

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:
NDA 20-699/S-039

Name: Effexor XR Extended-Release Capsules

Generic Name: venlafaxine hydrochloride

Sponsor: Wyeth Pharmaceuticals Inc.

Approval Date: 03/19/04

Indications: For the treatment of major depressive disorder, generalized anxiety disorder and social anxiety disorder.

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**APPLICATION NUMBER:
NDA 20-699/S-039**

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APPLICATION NUMBER:
NDA 20-699/S-039

APPROVAL LETTER



NDA 20-151/S-027
NDA 20-699/S-039/S-050

Wyeth Pharmaceuticals, Inc.
Attention: Kenneth R. Bonk
Director, Worldwide Regulatory Affairs
P.O. Box 8299
Philadelphia, PA 19101-1245

Dear Mr. Bonk:

Please refer to your supplemental new drug applications dated April 16, 2003, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Effexor (venlafaxine hydrochloride) Immediate Release Tablets (NDA 20-151) and Effexor XR (venlafaxine hydrochloride) Extended Release Capsules.

We acknowledge receipt of your submissions dated December 9, and December 3, 2003, to the Effexor and Effexor XR applications, 20-151/S-027 and 20-699/S-039, respectively.

These submissions constituted a complete response to our September 16, 2003 action letter.

We additionally acknowledge receipt of your supplemental new drug application dated February 13, 2004 (S-050), submitted for Effexor XR (venlafaxine hydrochloride) Extended Release Capsules.

Supplemental applications 20-151/S-027 and 20-699/S-039 submitted as "Changes Being Effected" supplemental applications, provide for the following revisions to product labeling:

1. The revision of the **PRECAUTIONS-Drug Interactions-Lithium** section to add a cross reference to the section on **CNS-Active Drugs**.
2. The revision of the **PRECAUTIONS-Drug Interactions-CNS-Active Drugs** section to add new language on the potential for serotonin syndrome.
3. The revision of the **ADVERSE REACTIONS-Postmarketing Reports** section to add the terms dyskinesia and rhabdomyolysis.
4. The revision of the **DOSAGE AND ADMINISTRATION-Discontinuing Effexor** section to add the term "seizure" to the list of discontinuation symptoms.

We note that you have incorporated revisions to the **PRECAUTIONS-Drug Interactions-CNS-Active Drugs** and **OVERDOSAGE-Human Experience** sections of labeling as requested in our September 16, 2003 action letter.

Additionally, we note your commitment to provide the Agency with more information for the terms rhabdomyolysis, extrapyramidal symptoms, and tardive dyskinesia as requested in our September 16, 2003 action letter. The other request, contained in our September 16, 2003 letter, pertaining to seizures in the **DOSAGE AND ADMINISTRATION-Discontinuing Effexor** section of labeling was submitted as a separate supplement (20-151/S-030 and 20-699/S-048). These submissions will be addressed in a separate letter.

Supplemental application 20-699/S-050 provides for corrections to vital sign and weight information contained in Effexor XR labeling regarding placebo-controlled studies in Social Anxiety Disorder (SAD).

We have completed the review of your submissions, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in your December 9, 2003, and February 13, 2004, labelings. Accordingly, these applications are approved effective on the date of this letter.

Please submit the copies of final printed labeling (FPL) electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA* (January 1999). Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved NDAs 20-151/S-027 and 20-699/S-039/S-050." Approval of this submission by FDA is not required before the labeling is used.

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, call Paul David, R.Ph., Senior Regulatory Project Manager, at (301) 594-5530.

Sincerely,

{See appended electronic signature page}

Russell Katz, M.D.
Director
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

Russell Katz
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APPLICATION NUMBER:

NDA 20-699/S-039

APPROVABLE LETTER



Food and Drug Administration
Rockville MD 20857

NDA 20-151/S-027
NDA 20-699/S-039

Wyeth Pharmaceuticals
Attention: Tracy D. Rockney, JD
Director, Global Brand Management
Worldwide Regulatory Affairs
P.O. Box 8299
Philadelphia, PA 19101-1245

Dear Ms. Rockney:

We acknowledge receipt of your supplemental new drug applications dated April 16, 2003, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Effexor (venlafaxine hydrochloride) Immediate Release Tablets (NDA 20-151) and Effexor XR (venlafaxine hydrochloride) Extended Release Capsules.

The above submissions, submitted as "Changes Being Effected" supplemental applications, provide for the following revisions to product labeling:

1. The revision of the **PRECAUTIONS-Drug Interactions-Lithium** section to add a cross reference to the section on **CNS-Active Drugs**.
2. The revision of the **PRECAUTIONS-Drug Interactions-CNS-Active Drugs** section to add new language on the potential for serotonin syndrome.
3. The revision of the **ADVERSE REACTIONS-Postmarketing Reports** section to add language on extrapyramidal symptoms and add the term "rhabdomyolysis".
4. The revision of the **DOSAGE AND ADMINISTRATION-Discontinuing Effexor** section to add the term "seizure" to the list of discontinuation symptoms.

We have completed our review of these supplemental applications, and they are **approvable**.

