CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-104

MEDICAL REVIEW(S)

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: May 19, 2008

FROM: Thomas P. Laughren, M.D.
Director, Division of Psychiatry Products
HFD-130

SUBJECT: REMS requirements for approval action for Venlafaxine Hydrochloride Extended Release Tablets for major depressive disorder (MDD) and social anxiety disorder

TO: File NDA 22-104
[Note: This memo should be filed with the sponsor's 3-19-08 complete response to our 2-26-08 action letter.]

Risk Evaluation and Mitigation Strategy (REMS) Requirements – Venlafaxine Hydrochloride Extended Release Tablets

Title IX, Subtitle A, Section 901 of the Food and Drug Administration Amendments Act of 2007 amended the Federal Food, Drug, and Cosmetic Act to authorize FDA to require the submission of a Risk Evaluation and Mitigation Strategy (REMS) for an approved drug if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks (section 505-1(a)). Section 505-1(a) provides the following factors:

(A) The estimated size of the population likely to use the drug involved;
(B) The seriousness of the disease or condition that is to be treated with the drug;
(C) The expected benefit of the drug with respect to such disease or condition;
(D) The expected or actual duration of treatment with the drug;
(E) The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug
(F) Whether the drug is a new molecular entity.

After consultations between the Office of New Drugs and the Office of Surveillance and Epidemiology, we have determined that Venlafaxine Hydrochloride Extended Release Tablets are associated with numerous safety risks, including an increased risk of suicidality in children, adolescents, and young adults in short-term studies of MDD and other psychiatric disorders. We determined that a REMS is necessary to ensure that the benefits of this product outweigh its risks.

In reaching this determination, we considered the following:

A. While it is not possible to estimate the size of the population likely to use Venlafaxine Hydrochloride Extended Release Tablets, the number of patients affected with MDD and social anxiety disorder in the United States are approximately 15 and 5 million, respectively.

B. Venlafaxine Hydrochloride Extended Release Tablets will be approved to treat major depressive disorder (MDD) and social anxiety disorder, serious medical conditions. Complications of MDD and social anxiety disorder can include disturbances in mood, interest, sleep, concentration and appetite as well as social and occupational dysfunction. Patients with MDD and social anxiety disorder have an increased risk of suicide.

C. Venlafaxine Hydrochloride Extended Release Tablets have been shown to reduce the signs and symptoms of MDD and social anxiety disorder in adult patients.

D. The expected duration of therapy with Venlafaxine Hydrochloride Extended Release Tablets in patients who obtain a clinical response will minimally be 6 months to a year, and may be for many years; MDD and social anxiety disorder are considered life-long diseases, although the severity of symptoms may vary over time. (See Clinical Team memos under Efficacy.)

E. Known serious risks with use of Venlafaxine Hydrochloride Extended Release Tablets include potential clinical worsening of suicide risk in children and young adults, precipitation of a manic episode, potential hepatotoxicity, increased agitation/insomnia, changes in appetite, and hypertension. (See Clinical Team memos under Safety.)

F. Venlafaxine Hydrochloride Extended Release Tablets are a member of the class of antidepressants known as serotonin and norepinephrine reuptake inhibitors. Venlafaxine Hydrochloride Extended Release Tablets have been available in the U.S. for years as Effexor XR.

In accordance with section 505-1 of the FDCA, as one element of a REMS, FDA may require the development of a Medication Guide as provided for under 21 CFR Part 208. Under 21 CFR 208, the sponsor is responsible for ensuring that the Medication Guide is available for distribution to patients who are dispensed Venlafaxine Hydrochloride Extended Release Tablets. Pursuant to 21 CFR Part 208, FDA has determined that Venlafaxine Hydrochloride Extended Release Tablets pose a serious and significant public health concern requiring the distribution of a Medication Guide. The Medication Guide is necessary for patients' safe and effective use of Venlafaxine Hydrochloride Extended Release Tablets. FDA has determined that Venlafaxine Hydrochloride Extended Release Tablets is a product that has serious risks of which patients should be made aware because information concerning the risks could affect patients' decisions to use, or continue to use, Venlafaxine Hydrochloride Extended Release Tablets.

The only elements of the REMS will be a Medication Guide and a timetable for submission of assessments of the REMS.

cc:
Orig NDA 22-104
HFD-130/TLaughren/MMathis/NKhin/RGrewal

DOC: Venlafaxine Hydrochloride Extended Release Tablets_Laughren_AP Memo.doc

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/s/

Thomas Laughren
5/19/2008 02:19:37 PM
MEDICAL OFFICER

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: February 15, 2008

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 12-28-2007 submission in response to the 10-04-2007 approvable letter)

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 original NDA application included the results of four bioequivalence studies (protocols 10672001, 10572001 R04-0776, and R04-778). We issued an approvable letter on 10/04/2007. In the AE letter, it was noted that we should have an agreement with the sponsor that they would adopt the dissolution method and specification proposed by the Agency before the application may be approved. In addition, the AE letter also provided a list of labeling deficiencies that the sponsor should address prior to the product approval.

