CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-151/
S-016, 19, 20, 21, 22, 23, & 25

APPROVABLE LETTER(S)

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-151/S-022/S-023
NDA 20-699/S-026/S-027

Wyeth-Ayerst
Attention: Timothy Ressler
Director, Worldwide Regulatory Affairs
P.O. Box 8299
Philadelphia, PA 19101-1245

Dear Mr. Ressler:

Please refer to the following supplemental new drug applications 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.

NDA	Supplement	Submission Date
20-151	S-022	March 8, 2002
20-151	S-023	May 31, 2002
20-699	S-026	March 12, 2002
20-699	S-027	May 31, 2002

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

20-151/S-022
20-699/S-026

1. Minor revisions to the **WARNINGS-Sustained Hypertension** section of labeling for editorial clarification and to harmonize the Effexor and Effexor XR labelings.
2. The addition of the terms "neutropenia" and "pancytopenia" to the **ADVERSE REACTIONS-Postmarketing Reports** section.

20-151/S-023
20-699/S-027

1. The addition of a paragraph under the **PRECAUTIONS-General-Changes in Appetite and Weight** section to state that the safety and efficacy of venlafaxine therapy in combination with weight loss agents, including phentermine, have not been established.
2. The addition of the terms "pulmonary eosinophilia" to the **ADVERSE REACTIONS-Postmarketing Reports** section.

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

In general, the proposed labeling changes are acceptable. We note, however, that you have not addressed our requested revisions to labeling as conveyed in the Agency approvable letter to supplemental applications 20-151/S-016/S-019/S-020/S-021 and 20-699/S-014/S-018/S-021/S-023 dated January 10, 2002.

These applications cannot be approved until there is final resolution with the CBE changes made under the above applications.

We believe that the main point of contention resides with the description of the cholesterol changes when patients are chronically administered venlafaxine. We have consulted the data provided by you to our safety group, and based upon their review of these data, we are requesting the following changes to labeling:

Effexor Labeling

PRECAUTIONS-General-Serum Cholesterol Elevation

Clinically relevant increases in serum cholesterol were recorded in 5.3% of venlafaxine-treated patients and 0.0% of placebo-treated patients treated for at least 3 months in placebo-controlled trials (see **ADVERSE REACTIONS-Laboratory Changes**). Measurement of serum cholesterol levels should be considered during long-term treatment.

ADVERSE REACTIONS-Laboratory Changes

Of the serum chemistry and hematology parameters monitored during clinical trials with Effexor, a statistically significant difference with placebo was seen only for serum cholesterol. In premarketing trials, treatment with Effexor tablets was associated with a mean final on-therapy increase in total cholesterol of 3 mg/dL.

Patients treated with Effexor tablets for at least 3 months in placebo-controlled 12-month extension trials had a mean final on-therapy increase in total cholesterol of 9.1 mg/dL compared to a decrease of 7.1 mg/dL among placebo-treated patients. This increase was duration dependent over the study period and tended to be greater with higher doses. Clinically relevant increases in serum cholesterol, defined as 1) a final on-therapy increase in serum cholesterol $\geq$50 mg/dL from baseline and to a value $\geq$261 mg/dL or 2) an average on-therapy increase in serum cholesterol $\geq$50 mg/dL from baseline and to a value $\geq$261 mg/dL, were recorded in 5.3% of venlafaxine-treated patients and 0.0% of placebo-treated patients (see **PRECAUTIONS-General-Serum Cholesterol Elevation**).

Effexor XR Labeling

PRECAUTIONS-General-Serum Cholesterol Elevation

Clinically relevant increases in serum cholesterol were recorded in 5.3% of venlafaxine-treated patients and 0.0% of placebo-treated patients treated for at least 3 months in placebo-controlled trials (see **ADVERSE REACTIONS-Laboratory Changes**). Measurement of serum cholesterol levels should be considered during long-term treatment.

ADVERSE REACTIONS-Laboratory Changes

[Please insert the mean placebo changes for the major depressive disorder and GAD trials.]