In general, the proposed labeling changes are acceptable. Before these applications may be approved, however, it will be necessary for you to revise the labeling as follows:

1. Under **PRECAUTIONS-Drug Interactions-CNS-Active Drugs**, the statements regarding lack of a systematic evaluation of the co-administration of venlafaxine with CNS-active drugs and the cautionary advice regarding such co-administration should be

2. Under **OVERDOSAGE-Human Experience**, the term "rhabdomyolysis" should be added to the list of postmarketing events reported in association with venlafaxine overdose.
3. Under **DOSAGE AND ADMINISTRATION-Discontinuing Effexor**, mention of postmarketing reports of seizures should be added

Additionally, we are concerned with your proposed placement of the term "rhabdomyolysis" in the **ADVERSE REACTIONS-Postmarketing Reports** section. In order to more fully evaluate the risk of rhabdomyolysis in association with venlafaxine, we are requesting the following information:

- Narrative summaries of the postmarketing cases (include the original MedWatch or CIOMS form).
- A reporting rate for rhabdomyolysis (# of postmarketing cases/estimate of person-time exposure).
Please provide the method by which the person-time exposure was estimated.
- A background rate for rhabdomyolysis.
- Narrative summaries for any cases of rhabdomyolysis that occurred during the clinical development program of any formulation of venlafaxine.
- If there were any cases in the clinical development program, please provide an incidence rate based on the person-time exposure in the development program.

Your labeling supplement also calls for adding the term "dyskinesia" to the parenthetical expression "(including tardive dyskinesia)" that follows "extrapyramidal symptoms" in the **ADVERSE REACTIONS-Postmarketing Reports** section of labeling.

In order to more fully evaluate the risk of all extrapyramidal symptoms (including dyskinesia and tardive dyskinesia) in association with venlafaxine, we are requesting the following information:

- Narrative summaries of the postmarketing cases (include the original MedWatch or CIOMS form).
- A reporting rate for all extrapyramidal symptoms and a separate reporting rate for tardive dyskinesia (# of postmarketing cases/estimate of person-time exposure).
Please provide the method by which the person-time exposure was estimated.
- A background rate for extrapyramidal symptoms and tardive dyskinesia.
- Narrative summaries for any cases of extrapyramidal symptoms that occurred during the clinical development program of any formulation of venlafaxine.
- If there were any cases in the clinical development program, please provide an incidence rate based on the person-time exposure in the development program.

In addition, all previous revisions as reflected in the most recently approved labeling must be included. To facilitate review of your submission, please provide a highlighted or marked-up copy that shows the changes that are being made.

Please submit 20 paper copies of the final printed labeling (to each application) ten of which are individually mounted on heavy weight paper or similar material. Alternatively, you may submit the FPL electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDAs* (January 1999).

If additional information relating to the safety or effectiveness of these drugs becomes available, revision of the labeling may be required.

Within 10 days after the date of this letter, you are required to amend the supplemental applications, notify us of your intent to file amendments, or follow one of your other options under 21 CFR 314.110. In the absence of any such action FDA may proceed to withdraw the applications. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

This product may be considered to be misbranded under the Federal Food, Drug, and Cosmetic Act if it is marketed with these changes prior to approval of this supplemental application.

If you have any questions, call Paul David, R.Ph., Senior Regulatory Project Manager, at (301) 594-5530.

Sincerely,

{See appended electronic signature page}

Russell Katz, M.D.
Director
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

Russell Katz
9/16/03 08:27:32 AM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-699/S-039

MEDICAL REVIEW(S)

Review and Evaluation of Clinical Data
NDA #20-699

Sponsor: Wyeth
Drug: Effexor XR (venlafaxine HCl extended-release capsules)
Indications: MDD, GAD, SAD
Material Submitted: Special Supplement - CBE
SLR-039
Correspondence Date: April 16, 2003
Date Received: April 17, 2003

I. Background

Wyeth has submitted this CBE labeling supplement to add safety information relevant to Effexor XR regarding 1) drug interactions possibly resulting in serotonin syndrome, 2) postmarketing spontaneous reports of extrapyramidal symptoms and rhabdomyolysis, and 3) seizures when discontinuing venlafaxine.

Additionally, there are 4 editorial changes proposed.

Final printed labeling which incorporates these changes is provided and was to be used in production no earlier than June 2003.

II. CBE Labeling Changes

Labeling changes related to drug interactions with the potential for serotonin syndrome and postmarketing spontaneous reports of extrapyramidal symptoms, rhabdomyolysis, and discontinuation-related seizures are identical to those proposed for Effexor, the immediate-release formulation of venlafaxine, in CBE supplement SLR-027 to NDA 20-151, which was submitted to the Agency simultaneously with this submission. The basis for these changes was reviewed in detail in the clinical review of that supplement dated 8-6-03 and the reader is referred to that review for further details.

The editorial changes in this supplement are as follows:

WARNINGS/Sustained Hypertension

The paragraph describing blood pressure data from Social Anxiety Disorder trials has been combined with the paragraph describing data from the Major Depressive Disorder and Generalized Anxiety Disorder studies.