The sponsor submitted their response to the AE letter on 12/28/07. This submission was reviewed by Kofi Kumi, Ph.D., from the Office of Clinical Pharmacology (review dated 2/11/08), and Sherita McLamore, Ph.D., Chemistry Reviewer, ONDQA.

2.0 CHEMISTRY

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 a brief review will be generated by the CMC reviewer. At the time of completion of this memo, the CMC review has not been finalized yet. I am not aware of any CMC issues that would preclude an approvable action.

3.0 PHARMACOLOGY/TOXICOLOGY

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

4.0 CLINICAL PHARMACOLOGY

Although the sponsor has accepted the dissolution method proposed in the AE letter, [redacted] b(4)

Dr. Kumi reviewed the dissolution profiles of the bio-lots for each dosage strength. As noted in his review, it was observed that the behaviors of the release characteristics are comparable between the dosage strength. It is not anticipated that the Agency's proposed specification would result in significant batches failing the dissolution specification. OCP recommends that the sponsor adopt the Agency's proposed specification for all strengths of Venlafaxine Extended Release tablets. OCP also 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

No new clinical data that would require a review in this submission. Dr. Greg Dubitsky provided labeling comments.

6.0 LABELING AND ACTION LETTER

Osmotica's proposed labeling changes in the new PLR format submitted in this AE response would still require extensive modifications before we could take an approval action. Since this AE response was submitted, there were some labeling revisions to the innovator Effexor XR labeling. These revisions should be incorporated in this Venlafaxine Extended Release product labeling. We should provide our labeling comments to the sponsor in our action letter.

7.0 CONCLUSION AND RECOMMENDATION

I recommend the Division issue another 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 labeling deficiencies are adequately addressed.

cc:
HFD-130/Laughren/Mathis/Dubitsky/Grewal
File: NDA22104/Memo_022008

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/s/

Ni Aye Khin
2/15/2008 11:11:57 AM
MEDICAL OFFICER

Review and Evaluation of Clinical Data
NDA #22-104

Sponsor:	Osmotica Pharmaceutical
Drug:	Venlafaxine Extended-Release Tablets
Indications:	Major Depression Social Anxiety Disorder
Material Submitted:	505(b)(2) New Drug Application
Correspondence Date:	December 11, 2006
Date Received:	December 12, 2006
PDUFA Goal Date:	October 12, 2007

I. Regulatory Background

Venlafaxine is a serotonin and norepinephrine reuptake inhibitor made by Wyeth Pharmaceuticals. It was first approved on 12-28-93 as an immediate-release tablet formulation (Effexor) for the treatment of major depressive disorder (MDD) under NDA 20-151. Subsequently, Wyeth developed an extended-release capsule (Effexor XR) which was approved on 10-20-97 for the treatment of MDD under NDA 20-699. Thereafter, Effexor XR was approved for generalized anxiety disorder (GAD)(3-11-99), prevention of recurrence and relapse in MDD (5-2-01), social anxiety disorder (2-11-03), and panic disorder (11-18-05).

Osmotica Pharmaceutical Corporation of Wilmington, NC, has developed an extended-release tablet formulation of venlafaxine under IND 71,288, which was received on 10-24-05. On 12-11-06, Osmotica submitted NDA 22-104 under the provisions of section 505(b)(2) of The Federal Food, Drug, and Cosmetic Act to obtain marketing approval for 37.5mg, 75mg, 150mg, and 225mg strengths of this product. That submission contains Osmotica's certification that their product and claims will not infringe on patents for the Wyeth product. On 2-23-07, representatives for Osmotica notified Wyeth that a 505(b)(2) application for venlafaxine extended-release tablets had been filed by the FDA on 2-10-07. In that notification, they contend that since the tablets are not encapsulated spheroids (which are found in Effexor XR capsules), the tablets cannot literally infringe on the Wyeth patents. Also, since the tablets do

not function in substantially the same way as the encapsulated spheroids, this is not an infringement on any claim under the Wyeth patents. On 4-20-07, Wyeth filed a lawsuit against Osmotica in Federal Court to prevent the sale of venlafaxine extended-release tablets.[1]

During development bioequivalence to the innovator Effexor XR was evaluated in the following studies:

- 37.5mg single-dose, randomized, four-period crossover study in fed and fasted conditions (10672001).[2]
- 75mg single-dose, randomized, four-period cross-over study in fed and fasted conditions (10572001).
- 225mg single-dose, randomized, two-period crossover study under fed conditions (R04-0776).

