One dose
10943701	32	20 male/11 female; age 18 to 54 years	32			32
10943702	32	19 male/9 female; age 19 to 53 years	2	30 (fed vs fasted)		
Indian studies						
C09173	18	18 male; age 20 to 42 years	18		17	18

CB081206	18	18 male; age 19 to 37 years			18	18
Total	*100*		*52*	*30*	*35*	*68*
			82			

Source: Table 2.7.4.2 on page 10 of the Summary of Clinical Safety.

8.2.2. **Relevant characteristics of the safety population:**

The two US studies had male/female enrolled in a 2:1 ratio and the two Indian studies included male subjects only. There were no elderly subjects in any of the four PK studies.

8.2.3. **Adequacy of the safety database:**

Product safety of meloxicam ODT is primarily based on referencing the Agency's prior findings for Mobic® based on relative bioavailability data that established bioequivalence between the two products. This approach was based on previous agreement between the Applicant and the Review Division.

8.3. Adequacy of Applicant's Clinical Safety Assessments

8.3.1. **Issues Regarding Data Integrity and Submission Quality**

None.

8.3.2. **Categorization of Adverse Events**

AEs were categorized by body systems and grouped under two treatments: meloxicam ODT and Mobic® for comparison.

8.3.3. **Routine Clinical Tests**

Routine clinical tests included vital signs at baseline (pre dose) and at 5 hours post dose in the two US studies and at frequent intervals up to 12 hours pose dose in the two Indian studies. Sampling for routine hematology and chemistry laboratory tests were collected at screening within 3-4 weeks prior to the initial dose and up to 72 hours post dose.

8.4. Safety Results

8.4.1. **Deaths**

No deaths occurred in any of the clinical studies.

8.4.2. **Serious Adverse Events**

No serious adverse events were reported in any of the clinical studies.

8.4.3. **Dropouts and/or Discontinuations Due to Adverse Effects**

There were no dropouts due to AEs.

8.4.4. Significant Adverse Events

There were no reports of significant AEs.

8.4.5. Treatment Emergent Adverse Events and Adverse Reactions

Less than 10% subjects had any treatment emergent adverse events (TEAE). Only a few AEs were reported in more than one subject, including blood pressure decreased in two subjects treated with meloxicam ODT and three treated with Mobic®, headache in two subjects treated with meloxicam ODT, and alanine aminotransferase increased in two subjects treated with Mobic®. All AEs were classified as mild and mostly resolved spontaneously.

Table 3 Summary of Treatment Emergent Adverse Events, PK Studies

MedDRA System Organ Class and Preferred Term	**Meloxicam ODT 15 mg N=100**	**Mobic® 15 mg N=100**
Any TEAE	9 (9.0)	9 (9.0)
Gastrointestinal disorders	**1 (1.0)**	**1 (1.0)**
Nausea	0	1 (1.0)
Toothache	1 (1.0)	1 (1.0)
Investigations	**5 (5.0)**	**7 (7.0)**
Alanine aminotransferase increased	0	2 (2.0)
Aspartate aminotransferase increased	1 (1.0)	0
Blood pressure decreased	2 (2.0)	3 (3.0)
Blood pressure increased	1 (1.0)	1 (1.0)
Hemoglobin decreased	0	1 (1.0)
Heart rate increased	1 (1.0)	0
White blood cell count increased	1 (1.0)	0
Musculoskeletal and connective tissue disorders	**1 (1.0)**	**0**
Groin pain	1 (1.0)	0
Nervous system disorder	**2 (2.0)**	**1 (1.0)**
Headache	2 (2.0)	1 (1.0)

Source: Table 2.7.4.5 on page 14 of the Summary of Clinical Safety.

