

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**22-104**

**APPROVAL LETTER**



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

NDA 22-104

**NDA APPROVAL**

Osmotica Pharmaceutical Corp.  
Attention: Mark S. Aikman  
VP Regulatory Affairs & Quality Assurance  
1205 Culbreth Drive, Suite 200  
Wilmington, NC 28405

Dear Mr. Aikman:

Please refer to your new drug application (NDA) dated December 11, 2006, received December 12, 2006, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for venlafaxine hydrochloride extended release 37.5 mg, 75 mg, 150mg, and 225 mg tablets.

We acknowledge receipt of your submissions dated March 6, 2008, March 19, 2008, April 30, 2008, May 2, 2008 and May 14, 2008. Your submission dated March 19, 2008 constituted a complete response to our February 26, 2008 action letter.

This new drug application provides for the use of Venlafaxine hydrochloride Extended Release tablets for the treatment of Major Depressive Disorder (MDD) and Social Anxiety Disorder.

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

We are waiving the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of prescribing information. This waiver applies to all future supplements containing revised labeling unless we notify you otherwise.

**REQUIRED PEDIATRIC ASSESSMENTS**

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indications in pediatric patients unless this requirement is waived, deferred, or inapplicable.

This product is appropriately labeled for use in all relevant pediatric populations. Therefore, no additional pediatric studies are needed at this time.

**RISK EVALUATION AND MITIGATION STRATEGIES (REMS) REQUIREMENT**

Title IX, Subtitle A, Section 901 of Food and Drug Administration Amendments Act of 2007 (FDAAA) amended the FDCA to authorize FDA to require the submission of a Risk Evaluation and Mitigation Strategy (REMS) if the Secretary determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks (section 505-1(a)(1)). This provision took effect on March 25, 2008.

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, you are responsible for ensuring that the Medication Guide is available for distribution to patients who are dispensed Venlafaxine hydrochloride Extended Release. Pursuant to 21 CFR Part 208, FDA has determined that Venlafaxine hydrochloride Extended Release poses 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. FDA has determined that Venlafaxine hydrochloride Extended Release 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. Antidepressants, including Venlafaxine hydrochloride Extended Release, 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.

Your proposed REMS, submitted on May 12, 2008, is approved. The REMS consists of the Medication Guide included with this letter and the timetable for submission of assessments of the REMS included in your May 12, 2008 submission. The timetable you submitted is as follows:

1 <sup>st</sup> FDAAA assessment:	November 2009 (18 months from approval)
2 <sup>nd</sup> FDAAA assessment:	May 2011 (3 years from approval)
3 <sup>rd</sup> FDAAA assessment:	May 2015 (7 years from approval)

Information needed for assessment of the REMS should include but may not be limited to:

- a. A survey of patients' understanding of the serious risks of Venlafaxine hydrochloride
- b. A report on periodic assessments of the distribution and dispensing of the Medication Guide in accordance with 21 CFR 208.24
- c. A report on failures to adhere to distribution and dispensing requirements, and corrective actions taken to address noncompliance

Use the following designator to prominently label all submissions, including supplements, relating to this REMS:

**Risk Evaluation and Mitigation Strategy (REMS)**

**POSTMARKETING REQUIREMENTS UNDER 505(o)**

Title IX, Subtitle A, Section 901 of FDAAA amended the FDCA to authorize FDA to require holders of approved drug and biologic product applications to conduct postmarketing studies and

clinical trials for certain purposes, if FDA makes certain findings required by the statute (section 505(o)(3)(A), 21 U.S.C. 355(o)(3)(A)). This provision took effect on March 25, 2008.

We have determined that Venlafaxine hydrochloride Extended Release has the potential to cause adverse events in patients by dose dumping if consumed with alcohol, which is an unexpected serious risk.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to identify an unexpected serious risk of dose dumping that, based on available data, have the potential to occur with Venlafaxine hydrochloride Extended Release.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA has not yet been established and is not sufficient to identify an unexpected serious risk of dose dumping.

Therefore, based on appropriate scientific data, FDA has determined that you are required, pursuant to section 505(o)(3) of the FDCA, to conduct the following postmarketing study of Venlafaxine hydrochloride Extended Release:

**1. Dose Dumping and Ethanol Dissolution Study**

You are required to conduct a study to investigate dose-dumping in the presence of alcohol by performing dissolution studies for all Venlafaxine hydrochloride Extended Release strengths using the accepted dissolution conditions with the addition of \_\_\_\_\_ of ethanol to the dissolution media. The accepted dissolution method is:

b(4)

Apparatus: USP Apparatus II (Paddle)

Speed: 50 rpm

Media: Water at 37°C

Volume: 900 mL

The timetable you submitted on December 28, 2007 states that you will conduct this study according to the following schedule:

Final Report Submission: No later than 6 months from the date of approval.