For the 150mg tablet, Osmotica has requested a bio-waiver since the tablets are dose-proportional for the 75, 150, and 225mg strengths.

During the 1-25-07 Filing Meeting, the Office of Clinical Pharmacology (OCP) review team noted that the application was deficient in that it lacked a steady-state study of bioequivalence comparing the highest strength (225mg) to Effexor XR under fed conditions.[3] It was stipulated by the OCP team that if the study report was submitted by 6-30-07, then the study would be reviewed during the current review cycle. The sponsor agreed to conduct such a study expeditiously and the application was filed on 2-10-07, with a User Fee Goal Date of 10-12-07. This study (R04-0778) was completed and the report was submitted to the application on 6-28-07.

Bioequivalence data from the above four studies will be reviewed in detail by the OCP review team and will not further discussed in this review, which will focus on important clinical safety data from these trials and labeling for the tablet formulation.

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[1] See: http://patentdocs.typepad.com/patent_docs/ files/ wyeth_v_osmotica.pdf.

[2] The fed state is the recommended dosing condition for Effexor XR and the extended-release tablet.

[3] Effexor XR is not marketed in the 225mg strength; thus, a 150mg capsule was co-administered with a 75mg capsule to constitute an Effexor XR dose of 225mg.

II. Materials Reviewed

The following materials were reviewed.

Submission Date	Materials
December 11, 2006	10672001 Study Report 10572001 Study Report R04-0776 Study Report JMP Datasets Case Report Forms Waiver Request for 150mg and 225mg Debarment Certification Financial Disclosure Certification Patent Certification
January 19, 2007	PREA Waiver Request
January 31, 2007	PLR Labeling
March 20, 2007	Patent Amendment
June 28, 2007	R04-0778 Study Report JMP Datasets Case Report Forms Financial Disclosure Certification
July 24, 2007[4]	Osmotica Proposed Labeling

III. Financial Disclosure

On 11-27-06, Mark S. Aikman, Pharm.D., Vice President, Regulatory Affairs and Quality Assurance, Osmotica Pharmaceutical Corp., certified that Osmotica had not entered into any financial arrangement with the principal or sub-investigators from studies 10672001, 10572001, and R04-0776 whereby the value of the compensation could have been affected by the outcome of the study. Also, he certified that each investigator required to disclose a proprietary interest in the product or significant equity interest in the sponsor did not disclose any such interests. He further certified that none of these investigators was the recipient of significant payments of other sorts.

This certification was updated on 6-18-07 to include the principal and sub-investigators for study R04-0778.

[4] Submitted via Email to the Project Manager, William Bender.

IV. Review of Clinical Safety Data

Given the extensive safety experience to date with Effexor and Effexor XR, the relatively brief duration of the bioequivalence studies, and the subject samples for these studies (healthy volunteers), the conducted studies are not capable of producing meaningful new safety data that could be extrapolated to the clinical use of venlafaxine products. Therefore, this safety review will focus only on the more serious adverse experiences from the four bioequivalence studies, that is, any deaths and other events classified as serious and any adverse experiences that led to premature discontinuation from the study, based on my review of the individual study reports.

A. Deaths

There were no deaths in any of the studies.

B. Non-Fatal Serious Adverse Events

There were no non-fatal serious adverse events in any of the studies.

C. Adverse Events Resulting in Dropout

Adverse events led to dropout in only the two high dose (225mg) studies. In study R04-0776, three subjects dropped out due to adverse events:

- subject 06 - headache, nausea, and vomiting.
- subject 13 - vomiting.
- subject 31 - nausea and vomiting.

In study R04-0778, one subject discontinued due to an adverse experience:

- subject 19 - vomiting.

None of these events is considered unexpected with venlafaxine, especially considering the administration of the 225mg dose without titration to healthy volunteers.

V. Pediatric Plan

On 1-19-07, Osmotica requested a full waiver of the PREA (Pediatric Research Equity Act) requirement for pediatric

studies. This request is based on the provisions of PREA sections 505B(a)(4)(A)(ii) and 505B(a)(4)(A)(iii) and the following factors:

- Effexor XR labeling carries a Box Warning which conveys an increased risk of suicidality in children and adolescents who are prescribed this product. Venlafaxine extended-release tablets can be expected to confer the same risk in this population.
- adequate and well-controlled clinical trials of Effexor XR in pediatric patients with MDD and in pediatric patients with GAD failed to produce sufficient support for approval in these indications.
- Effexor XR capsules may be opened and sprinkled on applesauce for administration to children. This is not an option with venlafaxine extended-release tablets.

Thus, the sponsor argues that strong evidence suggests that this product would be ineffective or unsafe in all pediatric age groups. Also, venlafaxine extended-release tablets do not represent a meaningful therapeutic benefit over existing therapies for pediatric patients and are not likely to be used in a substantial number of pediatric patients.