8.4.6. Laboratory Findings

Changes in results of clinical laboratory tests were reported as AEs in five subjects as summarized in the table above. Aspartate aminotransferase increased in one subject and white blood cell count increased in one subject given meloxicam ODT and alanine aminotransferase increased in two subjects and hemoglobin decreased in one subject given Mobic®. The only noticeable findings based on shift table comparison of post dose (36-72 hours after the last dose) versus screening (3-4 weeks before the initial dose) lab values were a few more cases of

hematocrit and hemoglobin decrease and ALT/AST increase in the meloxicam ODT group than the Mobic® group. Taking into consideration of the time lag of several weeks between the screening labs and post study labs and the small sample size (only 50 had both screening and post study results) the findings could not be used to draw any conclusion.

8.4.7. Vital Signs

There were eight cases of changes in vital signs reported as AEs, seven as changes in blood pressure in both treatments groups and one as heart rate increased, all from the two US studies.

8.4.8. Electrocardiograms (ECGs)

Post study ECGs were not conducted.

8.4.9. QT

Not studied.

8.4.10. Immunogenicity

Not studied.

8.5. Analysis of Submission-Specific Safety Issues

None.

8.5.1. [Name Safety Issue]

8.6. Safety Analyses by Demographic Subgroups

Not applicable due to small sample size and minimal findings.

8.7. Specific Safety Studies/Clinical Trials

None.

8.8. Additional Safety Explorations

No additional safety exploration was conducted for meloxicam ODT.

8.8.1. Human Carcinogenicity or Tumor Development

None

8.8.2. Human Reproduction and Pregnancy

Refer to the review section 8.9.3 below.

8.8.3. **Pediatrics and Assessment of Effects on Growth**

The Applicant requested a full waiver for pediatric studies of osteoarthritis because studies are impossible or highly impracticable, a waiver of pediatric study in birth to less than 2 years of age for RA because studies are impossible or highly impracticable, a waiver of pediatric study in 2 to less than 16 years of age and weighing <60 kg for RA because the product fails to represent a meaningful therapeutic benefit over existing therapies for pediatric patients and is unlikely to be used in a substantial number of pediatrics in this age group. There are multiple formulations of other NSAIDs that are approved for use with formulations that are appropriate for use in patients down to 2 years of age. The requests of the waivers in all ages for RA and osteoarthritis are considered acceptable based on PeRC recommendation as fully described in the agreed Pediatric Study Plan.

8.8.4. **Overdose, Drug Abuse Potential, Withdrawal, and Rebound**

Meloxicam ODT is expected to have low potential for overdose and drug abuse and no known safety concerns regarding drug withdrawal and rebound.

8.9. **Safety in the Postmarket Setting**

Post-marketing data on Meloxicam ODT are not available because the drug has not yet been marketed.

Post-marketing safety of meloxicam was evaluated by the Applicant using citation database through MEDLINE® and EMBASE® covering the time period of January 2000 to June 2017. Relevant safety information included three cases of thrombocytopenia presented with bleeding (Hiran et al. 2003, Neki 2009, Ranieri et al. 2014), one case of rhabdomyolysis and anaphylactic reaction in a patient infected with Ross River virus (where meloxicam and acute RRV may both be contributing as concluded by the author, Al Kindi et al. 2012.), one case of repeated occurrence of psoriatic skin lesions (Ilknur et al. 2006), and one case of eosinophilic pneumonia (Karakatsani et al. 2003), all thought to be induced by meloxicam (Mobic®) by the study authors.

The case of rhabdomyolysis and anaphylactic reaction occurred in a 74-year-old man who "developed acute rhabdomyolysis after taking meloxicam for jaw pain. Symptoms included generalized myalgia, acute febrile illness, and generalized urticaria. Further investigation revealed elevated muscle enzymes and acute renal failure. The patient was positive for Ross River virus (RRV). Meloxicam was discontinued. He responded to conservative measures within two weeks. Oral aspirin challenge was negative, suggesting a drug-specific effect of meloxicam rather than a class effect."

The case of repeated occurrence of psoriatic skin lesions occurred in a 49-year-old man with a

16-year psoriasis history, who was taking meloxicam (Melox®, 15 mg/day) for the treatment of psoriatic arthritis. The patient developed skin symptoms and signs consistent with psoriatic skin lesions after being on meloxicam treatment for 16 days, while not having other medical conditions or taking other medications during the same time period. The skin lesion resolved in a few weeks after topical treatments but recurred later, about 8 days after the patient took two additional doses of meloxicam without consulting a physician.

