

**MEMORANDUM**

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

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**DATE:** September 26, 2007

**FROM:** Ni A. Khin, M.D.  
Team Leader  
Division of Psychiatry Products, HFD-130

**TO:** File NDA 22-104 (This overview should be filed with the 12-12-2006 submission)

**SUBJECT:** Recommendation of approvable action for Osmotica's Venlafaxine Extended-Release Tablets for MDD and SAD

**1. BACKGROUND**

Osmotica has submitted this 505(b)(2) NDA for an extended release formulation of venlafaxine on 12/12/2006. The sponsor is seeking marketing approval for 37.5, 75, 150, and 225 mg strength tablets of their product. This application is based on demonstrating bioequivalence to Wyeth's Effexor XR (velanfaxine extended release) currently available as the same mg strength capsules.

The application included the results of four bioequivalence studies (protocols 10672001, 10572001 R04-0776, and R04-778). This NDA was reviewed by Greg Dubitsky, M.D., Medical Officer, DPP (review dated 8/24/07), Kofi Kumi, Ph.D., from the Office of Clinical Pharmacology (review dated 9/20/07), and Sherita McLamore, Ph.D., Chemistry Reviewer, ONDQA (review dated 8/5/07). Dr. Linda Fossom provided labeling comments regarding non-clinical toxicology sections (review dated 9/7/07).

**2.0 CHEMISTRY**

According to the CMC review dated 8/5/07, the CMC reviewer recommended approvable action contingent upon an adequate response to the CMC concerns (which includes update the drug substance specification with a [REDACTED] acceptance criteria for the particle size or the sponsor to provide justification for such omission; relevant information pertaining to drug product reference standard; additional dissolution data, etc.); and acceptable recommendation from the Office of Compliance regarding site inspections. Based on our recent communication with the ONDQA assessment lead, Dr. Tom Oliver, the CMC team has received response from the sponsor, and indicated that an amendment will be generated by the CMC reviewer. At the time of completion of this memo, the CMC amendment has not been finalized yet.

**3.0 PHARMACOLOGY/TOXICOLOGY**

No new pharmacology/toxicology issues required for review in this submission. The proposed pharmacology/Toxicology sections appeared to be the same as for Effexor XR.

## 4.0 CLINICAL PHARMACOLOGY

The OCP review covered results from the following BE studies:

- Two 4-way Crossover Single-Dose Studies in Fed and Fasted Condition: 37.5 mg Venlafaxine Extended-release tablet compared to 37.5 mg Effexor XR Capsule in a study with 36 healthy adults (Protocol No. 10672001); 75 mg Venlafaxine Extended Release Tablet compared to 75 mg Effexor XR Capsule in a study with 30 healthy adult subjects (Protocol No. 10572001).
- One 2-way Crossover Single Dose Study in Fed Condition (Protocol No. R04-0776) comparing Venlafaxine Extended-release Tablets 225 mg and Effexor XR® Capsules 75 mg plus Effexor XR® Capsules 150 mg (N=36).
- One 2-way Multiple Dose, Randomized, 2-Period, Crossover Study in Fed Condition (Protocol No. R04-778) in which 225 mg Venlafaxine Hydrochloride Extended-release Tablets was compared to the combination of one 75 mg Effexor XR Capsule and one 150 mg Effexor XR Capsule administered daily for 7 days (N=33).

As Dr. Kumi noted in his review, data from these BE studies indicated that Venlafaxine ER Tablets 37.5 and 75 mg formulation (Osmotica) was bioequivalent to the respective strengths of Effexor® XR (Venlafaxine HCl) Extended-Release Capsules when administered under fed conditions. I note Dr. Kumi's conclusion that Venlafaxine Extended Release 75 mg is not bioequivalent to Effexor XR mg under fasting condition based on the finding that exposure in terms of AUC after administration of Venlafaxine Extended Release was equivalent to Effexor XR 75 mg while C<sub>max</sub> was about 19% higher under fasting condition. This is not expected to be clinically significant. Effexor XR label also recommends the drug to be taken with food.