Submit the protocol to your IND 71,288 with a cross-reference letter to your NDA. Submit all final report(s) to your NDA 22-104. Use the following designators to prominently label all submissions, including supplements, relating to this postmarketing study as appropriate:

- **Required Postmarketing Protocol under 505(o)**
- **Required Postmarketing Final Report under 505(o)**
- **Required Postmarketing Correspondence under 505(o)**

You are required to report periodically to FDA on the status of this postmarketing study pursuant to sections 505(o)(3)(E)(ii) and 506B of the FDCA, as well as 21 CFR 314.70. Under section 505(o)(3)(E)(ii), you are also required to periodically report to FDA on the status of any study or

clinical trial otherwise undertaken to investigate a safety issue associated with Venlafaxine hydrochloride Extended Release.

**POST MARKETING COMMITMENT**

We remind you of the following postmarketing study commitment agreed upon in your submission dated December 28, 2007:

**2. "Interim" Dissolution Specifications**

"Interim" Dissolution Specifications

37.5 mg		75 mg, 150 mg and 225 mg	
4 hour	—	4 hour	—
12 hour	—	12 hour	—
20 hour	NLT —	20 hour	NLT —

**b(4)**

The Agency acknowledges your commitment to submit dissolution data for 24 tablets on the first 12 batches at release or on all batches at release post approval for a period of 12 months, which ever comes first, for each strength. In the submission dated March 18, 2008 to the Agency, you committed to submit this data by 14 months post approval. In addition, you should provide justification, based on the data available after the requested testing period, why a single dissolution specification could not be adopted for all strengths of Venlafaxine hydrochloride Extended Release.

**Final Report Submission:** No later than 14 months from the date of approval.

Submit clinical protocols to your IND for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all study final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii), you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies, number of patients entered into each study. All submissions, including supplements, relating to these postmarketing study commitments should be prominently labeled "Postmarketing Study Commitment Protocol", "Postmarketing Study Commitment Final Report", or "Postmarketing Study Commitment Correspondence."

**In Vitro/In Vivo Correlations (IVIVC)**

The Agency also acknowledges your agreement to submit the data requested for the IVIVC. It is recommended that the IVIVC data be submitted with the requested dissolution data by 14 months post approval. The IVIVC could also facilitate the setting of a 'final' dissolution specification for this product if a single dissolution specification could not be proposed based on the data. Therefore, it is recommended, if possible, to use the IVIVC developed to propose a single dissolution specification. We recommend that you consult the Agency's Guidance for

Industry: Extended Release Oral Dosage Forms: Development, Evaluation and Application of IVIVC and submit the required data (e.g., details of model development including equations, data sets, and control files) for review. The guidance can be found at <http://www.fda.gov/cder/guidance/index.htm>.

**DISSOLUTION METHOD & INTERIM SPECIFICATIONS**

Method  
Apparatus: USP Apparatus II (Paddle)  
Speed: 50 rpm  
Media: Water at 37°C  
Volume: 900 mL

**“Interim” Dissolution Specifications**

37.5 mg		75 mg, 150 mg and 225 mg	
4 hour	—	4 hour	—
12 hour	—	12 hour	—
20 hour	NLT —	20 hour	NLT —

b(4)

**EXPIRY DATE**

An expiration date of 24 months has been assigned for this product based on the provided drug product stability data.

**CONTENT OF LABELING**

As soon as possible, but no later than 14 days from the date of this letter, please submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format as described at <http://www.fda.gov/oc/datacouncil/spl.html> that is identical to the enclosed labeling (text for the package insert and Medication Guide). Upon receipt, we will transmit that version to the National Library of Medicine for public dissemination. For administrative purposes, please designate this submission, “SPL for approved NDA 22-104.”

**CARTON AND IMMEDIATE CONTAINER LABELS**

Submit final printed carton and container labels as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (October 2005)*. Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission “**Final Printed Carton and Container Labels for approved NDA 22-104.**” Approval of this submission by FDA is not required before the labeling is used.

Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

**PROPRIETARY NAME**

If you choose to use a proprietary name for this product, the name and its use in the labels must conform to the specifications under 21 CFR 201.10 and 201.15. We recommend that you submit any proprietary name to the Agency for our review prior to its implementation.

**PROMOTIONAL MATERIALS**

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert(s) to:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Drug Marketing, Advertising, and Communications  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert(s), at the time of initial dissemination or publication, accompanied by a Form FDA 2253. For instruction on completing the Form FDA 2253, see page 2 of the Form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see [www.fda.gov/cder/ddmac](http://www.fda.gov/cder/ddmac).

**LETTERS TO HEALTH CARE PROFESSIONALS**

If you issue a letter communicating important safety related information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit an electronic copy of the letter to both this NDA and to the following address:

MedWatch  
Food and Drug Administration  
Suite 12B05  
5600 Fishers Lane  
Rockville, MD 20857

**REPORTING REQUIREMENTS**

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

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If you have any questions, call LCDR Renmeet Grewal, Senior Regulatory Project Manager, at (301) 796-1080.

Sincerely,

*{See appended electronic signature page}*

Thomas Laughren, M.D.  
Director  
Division of Psychiatry Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

Enclosure: Package Insert & Medguide



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/s/

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Thomas Laughren  
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