These considerations appear to meet the PREA provisions for granting a full waiver. I recommend that a full waiver be granted.

VI. DSI Inspection

The Division of Scientific Investigations (DSI) was consulted on 2-9-07 for inspection of study R04-0776. The results of this inspection were conveyed on 7-25-07 and the final classification was VAI (Voluntary Action Indicated).

VII. Labeling Review

This application is subject to the requirements for labeling in accordance with the new "Physician Labeling Rule" (PLR) format. However, it was decided at the Division level to waive this requirement since it would be very difficult, if not impossible, for Osmotica to revise labeling to conform to this format since they do not have access to the raw data underlying the innovator product labeling. Thus, the following review is based on the

sponsor's proposed revisions to Effexor XR labeling, as conveyed via Email from Osmotica on 7-24-07.

First, a few general comments about the sponsor's proposed labeling.

b(4)

b(4)

b(4)

One other general deficiency in the sponsor's labeling should be rectified: in numerous locations in labeling, the sponsor refers to Effexor XR (capsules) as "Venlafaxine Extended-release." In order to avoid confusion with the Osmotica extended-release product, all instances which specifically refer to the Wyeth extended-release formulation should add the qualifier "capsules," that is, Effexor XR should be described as "venlafaxine extended-release capsules" and the Osmotica product should be described as "venlafaxine extended-release tablets."

It should be noted that the evaluation of revisions to the DESCRIPTION and HOW SUPPLIED sections will be deferred to the chemistry review team. Also, assessment of changes to

[5] This was explained in their original Patent Certification and clarified in a subsequent 7-17-07 E-mail from Dr. Aikman.

the CLINICAL PHARMACOLOGY, Pharmacokinetics section will be deferred to the OCP review team.

Specific revisions to the clinical sections of labeling which, in my opinion, are necessary are delineated below.

Information in the following sections of labeling pertaining to suicidality and antidepressant drugs should be updated in accordance with our 8-1-07 (9:56AM) letter to Wyeth approving these labeling changes (NDA 20-699/S-075):

- Black Box.
- WARNINGS.
- PRECAUTIONS, Information for Patients.
- MEDICATION GUIDE.

The following sections pertaining to the use of venlafaxine in patients with liver disease should be updated in accordance with our 8-1-07 (8:18AM) letter to Wyeth approving these changes (NDA 20-699/S-055):

- CLINICAL PHARMACOLOGY, Pharmacokinetics, Special Populations, Liver Disease.
- DOSAGE AND ADMINISTRATION, Special Populations, Patients with Hepatic Impairment.

Also included in the last letter is the addition of information regarding an interaction study with metoprolol and venlafaxine, which should be added under PRECAUTIONS, Drug Interactions, Drugs Metabolized by Cytochrome P450 Isoenzymes, immediately after the section on imipramine.

The following sections pertaining to hyponatremia associated with venlafaxine, particularly in elderly patients, should be updated in accordance with our 8-7-07 letter to Wyeth requesting these changes:

- PRECAUTIONS, General, Hyponatremia.
- PRECAUTIONS, Geriatric Use.

Under PRECAUTIONS, General, the section entitled "Interstitial Lung Disease and Eosinophilic Pneumonia" in current Effexor XR labeling should be added immediately after the section regarding serum cholesterol elevation.

Table 4, which depicts common adverse events leading to discontinuation, should add the following immediately under

the table title to describe the presented figures: "Percentage of Patients Discontinuing Due to Adverse Event."

Table 5 (AE's from MDD studies) contains a numerical error: the placebo reporting rate for hypertension should be 1%, not 4%.

Table 6 (AE's from SAD studies) has omitted the footnote notation ([6]) immediately after Abnormal Vision.

Under ADVERSE REACTIONS, Other Adverse Events Observed During the Premarketing Evaluation of Venlafaxine Immediate-release and Venlafaxine Hydrochloride Extended-release, the second paragraph indicates that adverse events listed in Tables 3, 4, 5, and 6 have been excluded from the listing in this section. [redacted] b(4)

Under ADVERSE EVENTS, Postmarketing Reports, the phrase "interstitial lung disease (including pulmonary eosinophilia)" may be deleted since it is now discussed under PRECAUTIONS, General.

VIII. Conclusions and Recommendations

From a clinical perspective, this application may be approved following agreement on the above labeling issues.

Gregory M. Dubitsky, M.D.
August 24, 2007

cc: NDA #22-104
HFD-130 (Div. File)
HFD-130/Dubitsky
/Levin
/Khin
/Laughren
/Bender

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/s/

Greg Dubitsky
8/24/2007 02:33:52 PM
MEDICAL OFFICER

Ni Aye Khin
8/24/2007 05:49:43 PM
MEDICAL OFFICER
I agree that this NDA be considered for approval
from a clinical perspective. See labeling recommendations.