PRECAUTIONS/General/Insomnia and Nervousness

In Table 1, the horizontal line separating the indications and the treatment arms has been deleted.

ADVERSE REACTIONS

In the prefatory paragraph, the word "and" has been removed and a comma has been added for grammatical correctness.

ADVERSE REACTIONS/Adverse Findings Observed in Short-Term, Placebo-Controlled Studies with Effexor XR/Adverse Events Occurring at an Incidence of 2% or More Among Effexor XR-Treated Patients

A closing parenthesis has been added to the third parenthetical phrase in the first paragraph.

III. Conclusions and Recommendations

As with the corresponding supplement for Effexor (NDA 20-151/SLR-027), there are three minor modifications to the sponsor's proposal that are recommended:

1) under PRECAUTIONS/Drug Interactions/CNS-Active Drugs, the statements regarding lack of a systematic evaluation of the co-administration of venlafaxine with CNS-active drugs and the cautionary advice regarding such co-administration should be []

2) under OVERDOSAGE/Human Experience, the term "rhabdomyolysis" should be added to the list of postmarketing events reported in association with venlafaxine overdose.

3) under DOSAGE AND ADMINISTRATION/Discontinuing Effexor, mention of postmarketing reports of seizures should be added []



I have no objection to any of the proposed editorial changes.

If the sponsor agrees to implement the above recommended modifications with the next printing of labeling, this supplement may be approved.

Gregory M. Dubitsky, M.D.
August 6, 2003

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cc: NDA #20-699
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HFD-120/GDubitsky
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/s/

Greg Dubitsky
8/6/03 05:05:22 PM
MEDICAL OFFICER

Thomas Laughren
8/7/03 08:15:58 AM
MEDICAL OFFICER

Review and Evaluation of Clinical Data
NDA #20-699

Sponsor: Wyeth Pharmaceuticals
Drug: Effexor XR
Indication: Depression, GAD, SAD
Material Submitted: SLR-039: Response to Approvable Letter
Correspondence Date: December 3, 2003
Date Received: December 4, 2003

I. Background

On 4-16-03, Wyeth submitted a CBE labeling supplement (SLR-039) to add safety information to Effexor XR labeling regarding: 1) drug interactions possibly resulting in serotonin syndrome, 2) postmarketing spontaneous reports of dyskinesia and rhabdomyolysis, and 3) reports of seizures when discontinuing venlafaxine. Also, there were four editorial changes proposed.

This supplement was reviewed by the undersigned on 8-6-03 and was discussed at the Division level at a meeting on 9-4-03 which included the Division Safety Team. Subsequently, we issued a letter on 9-16-03 which indicated that this supplement was approvable. Before approval, we stated that the sponsor would need to make specific revisions to their proposed labeling changes (under the PRECAUTIONS, OVERDOSAGE, and DOSAGE AND ADMINISTRATION sections). In this letter, we also asked that they submit additional data regarding reports of rhabdomyolysis and dyskinesia, tardive dyskinesia, and extrapyramidal symptoms (EPS).¹

The current submission addresses two of the issues raised in the approvable letter: revisions to the Drug Interactions subsection under PRECAUTIONS regarding CNS-active drugs and the addition of an adverse event term to the Human Experience subsection under OVERDOSAGE. Wyeth indicates that they will address the revision to information regarding seizures associated with discontinuation of Effexor under DOSAGE AND ADMINISTRATION as well as our request for more information on reports of

¹ See the approvable letter for details.

rhabdomyolysis, EPS, and tardive dyskinesia in later submissions.

II. Review of Response to Approvable Letter

A. PRECAUTIONS/Drug Interactions/CNS-Active Drugs

In the original CBE supplement, the sponsor [] statements regarding lack of a systematic evaluation of the co-administration of venlafaxine with CNS-active drugs and cautionary advice regarding such co-administration. In our 9-16-03 letter, []

The sponsor has [] language and added a parenthetical phrase "except in the case of those CNS-active drugs noted above" to indicate that there have been studies conducted to examine the potential interaction between venlafaxine and some CNS-active drugs, such as diazepam, which are described in previous sections of this section of labeling.

This change is annotated on page 355 of this submission (under Tab 2) and is acceptable.

B. OVERDOSAGE/Human Experience

In the original supplement, the adverse event term "rhabdomyolysis" was added to the Postmarketing Reports subsection under ADVERSE REACTIONS. Since several of these cases were observed following an overdose of venlafaxine, we asked in our letter that this term also be added to the list of events reported in association with venlafaxine overdose in the postmarketing period (i.e., to the last paragraph under OVERDOSAGE/Human Experience).

The sponsor has complied with this request. This change is annotated on page 369 of this submission (under Tab 2).

III. Conclusions and Recommendations

This is an incomplete response to our 9-16-03 approvable letter for this supplement. The responses to the first two of the three items necessary for approval are described above and are acceptable. Final approval must await their response to the third item. i.e., our request to add mention of postmarketing reports of seizures to the

Discontinuing Effexor subsection under DOSAGE AND
ADMINISTRATION.

Gregory M. Dubitsky, M.D.
March 2, 2004

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