Venlafaxine 225 mg extended release tablet (highest strength; Osmotica) was also demonstrated to be bioequivalent to Effexor 225 (150 + 75) mg XR capsules after a single dose administration under fed conditions. The AUC and C<sub>max</sub> (90% CI) were within the regulatory criteria of 80 to 125% (i.e., AUC: 2431, 2254 ng-hr/ml; C<sub>max</sub>: 132, 130 ng/ml, test product vs. reference, respectively).

It was noted in the OCP review that the 75 mg, 150 mg, and 225 mg are compositionally proportional and the dissolution profiles of these strengths are similar. The OCP recommended a waiver of bioequivalence study for the 150 mg Venlafaxine Extended Release Tablets should be granted. OCP also recommended that the sponsor should conduct studies to investigate dose-dumping in the presence of alcohol as part of Phase IV commitment.

Although the dissolution method proposed by the sponsor was acceptable, OCP has proposed an alternate dissolution specification limit. They provided some labeling comments for the PK section. We should convey both dissolution specification limit and labeling comments by OCP in our action letter.

## 5.0 CLINICAL DATA

I concur with Dr. Dubitsky that the conducted BE studies are not capable of producing new safety data that could be extrapolated to the clinical use of venlafaxine. Dr. Dubitsky's clinical review

was focused on the SAEs and AE discontinuation from the BE studies. It was noted there were no deaths or SAEs. A total of 4 subjects who were on venlafaxine 225 mg dose discontinued due to adverse events but none of these events is considered unexpected with venlafaxine.

## **6.0 DSI INSPECTIONS**

The pivotal site, [REDACTED], for study R04-0776 was inspected. DSI noted an inspectional finding that sample concentrations [REDACTED] could not be assured for subjects 15, 16, 18 and 20. The OCP recalculation of AUC and Cmax without these 4 subjects found no major impact on study data as the recalculated 90% CI still indicated that 225 mg venlafaxine extended release tablets (Osmotica) are bioequivalent to 225 mg Effexor XR capsule dose.

## **7.0 LABELING AND ACTION LETTER**

The sponsor intends to make labeling claim on [REDACTED] indications: MDD, SAD [REDACTED].  
[REDACTED]

The OCP review indicates that the sponsor's proposals for the majority of Clinical Pharmacology sections are acceptable. There were some labeling modifications under the Pharmacokinetics subsection.

Since this NDA was submitted in December 2006, there were some labeling revisions to the innovator Effexor XR labeling. In particular, the changes included the language in regards to suicidality in young adults in the black box warnings and medication guide; use of venlafaxine in patients with liver disease; hyponatremia; and additional information regarding an interaction study with metoprolol.

The Division is aware that it will be difficult for Osmotica to revise the labeling to conform to the new PLR format as they do not have access to the raw data underlying the innovator product labeling. This application is subject to the requirements for the labeling according to the new PLR format. During the review cycle, Osmotica submitted the labeling in the new PLR format. This will require further modifications prior to taking a final action. With our action letter, we should provide a copy of PLR labeling guidance and a list of labeling deficiencies.

## **11.0 CONCLUSION AND RECOMMENDATION**

In my opinion, the sponsor has provided sufficient evidence to demonstrate that Osmotica's venlafaxine Extended release tablets (37.5, 75 and 225 mg strengths) are bioequivalent to Effexor XR. As recommended by OCP, we should give a waiver of BE study for the 150 mg strength. I recommend the Division issue an approvable letter for this NDA. We should consider approval of this application when the dissolution specification is set; any CMC issues for this product are resolved; and an agreement is reached with the sponsor regarding the language in the labeling.

cc:

HFD-130/Laughren/Mathis/Dubitsky/Bender

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/s/

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MEDICAL OFFICER