CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205208Orig1s000

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: October 4, 2013

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

SUBJECT: Cross Discipline Team Leader Review

NDA/Supp#: 205208

Proprietary/ Established name: Desvenlafaxine (b) (4) 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 Teva Pharmaceuticals USA for desvenlafaxine fumarate extended release (ER) formulation, 50 mg and 100 mg strengths, 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).

This developmental program is under IND 113629. Teva requested a pre-IND and a pre-NDA meeting with FDA on December 6, 2011 and October 16, 2012 to discuss the developmental program and a proposed 505(b) (2) application. Both meetings were cancelled by Teva after received satisfactory response from the division.

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. The efficacy and safety

of this formulation were relying on FDA's previous experience with Pristiq and information included in the Pristiq labeling.

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. Banu S. Zolnik, PhD., is the ONDQA Biopharmaceutics reviewer for this NDA. Dr. Zolnik reviewed the dissolution methodology and acceptance criteria, and the *in vitro* alcohol dose dumping study. Dr. Zolnik concluded in the review that the dissolution method and acceptance criteria for desvenlafaxine fumarate after incorporated FDA's recommendations are deemed acceptable, and *in vitro* alcohol dose dumping studies for both strengths did not indicate any dose dumping in presence of alcohol.

Mohan K. Sapru, PhD., is the chemistry reviewer for this submission. Dr. Sapru identified several deficiencies regarding DMF # 26379 and the NDA submission. These deficiencies had been communicated to the applicant via a mid-cycler review deficiency letter and the deficiencies have been satisfactorily addressed by the sponsor. Specifically, based on Agency recommendation, the DMF holder has agreed to change the designation of starting materials. The sponsor has committed to carry out stability studies on the first three commercial batches under both long-term storage conditions as well as accelerated storage conditions. For environmental assessment, Dr. Sapru agreed with a categorical exclusion. From the CMC perspective, there is no outstanding CMC issue. However, the Office of Compliance has not, as yet, issued an 'acceptable' recommendation for all the relevant manufacturing and testing facilities yet. A final recommendation from CMC cannot be made at this time.

2. Nonclinical Pharmacology/Toxicology

Shiny V. Mathew, Ph.D., is the pharmacology/Toxicology reviewer for this submission. She stated in her review that no impurities, degradants, or novel excipients in desvenlafaxine Fumarate Extended Release tablets that would require additional toxicological characterization have been identified. She recommended an approval action.

3. Clinical Pharmacology/Biopharmaceutics

Kofi Kumi PhD is the clinical pharmacological reviewer. In this submission, the sponsor has included the results from the following bioequivalent and bioavailability studies:

Study 53811: An Open-Label, Single-Center, Randomized, Single-Dose, Two-Period, Two-Treatment, Two-Sequence Crossover Study to Compare the Bioequivalence of Desvenlafaxine Fumarate Extended-Release Tablets, Equivalent to 100 mg Desvenlafaxine to Pristiq® Extended-Release Tablets, 100 mg Under Fasted Conditions

Study 53711: An Open-Label, Single-Center, Randomized, Single-Dose, Two-Period, Two-Treatment, Two-Sequence Crossover Study to Compare the Bioequivalence of

Desvenlafaxine Fumarate Extended-Release Tablets, Equivalent to 100 mg Desvenlafaxine to Pristiq® Extended-Release Tablets, 100 mg Under Fed Conditions

Study 2012-2833: A Single-Dose, Comparative Bioavailability Study of One Formulation of Desvenlafaxine Fumarate Extended Release Tablets, Equivalent to 50 mg Desvenlafaxine and One Formulation of Pristiq® Extended Release Tablets, 50 mg under Fasting and Fed Conditions.

Bioequivalence and food effect

Kofi Kumi PhD reviewed these studies and concluded in his review that desvenlafaxine fumarate Extended Release (ER) tablet was bioequivalent to Pristiq® (desvenlafaxine succinate) ER Tablet under fasting at 50 mg and 100 mg strengths, respectively. The 90% confidence interval (CI) of the mean ratio falls within the regulatory criteria of 80% to 125%.

When desvenlafaxine fumarate ER tablet was administered under fed conditions compared to when given under fasting conditions, Cmax increased by about 19% and AUC by about 7%. The increase in Cmax was significant numerically but it is not expected to be clinically significant. When the reference drug, Pristiq, was administered under fed compared to fasting conditions, Cmax is reported to increase by about 16% with no significant increase in AUC. Therefore, like Pristiq, desvenlafaxine fumarate ER should be recommended to be taken with or without food.

Issues Related to Clinical and Bioanalytical Site Inspections

The bioequivalence studies were inspected by The Division of Bioequivalence and GLP Compliance (DBGLPC), the Office of Scientific Investigations (OSI). DBGLPC recommended that DPP exclude the data for subjects 15 and 34 in Study 53711 due to deficiencies with the analytical runs for these subjects. The OCP review team re-run the statistical analysis excluding subjects 15 and 34 and concluded that the results based on the recalculated data are consistent with the results obtained when all the subjects were included in the analysis. Therefore the overall conclusions remain unchanged and desvenlafaxine fumarate 100 mg ER is bioequivalent to Pristiq ER 100 mg under fasting conditions.

The OCP review team recommended an approval action on this NDA.

4. Clinical

This application was reviewed by Glenn Mannheim, MD, from the clinical team. All three clinical studies conducted in this NDA were bioequivalent (relative bioavailability to Pristiq) studies. There were no efficacy or safety studies conducted under this NDA.

A total of 84 subjects were enrolled in these 3 studies, of which 76 completed studies. No deaths or severe adverse events were reported. The commonly reported adverse events

(AEs) are headache, nausea, somnolence, emesis, diarrhea, dizziness, etc. These findings are consistent with current desvenlafaxine label. Dr. Mannheim stated in his review that a slight numerical excess of adverse events (nausea, emesis, somnolence) compared to equal doses of Pristiq were present when desvenlafaxine fumarate ER tablets were taken on an empty stomach in studies 53711 and 2012-2883. However, given the small numbers of subjects and limited exposures, no definitive conclusions as to ultimate safety differences can be made.

Dr. Mannheim concluded that in general desvenlafaxine fumarate ER tablet, 50 and 100 mg were well tolerated in these studies. There was no new safety signals identified from these 3 clinical studies in this program. He recommend that this NDA to be approved.

5. OPDP

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

6. OSI Inspection

The Division of Bioequivalence and GLP Compliance (DBGLPC), the Office of Scientific Investigations (OSI), conducted audits of the clinical and analytical portions for the three bioequivalence studies: Study 53711, 53811, and 2012-2883. The DBGLPC reviewer, Jyoti Patel PhD, concluded that the clinical and analytical data from studies 53711, 53811 and 2012-2883 are acceptable for further agency review with the 2 exceptions for study 53711. These two deficiencies has been reviewed and appropriately addressed by the clinical and OCP review teams.

7. Labeling

Several revisions of physician labeling had been recommended by the review division, 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. These studies currently are ongoing. 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 fumarate until the innovator completes their pediatric studies. PeRC met with the Division on September 18, 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 with other reviews that the sponsor has submitted sufficient data to show that Desvenlafaxine Fumarate Extended-Release Tablets 50 mg and 100 mg are 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
10/04/2013