Patients treated with Effexor tablets (the immediate-release form of venlafaxine) for at least 3 months in placebo-controlled 12-month extension trials had a mean final on-therapy increase in total cholesterol of 9.1 mg/dL compared to a decrease of 7.1 mg/dL among placebo-treated patients. This increase was duration dependent over the study period and tended to be greater with higher doses. Clinically relevant increases in serum cholesterol, defined as 1) a final on-therapy increase in serum cholesterol $\geq$50 mg/dL from baseline and to a value $\geq$261 mg/dL or 2) an average on-therapy increase in serum cholesterol $\geq$50 mg/dL from baseline and to a value $\geq$261 mg/dL, were recorded in 5.3% of venlafaxine-treated patients and 0.0% of placebo-treated patients (see **PRECAUTIONS-General/Serum Cholesterol Elevation**).

The Division would be happy to discuss these changes with you in order to facilitate closure to these supplements.

We additionally request that you respond to this letter within 30 days of the signature date.

If you concur with our requested changes, 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.

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
7/2/02 03:57:18 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-151/S-016/S-019/S-020/S-021
NDA 20-699/S-014/S-018/S-021/S-023

Wyeth-Ayerst
Attention: Timothy Ressler
Director, Worldwide Regulatory Affairs
P.O. Box 8299
Philadelphia, PA 19101-1245

Dear Mr. Ressler:

Please refer to the following supplemental new drug applications 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.

NDA	Supplement	Dated
20-151	S-019	9-29-00
20-151	S-020	6-26-01
20-151	S-021	9-27-01
20-699	S-018	9-29-00
20-699	S-021	6-26-01
20-699	S-023	9-13-01

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

20-151/S-019
20-699/S-018

These supplements provide for revisions to the **PRECAUTIONS-General-Use in Patients with Concomitant Illness**, **ADVERSE REACTIONS-Incidence in Controlled Trials-Vital Sign Changes and ECG Changes**, and **DOSAGE AND ADMINISTRATION-Initial Treatment** sections to incorporate information regarding a dose dependent increase in heart rate as requested in Agency letters dated September 13, 1999, and June 14, 2000.

20-151/S-020
20-699/S-021

These supplements provides for the following changes:

1. The revision to the first sentence under the **CONTRAINDICATIONS** section to include excipient hypersensitivity.

2. The addition of a new subsection under the **PRECAUTIONS-Pregnancy** section entitled **Non-teratogenic Effects**.

20-151/S-021
20-699/S-023

These supplements provides for the following revisions:

1. The addition of a new subsection to the **PRECAUTIONS-General** section entitled **Abnormal Bleeding**. This new subsection completely replaces the previous subsection entitled [ ] [ ] which was originally submitted under NDAs 20-151/SLR-016 and 20-699/SLR-014, and it incorporates most of the revisions to this section as requested in Agency letters dated June 12, 2000, July, 20, 2000, and March 20, 2001.
2. The revision of the **PRECAUTIONS-Information for Patients-Concomitant Medications** section to indicate that patients should advise their physicians if they are taking, or plan to take, any herbal medications.
3. The addition of several terms to the **ADVERSE REACTIONS-Postmarketing Reports** section. It is also noted that the term [ ] has been deleted from this section as requested in Agency letters dated June 12, and July 20, 2000.
4. This supplement also incorporates labeling changes, approved on draft labeling, for NDAs 20-151/S-017/S-018 and 20-699/S-015/S-016 providing for the prevention of depression relapse/recurrence (approved in an Agency letter dated May 2, 2001) and NDA 20-699/S-007 providing for longer-term use for the Generalized Anxiety Disorder (GAD) indication (approved in an Agency letter dated July 13, 2000).

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 address the following revisions to labeling:

1. In the Effexor XR labeling, NDA 20-699, under the **DOSAGE AND ADMINISTRATION-Initial Treatment** section, the reference to the new information under the **PRECAUTIONS-General-Use in Patients with Concomitant Illness** has been added at the end of the dosing instructions for patients with GAD but was inadvertently omitted at the end of dosing instructions for patients with depression. Since the information applies to both patient populations, the reference should be added to the end of the latter section as well.

2. The Agency has requested in letters dated June 12, 2000, July, 20, 2000, and March 20, 2001, that you revise the labeling for both Effexor and Effexor XR in the **ADVERSE REACTIONS- Laboratory Changes** section of labeling as well as add a new subsection under the **PRECAUTIONS-General** section entitled **Serum Cholesterol Elevation**. We have completed our response to your submissions dated September 6, September 20, and October 26, 2001 responding to our letters. After reviewing this information, we still do not concur with your proposed revisions regarding serum cholesterol which were submitted as "Changes Being Effected" supplemental applications to 20-151/S-016 and 20-699/S-014. Again, we are requesting that you make the following revisions to product labeling:

   [The addition of a new subsection under the **PRECAUTIONS** section.]

