CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

211210Orig1s000

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	(electronic stamp)
From	Sharon Hertz, MD
Subject	Division Director Summary Review
NDA #	211210
Applicant Name	TerSera Therapeutics LLC
Date of Submission	December 21, 2017
PDUFA Goal Date	October 19, 2018
Proprietary Name / Established (USAN) Name	Qmiiz ODT/ meloxicam orally disintegrating tablet
Dosage Forms / Strength	Orally disintegrating tablet, 7.5 mg and15 mg.
Proposed Indication(s)	For the relief of the signs and symptoms of osteoarthritis, rheumatoid arthritis, and pauci-articular or polyarticular course juvenile rheumatoid arthritis in patients who weigh ≥ 60 kg.
Action:	Approval

Material Reviewed/Consulted OND Action Package, including:	
Medical Officer Review	Christina Fang, MD
Pharmacology Toxicology Review	Armaghan Emami, PhD, Jay Chang, PhD, R. Daniel Mellon PhD
OPQ Review	Fred Burnett, Donna Christner, Vekateswara Pavuluri, Julia Pinto, Rebecca Dombrowski, Pei-I, Peng Duan, Kelly Kitchens, Steven Kinsley, Caryn McNab
Microbiology Review	
Clinical Pharmacology Review Pharmacogenomics Review	Deep Kwatra, PhD, Yun Xu, PhD Oulseyui Adeniyi, PhD, Christian Grimstein, PhD
OSE/DMEPA	Cameron Johnson, PharmD, Otto L. Townsend, PharmD
OPDP/DCDP	Koung Lee, Samuel Skariah
OMP/DMPP	Susan Redwood, MPH, BSN, RN, Barbara Fuller, RN, MSN, CWOCN, LaShawn Griffiths, MSHS-PH, BSN, RN

OND=Office of New Drugs
OSE= Office of Surveillance and Epidemiology
OSI=Office of Scientific Investigations
OPDP=Office of Prescription Drug Promotion
OMP=Office of Medical Policy Initiatives
OPQ= Office of Pharmaceutical Quality
DMEPA=Division of Medication Errors Prevention
DCDP=Division of Consumer Drug Promotion
DMPP=Division of Medical Policy Programs

Signatory Authority Review Template

1. Introduction

This is a 505(b)(2) application for Qmiiz ODT (meloxicam) orally disintegrating tablets in 7.5 mg and 15 mg dosage strengths. The applicant has referenced Mobic (meloxicam tablets, NDA 020938, approved April 13, 2000, Boehringer Ingelheim Pharmaceuticals Inc) as the listed drug and is relying on the agency's prior findings of efficacy and safety for Mobic.

2. Background

No new safety or efficacy studies were conducted in support of this application. The applicant conducted single-dose relative bioavailability studies in the fasted and fed states comparing Qmiiz and Mobic, and another study comparing the two products at steady state. As a product intended for daily use for chronic illnesses, any delay in Tmax from food would not be expected to have a clinically important effect on efficacy. This concept was supported by a comparison of meloxicam levels at steady state.

3. CMC/Device

The dose strengths for Qmiiz oral tablets are 7.5 and 15 mg that are compositionally proportional. The sponsor proposed dosing regimen of once daily for either strengths. The proposed dosing regimen for both strengths is similar when compared to reference Mobic 7.5 and 15 mg tablets, which are both dosed once daily.

The following was excerpted from the OPQ review:

> **Review Summary:** Brand Name™ (Meloxicam) orally disintegrating tablets are available in two dosage strengths, 7.5 mg and 15 mg; debossed with either 7.5 or 15 as identifying logo, prepared by freeze-drying process in preformed blisters and sealed with lidding foil, and are further packaged in to 10, 30 or 90 count cartons. Drug substance particles size, quantities of functional excipients, and processing parameters were adequately evaluated during product development stage for assuring control of drug product quality characteristics at release and through the end shelf-life. Except for orange flavor, all other excipients used are compendial grade. All in-house analytical methods used in testing of the drug product were adequately validated for intended use.
>
> Based on available stability data, ***a shelf-life of 36 months for Meloxicam ODT 15 mg*** and a ***tentative shelf-life of 24 months for Meloxicam ODT 7.5 mg*** may be granted,

when the drug products are labeled as "Store at 20° -25° C (68° -77° F), with excursions permitted between 15° C and 30° C (59° -86° F) [See USP Controlled Room Temperature]. Avoid high humidity and excessive heat above 40°C (104°F)".

