



NDA 20-699 / S-083

NDA 20-151 / S-052

Wyeth Pharmaceuticals, Inc.  
Attention: Kim McCormick, Pharm.D.  
Senior Manager, Global Regulatory Affairs  
P.O. Box 8299  
Philadelphia, PA 19101-8299

Dear Dr. McCormick:

Please refer to your supplemental new drug applications dated and received January 31, 2008, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Effexor XR (venlafaxine HCl) Extended Release Capsules and Effexor (venlafaxine HCl) Immediate Release.

These "Changes Being Effected" supplemental new drug applications provide for revisions to the package insert, pertaining to the risk of bleeding events, as requested in the Agency letter of January 3, 2008.

The revisions are as follows:

### **PRECAUTIONS**

#### **Abnormal Bleeding**

There have been reports of abnormal bleeding (most commonly ecchymosis) associated with venlafaxine treatment. While a causal relationship to venlafaxine is unclear, impaired platelet aggregation may result from platelet serotonin depletion and contribute to such occurrences. SSRIs and SNRIs, including Effexor, may increase the risk of bleeding events. Concomitant use of aspirin, nonsteroidal anti-inflammatory drugs, warfarin, and other anti-coagulants may add to this risk. Case reports and epidemiological studies (case-control and cohort design) have demonstrated an association between use of drugs that interfere with serotonin reuptake and the occurrence of gastrointestinal bleeding. Bleeding events related to SSRIs and SNRIs use have ranged from ecchymoses, hematomas, epistaxis, and petechiae to life-threatening hemorrhages.

Patients should be cautioned about the risk of bleeding associated with the concomitant use of Effexor and NSAIDs, aspirin, or other drugs that affect coagulation.

#### **Information for Patients**

Patients should be cautioned about the concomitant use of Effexor and NSAIDs, aspirin, warfarin, or other drugs that affect coagulation since combined use of psychotropic drugs that interfere with serotonin reuptake and these agents has been associated with an increased risk of bleeding (see PRECAUTIONS, Abnormal Bleeding).

## **Drug Interactions**

### **Drugs that Interfere with Hemostasis (e.g., NSAIDs, Aspirin, and Warfarin)**

Serotonin release by platelets plays an important role in hemostasis. Epidemiological studies of the case-control and cohort design that have demonstrated an association between use of psychotropic drugs that interfere with serotonin reuptake and the occurrence of upper gastrointestinal bleeding have also shown that concurrent use of an NSAID or aspirin may potentiate this risk of bleeding. Altered anticoagulant effects, including increased bleeding, have been reported when SSRIs and SNRIs are coadministered with warfarin. Patients receiving warfarin therapy should be carefully monitored when Effexor is initiated or discontinued.

We have completed our review of these supplemental new drug application and they are approved, effective on the date of this letter, for use as recommended in the final printed labeling (FPL) submitted on January 31, 2008 (copy attached).

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

MEDWATCH  
Food and Drug Administration  
5515 Security Lane  
HFD-001, Suite 5100  
Rockville, MD 20852

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, email CAPT Steven D. Hardeman, R.Ph., Chief, Project Management Staff, at [Steven.Hardeman@FDA.HHS.GOV](mailto:Steven.Hardeman@FDA.HHS.GOV).

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

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/s/

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Thomas Laughren  
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