The case of eosinophilic pneumonia occurred in a 23-yr-old nonsmoking, immunocompetent man with a history of allergic rhinitis and nasal polyps and no history of bronchial asthma or known prior exposure to any pulmonary toxin or irritant. The patient presented with low grade fever and dry coughs after taking oral meloxicam at 7.5 mg per day for 4 days for shoulder pain due to strain. Diagnostic findings were consistent with eosinophilic pneumonia. Drug reaction was considered most likely cause of the event since multiple differential diagnostic workup tests were negative for other etiologies. The patient responded to oral methylprednisolone treatment and recovered.

There were three literature reports of controlled studies of meloxicam on ovulation. The findings were consistent with reversible and dose-dependent inhibition of ovulation by meloxicam expressed as delay in follicular rupture.

Literature search on post-marketing safety of Mobic® conducted by the Applicant did not identify any new relevant articles that discuss association between meloxicam with any of the following: CV thrombotic events, gastrointestinal (GI) bleeding (except the thrombocytopenic cases mentioned above), ulceration, or perforation, hepatic toxicity, hypertension, congestive heart failure and edema, renal toxicity and hyperkalemia, exacerbation of asthma related to aspirin sensitivity, or premature closure of fetal ductus arteriosus.

The most recent review of literature covering the time period from June 1, 2017 to February 21, 2018 as included in the 120-day safety update did not reveal any new safety findings on the use of meloxicam that would alter the findings described in the current Mobic® labeling.

One literature article (Yue et al 2018) reported differential increases of risks for acute kidney injury (AKI) in patients taking antiviral drugs concomitantly with an NSAID. The author had analysis using the FDA AERS database between January 2004 and June 2012 and found that the risks for AKI were similar for patients taking valacyclovir or acyclovir alone but increased from 8.6% to 19.4% with concomitant use of valacyclovir and an NSIAD and from 8.7% to 10.5% with concomitant use of acyclovir and an NSIAD. Drug interaction is suspected and needs to be explored further.

8.9.1. **Safety Concerns Identified Through Postmarket Experience**

Of the AEs reported as post-marketing experience associated with the use of Mobic® from literature anaphylactic reactions are listed under Warnings and Precautions and

thrombocytopenia is listed as one of the AEs in the category of <2% reported in clinical trials in Mobic® labeling. Rhabdomyolysis, psoriatic skin lesions, and eosinophilic pneumonia have not been mentioned in the Mobic® labeling and each appeared to have occurred in a patient with concurrent medical conditions or past medical history contributing to the development of the AE, such as concurrent Ross River viral infection and anaphylactic reactions in the case of rhabdomyolysis, recurrence of skin lesions in a patient already having a 16-year history of psoriasis, and eosinophilic pneumonia in a patient with a history of allergic nasal conditions. Therefore, they need to be explored further and may be added to the Mobic® and meloxicam ODT labeling in the future when more cases are identified.

8.9.2. **Expectations on Safety in the Postmarket Setting**

The safety profile for meloxicam ODT is expected to be similar to that of Mobic®.

8.9.3. **Additional Safety Issues from Other Disciplines**

Dr. Christos Mastroyannis from consulting Division of Pediatric and Maternal Health (DPMH) performed a detailed review about the effect of Mobic® and NSAIDs on pregnancy (no new data), lactation (no new human data), females and males of reproductive potential (following NSAID class labeling) and made a number of recommendations on corresponding labeling sections, including warnings and precautions about premature closure of fetal ductus arteriosus (Section 5.10), use in specific populations with regard to pregnancy, lactation, females and males of reproductive potential (Section 8.1, 8.2, and 8.3), and patient counseling information (Section 17) on female fertility and fetal toxicity (refer to the DPMH review in DARRTS dated August 29, 2018 for detail).