PRECAUTIONS-Serum Cholesterol Elevation

[redacted]

[The following revisions to the **ADVERSE REACTIONS-Laboratory Changes** section. Please note that the first paragraph remains the same except for the deletion of the sentence [redacted]. Additionally, we request that you insert the mean change in cholesterol values with the appropriate numbers.]

[redacted]

3. The subsection under the **DOSAGE AND ADMINISTRATION** section entitled [redacted] should be revised to state **Maintenance Treatment** as stated in the Agency letter dated May 2, 2001.

4. In the Effexor labeling, NDA 20-151,, under the **DOSAGE AND ADMINISTRATION-Maintenance Treatment** section, this paragraph contains misworded language, i.e., the second and third sentences run together and omit the text "... was demonstrated. A second longer term study...". Please revise this section in accordance with the Agency letter dated May 2, 2001.

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
1/10/02 08:09:09 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville MD 20857

NDA 20-151/S-016

Wyeth-Ayerst
Attention: Kenneth R. Bonk
Associate Director, U.S. Regulatory Affairs
P.O. Box 8299
Philadelphia, PA 19101-1245

Dear Mr. Bonk:

Please refer to your supplemental new drug application dated April 25, 2000 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Effexor (venlafaxine hydrochloride) Immediate Release Tablets.

This supplemental new drug application proposes the following revisions to product labeling:

1. The addition of a new subsection entitled **Hyponatremia** under the **PRECAUTIONS-General** section.
2. The addition of a new subsection entitled [ ] under the **PRECAUTIONS-General** section.
3. The revision to the **ADVERSE REACTIONS-Adverse Findings Observed in Short-Term, Placebo-Controlled Studies-Laboratory Changes** section to provide for information regarding increases in serum cholesterol with longer-term use.
4. The addition of the term [ ] to the **ADVERSE REACTIONS-Postmarketing Reports** section.
5. The revision to the **DRUG ABUSE AND DEPENDENCE-Physical and Psychological Dependence** and **DOSAGE AND ADMINISTRATION-Discontinuing Effexor XR** sections as requested and agreed upon in an Agency letter dated March 3, 2000.

We have completed our review of this supplemental application, and it is approvable. Before this application may be approved, however, we request that you address the following issues:

1. Under **PRECAUTIONS-General**, please provide the Agency with a more systematic overview of relevant clinical data to support the proposed section on [ ] [ ]. Specifically, we request that you evaluate your premarketing and postmarketing safety databases to better characterize these adverse events, adduce evidence to suggest that the risk of these events is increased with venlafaxine exposure, and provide more concrete guidance to the clinician on how to prevent or address the emergence of these experiences.

2. Under **PRECAUTIONS-General**, we request that you create a new subsection to address increases in serum cholesterol observed with longer-term venlafaxine treatment. The following language is requested:

"Serum Cholesterol Elevation

[redacted]

3. We request that the description of increases in serum cholesterol under **ADVERSE REACTIONS** be modified as follows to indicate the corresponding placebo statistics and to reference **PRECAUTIONS**:

[redacted]

4. The addition of the adverse event [redacted] to the listing under **Postmarketing Reports** adds no new information to labeling and should be omitted.

We note that this labeling supplement, S-016, was instituted under section 314.70(c) of the regulations and your proposed changes have already been made. However, before the Agency may approve this supplemental application, you will need to address the issues listed above.

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., Regulatory Project Manager, at (301) 594-5530.

Sincerely,

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

cc:
Archival NDA 20-151
HFD-120/Div. Files
HFD-120/P.David
HFD-120/R.Katz/T.Laughren/G.Dubitsky
HFD-120/R.Seevers
HF-2/MedWatch (with labeling)
HFD-002/ORM (with labeling)
HFD-101/ADRA (with labeling)
HFD-104/Peds/V.Kao (with labeling)
HFD-104/Peds/T.Crescenzi (with labeling)
HFD-40/DDMAC (with labeling)
HFI-20/Press Office (with labeling)
HFD-400/OPDRA (with labeling)
HFD-613/OGD (with labeling)
HFD-095/DDMS-IMT (with labeling)
HFD-810/DNDC Division Director
DISTRICT OFFICE

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