

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

204150Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

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

DATE: December 20, 2012

FROM: Jing Zhang, MD. PhD.
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HFD-130

SUBJECT: Cross Discipline Team Leader Review

NDA/Supp#: 204150

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

**Dosage forms/
Strength:** 50 mg and 100 mg tablets

Indication: Major Depressive Disorder in Adults

Recommendation: Tentative Approval

I. Introduction and Background

This is a 505 (b) (2) application for 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 two 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. John Duan PhD. is the ONDQA Biopharmaceutics reviewer for this NDA. He reviewed the in vitro

alcohol dose dumping study, the dissolution methodology and acceptance criteria, and the extended release claim and concluded that this formulation doesn't have alcohol dose dumping potential and the information and data provided are acceptable.

Mohan K. Sapru, PhD is the chemistry, manufacturing and control (CMC) reviewer for this submission. During the review, several deficiencies concerning the drug substance and the drug product were identified and communicated with the sponsor. All identified deficiencies had been satisfactorily addressed during this review cycle. The CMC team has recommended an approval action.

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 two bioequivalent studies, Study 413-11 and Study 455-11. The followings are summary of clinical pharmacology and biopharmaceutics findings from the clinical pharm team:

Bioequivalence

Desvenlafaxine (base) 50 mg and 100 mg ER are bioequivalent to Pristiq 50 mg and 100 mg ER tablets respectively under fasting condition. The following are the results (Table 1 and Table 2) for the comparison of Desvenlafaxine ER 100 mg and 50 mg tablets to Pristiq.

Table 1: Geometric Least Squares Mean, Ratios and 90% Confidence Interval for Desvenlafaxine 100 mg under fasting conditions

Parameters	Geometric Least Squares Mean			90% Confidence Interval
	Desvenlafaxine ER (Test- T)	Pristiq (Reference-R)	Ratio (T/R) (%)	
Cmax (ng/mL)	282.75	252.75	111.9	105.5 – 118.6
AUC _(0-t) (ng*h/mL)	6392.62	5869.84	108.9	100.4 – 118.2
AUC _(0-∞) (ng*h/mL)	6468.06	5937.48	108.9	100.5 – 118.1

Table 2: Geometric Least Squares Mean, Ratios and 90% Confidence Interval for Desvenlafaxine 50 mg under fasting conditions

Parameters	Geometric Least Squares Mean			90% Confidence Interval
	Desvenlafaxine ER (Test)	Pristiq (Reference)	Ratio (T/R) (%)	
Cmax (ng/mL)	121.41	117.47	103.4	95.08 – 112.35
AUC _(0-t) (ng*h/mL)	2729.88	2503.69	109.0	98.09 – 121.20
AUC _(0-∞) (ng*h/mL)	2778.84	2544.24	109.2	98.36 – 121.28

Food Effect

Administration of Desvenlafaxine (base) ER with a high fat meal (800 – 1000 calories) did not have a significant effect on the extent of absorption (AUC) but an increase of 23% in peak concentration (C_{max}). The review team did not think this increase is clinically significant. They concluded that desvenlafaxine ER (base) tablets can be given with or without food.

4. Clinical

This application was reviewed by Glenn Mannheim, MD from the clinical team. There were no important adverse events reported in the two clinical studies in this program.

5. DMEPA

The division of Medication Error Prevention and Analysis (DMEPA) conducted review of the labels and labeling received on November 29, 2012 and determined that the applicant had implanted all of their recommendations conveyed to the sponsor previously and no additional comments to the sponsor at this time.

6. OSI Inspection

The sites of bioequivalence studies were inspected by the Office of Scientific Investigations (OSI) and they concluded that the clinical and bioanalytical portions of the study 413-11 and 415-11 are acceptable.

7. Labeling

Multiple revisions of physician labeling had been recommended by the Division, the OCP review team, the Study Endpoints and Labeling Development (SEALD), the Division of Professional Promotion/Office of Prescription Drug Promotion (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 ascertainment 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) until the innovator completes their pediatric studies. PeRC met with the Division on Nov. 14, 2012 and agreed with the Division's requests.

9. Post Marketing Commitments or Requirements

No post marketing commitments or requirements are deemed necessary.

10. Risk Minimization Action Plan

No Risk Minimization Action Plan deemed necessary for this submission.

11. Conclusion and Recommendation

Even though all disciplines had completed their reviews and did not have pending issues to against approval, this application cannot be approved at this time because the RLD, Pristiq, is still protected by the New Molecular Entity Exclusivity granted by FDA until March 1, 2013. Therefore, I recommend a tentative approval of this application at this time.

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/s/

JING ZHANG
12/20/2012