8.10. **Integrated Assessment of Safety**

The safety of meloxicam ODT in the proposed indications is based on relative bioavailability data that demonstrated bioequivalence to the referenced meloxicam product (Mobic). Meloxicam ODT labeling will incorporate the safety information described in approved Mobic labeling, including what is generally known about NSAIDs.

Safety data in this NDA included only single-dose exposure in 100 healthy volunteers with findings limited to mild AEs reported in 10% subjects studied. Long-term safety data comparing meloxicam ODT and Mobic® had not been required based on the agreement of accepting demonstration of bioequivalence between the two products.

Postmarketing AEs from the use of Mobic® based on literature reports included cases of thrombocytopenia and anaphylactic reactions already covered in Mobic® labeling. Of the other postmarketing AEs not mentioned in the Mobic® labeling such as rhabdomyolysis, psoriatic skin lesions, and eosinophilic pneumonia, each was reported as a single case in a patient with either concurrent illness or past medical history suggesting co-contributing factors. They need to be explored and may be added to the Mobic® and meloxicam ODT labeling in the

future if additional cases are identified.

The reversible effects of meloxicam on the delay or prevention of rupture of ovarian follicles reported from three different studies in literature are already mentioned in the Mobic® labeling.

9. Advisory Committee Meeting and Other External Consultations

None.

10. Labeling Recommendations

10.1. Prescription Drug Labeling

A warning against the use of meloxicam ODT in patients with phenylketonuria was proposed because the ODT formulation contains phenylalanine (0.30 mg in the 7.5 mg tablet and 0.59 mg in the 15 mg tablet), which is a component of aspartame (an artificial sweetener). Patients with phenylketonuria have missing or reduced enzymes and/or enzyme dysfunction for phenylalanine metabolism and may have dangerous buildup of phenylalanine upon eating phenylalanine containing products including aspartame, which may lead to serious health consequence such as severe damage to central nervous systems. Therefore, phenylketonuria should be listed as one of the contraindications in the meloxicam ODT labeling.

10.2. Nonprescription Drug Labeling

Not applicable.

11. Risk Evaluation and Mitigation Strategies (REMS)

Not applicable.

12. Postmarketing Requirements and Commitments

None.

13. Appendices

13.1. References

Al Kindi M, Limaye V, Hissaria P (2012). Meloxicam-induced rhabdomyolysis in the context of an acute Ross River viral infection. Allergy Asthma Immunol Res. 4(1):52-54.

Hiran S, Mazumdar D, Sarma P (2003). Acute thrombocytopenic purpura due to meloxicam. JAPI. 51;531-532.

Karakatsani A, Chroneou A, Goulouris NG, Orphanidou D, Jordanoglou J (2003). Letter to the editor. Meloxicam-induced pulmonary infiltrates with eosinophilia: a case report. Rheumatology. 42(9):1112-1113.

Ilknur T, Fetil E, Akarsu S, Arda F, Sis B, Gunes AT (2006). Development of psoriasis after meloxicam. Letter to the editor. EJD. 16(4):444-445.

Neki NS (2009). Meloxicam-induced acute thrombocytopenic purpura. J Int Med Sci Acad. 22(4):203.

Ranieri MM, Bradley EF, Simon AB (2014). Meloxicam-induced thrombocytopenia. Pharmacotherapy. 34(2):e14-e17.

Yue et al (2018). Yue Z, Shi J, Li H, Li H. Association between concomitant use of acyclovir or valacyclovir with NSAIDs and an increased risk of acute kidney injury: data mining of FDA Adverse Event Reporting System. Biol Pharm Bull 2018;41(2):158-162.

13.2. Financial Disclosure

Study 10943701 and 10943702:

Covered Clinical Study (Name and/or Number): 10943701 and 10943702

Was a list of clinical investigators provided:	Yes ■	No ☐ (Request list from Applicant)
Total number of investigators identified: 6		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____		

Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

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/

CHRISTINA L FANG
10/03/2018

JOSHUA M LLOYD
10/03/2018