CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204683Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

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: June 18, 2013

FROM: Jing Zhang, MD. PhD.
Medical Team Leader, Division of Psychiatry Products
HFD-130

SUBJECT: Cross Discipline Team Leader Review

NDA/Supp#: 204683

Proprietary/ Established name: Desvenlafaxine (base) Extended Release Tablet

Dosage forms/ Strength: 50 mg and 100 mg tablets

Indication: Major Depressive Disorder in Adults

Recommendation: Approval

I. Introduction and Background

This is a 505 (b) (2) application from Osmotica Pharmaceutical for Khedezla, an extended release (once daily) formulation of desvenlafaxine base. The sponsor is seeking for an indication of major depressive disorder in adults. The reference listed drug (RLD) is Pristiq (desvenlafaxine succinate) that is developed by Wyeth and was approved for major depressive disorder on February 29, 2008 under NDA 21-992. Desvenlafaxine is a selective serotonin and norepinephrine reuptake inhibitor (SNRI).

The basis for this application is CMC information intended to support this new formulation and bioequivalence data obtained from three pharmacokinetic studies that the sponsor feels adequately demonstrate bioequivalence for these two formulations.

II. Summary of Conclusions and Recommendations from Review Teams

1. CMC

The drug product will be marketed in two strengths, 50 mg and 100 mg tablet. Elsbeth Chikhale, PhD., is the ONDQA Biopharmaceutics reviewer for this NDA. He reviewed the dissolution methodology and acceptance criteria; the in vitro alcohol dose dumping study; the extended release claim; (b) (4) She concluded that the dissolution method and acceptance criteria are acceptable; this formulation doesn't have alcohol dose dumping in vitro; the extended release claim is acceptable; (b) (4)

Shastri Bhamidipati, PhD., is the chemistry reviewer for this submission. In the review, he concluded that the applicant has provided adequate responses to the FDA CMC IR letters. Their latest supplement, S0011, of 24-Apr-2013 was reviewed to be acceptable. However, the site inspection result is still pending. A complete recommendation for approval from the CMC perspective can't be made until they receive acceptable site inspection result.

2. Nonclinical Pharmacology/Toxicology

This is a 505 (b) (2) submission. There are no unresolved nonclinical pharmacology/toxicology issues for this application.

3. Clinical Pharmacology/Biopharmaceutics

Kofi Kumi PhD is the clinical pharmacological reviewer. In this submission, the sponsor has included the results from three bioequivalent studies: OS230-1006, 11-VIN-478 and 11-VIN-479.

Bioequivalence
Khedezla® (Desvenlafaxine base) 100 mg ER tablet was demonstrated to be bioequivalent to Pristiq® (Desvenlafaxine succinate) 100 mg ER Tablet under fasting and fed conditions. Khedezla 50 mg ER tablet was demonstrated to be bioequivalent to Pristiq 50 mg ER tablet under fasting conditions. The plasma concentration time profiles after administration of Khedezla and Pristiq are similar suggesting that Khedezla exhibits similar extended release characteristics as Pristiq. Please reference to the review of Kofi Kumi PhD for detailed information.

Food Effect
The Tmax of desvenlafaxine after administration of Khedezla ER and Pristiq ER are comparable under fasting conditions. However, Khedezla median Tmax was later when the study was conducted under fed conditions. Both OCP and clinical team agreed that the difference in median Tmax when the study was conducted under fed conditions is not expected to be clinically relevant. Therefore, Kofi Kumi concluded that Khedezla can be administered with or without food. Please reference to the review of Kofi Kumi PhD for detailed information.

4. Clinical

This application was reviewed by Roberta Glass MD, from the clinical team. All clinical studies conducted in this NDA were bioequivalent (relative bioavailability to Pristiq) studies. There were no efficacy or safety studies conducted under this NDA. There was no new safety signals identified from these 3 clinical studies in this program.

5. OPDP

The Office of Prescription Drug Promotion (OPDP) conducted review of the sponsor proposed labels and made a few recommendations that have been incorporated in the final product labeling.

6. OSI Inspection

The Office of Scientific Investigations (OSI) inspected selected data from all 3 bioequivalence studies conducted in the US, Hungary, and India. The OSI reviewer, Jyoti Patel PhD, concluded that the clinical portions of study OS230-1006, and the data from the analytical and clinical portions of studies 11-VIN-478 and 11-VIN-479 are acceptable for further agency review.

7. Labeling

Several revisions of physician labeling had been recommended by review divisions, OCP team, OPDP, and the Patient Labeling Team (PLT)/the Office of Medical Policy Initiatives. We are still in the process negotiating the labeling with the sponsor. The final agreed upon labeling will be attached to the action letter when this NDA is taken action.

8. Pediatric Plan

At Pristiq approval on Feb. 29, 2008, FDA requested the innovator to conduct children and adolescent (7-17 years old) MDD studies to assess the safety and efficacy of desvenlafaxine in these population as a PREA requirement. (b) (4) Based upon this, the division requested 1) a full waiver for pediatric MDD studies in children less than 7 years old because of difficulties in the diagnosis and recruitment of children with major depressive disorder in these age groups; and 2) a deferral of children and adolescent (7 to 17 years old) MDD studies with desvenlafaxine (base) (b) (4) PeRC met with the Division on May 29, 2013, and agreed with the Division's requests.

9. Post Marketing Commitments or Requirements

No post marketing commitments are deemed necessary. See *8. Pediatric Plan* for pediatric post-marketing requirement.

10. Risk Minimization Action Plan

No Risk Minimization Action Plan deemed necessary for this submission.

11. Conclusion and Recommendation

I agree that the sponsor has submitted sufficient data to show that Khedezla® ER is bioequivalent to the marketed product Pristiq® ER. If the facility inspection result which is still pending is acceptable, I recommend that the division take an approval action on this submission.

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/s/

JING ZHANG
06/19/2013