A waiver for a dose proportionality study was granted based on the following information:

- The bioavailability of meloxicam and demonstration of bioequivalence of 15 mg meloxicam ODT to Mobic;
- Demonstration of linear PK between the 7.5 mg and 15 mg strengths, as described in the Mobic package insert;
- Compositional proportionality between the 7.5 mg and 15 mg strengths (b) (4)

(b) (4)

I concur with the conclusions reached by the chemistry review team regarding the acceptability of the manufacturing of the drug product and drug substance. There are no outstanding issues.

4. Nonclinical Pharmacology/Toxicology

The following was excerpted from the pharm/tox review:

> The TRADENAME Meloxicam ODT nonclinical program was based on the safety profile of Mobic and on the published pharmacology, PK, and toxicology literature. There are no novel excipients in the drug product and no impurities or degradation products in the meloxicam drug substance and drug product that exceed ICH regulatory thresholds. Therefore, additional nonclinical studies were not required to support the safety of this drug product formulation. From a pharmacology toxicology perspective, the NDA may be approved.

I concur with the conclusions reached by the pharmacology/toxicology reviewer that there are no outstanding pharm/tox issues that preclude approval.

5. Clinical Pharmacology

Qmiiz 15 mg was found to be bioequivalent to Mobic 15 mg in the fasted and fed states, however there was a significant delay in Tmax as noted by Dr. Kwatra. As meloxicam used daily for chronic disease, a steady-state exposure prediction was made to compare the steady-state meloxicam PK profiles after the administration of Mobic (15 mg) and Qmiiz (15 mg) when given under fed and fasted conditions. Overall, the results showed that Qmiiz dosed as 15 mg daily produced a meloxicam PK profile within the range of Mobic 15 mg daily under both fed and fasted conditions

As meloxicam is a substrate of CYP2C9, the applicant provided an analysis from literature of expected meloxicam levels in subjects who have poor metabolizer genotypes such as CYP2C9*3 and subjects who have the extensive metabolizer genotype CYP2C9*1. The applicant was asked to obtain the raw data and detailed information regarding bioanalytical methods from the authors of the publications, but was unsuccessful. In the absence of adequate information, the pharmacogenomics team could not make dosing recommendations, but did recommend inclusion of information in the label..

I concur with the conclusions reached by the clinical pharmacology and pharmacogenomics reviewers that there are no outstanding clinical pharmacology issues that preclude approval.

6. Clinical Microbiology

Not Applicable.

7. Clinical/Statistical-Efficacy

No new efficacy data were submitted in support of this application. The applicant is relying on the agency's previous finding of efficacy for Mobic.

8. Safety

Limited safety data were submitted in support of this application from single-dose pharmacokinetic findings. As described by Dr. Fang, there were no unusual findings. A review of the literature did not reveal any novel safety signals suitable for labeling.

9. Advisory Committee Meeting

There were no scientific questions requiring an advisory committee meeting.

10. Pediatrics

A waiver for pediatric studies was requested by the applicant and found acceptable by the Pediatric Research Committee.

11. Other Relevant Regulatory Issues

There are no other unresolved relevant regulatory issues

12. Labeling

The labeling reviews by Dr. Johnson and Dr. Lee revealed issues in the package insert, blister pack and carton labeling which were conveyed to the applicant and the changes were made as requested. A proprietary name review by Dr. Johnson for the name Qmiiz ODT was found acceptable. Recommendations from the patient labeling team were incorporated into the labeling. The labeling differences from Mobic are the instructions for use, formulation specific information, and the additional contraindication for use in patients with phenylketonuria because of the presence of aspartame in Qmiiz.

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action - Approval

- Risk Benefit Assessment

Qmiiz is a new formulation of meloxicam that can be expected to have comparable efficacy and safety as the referenced drug, Mobic, with the exception of the need for a contraindication for use in persons with phenylketonuria.

- Recommendation for Postmarketing Risk Management Activities

None

- Recommendation for other Postmarketing Study Commitments

None

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/

SHARON H HERTZ
10/19/2018