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APPLICATION NUMBER:

NDA 20-151/

S-016, 19, 20, 21, 22, 23, & 25

APPROVAL LETTER

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/S-022/S-023/S-025
NDA 20-699/S-014/S-018/S-021/S-023/S-026/S-027/S-034

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

Dear Ms. Rockney:

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 20-699).

NDA	Supplement	Submission Date	Agency Action
Effexor (venlafaxine hydrochloride) Immediate Release Tablets (NDA 20-151)			
20-151	S-016	4-25-00, and amended on 10-26-01	Approvable letters dated 7-20-00 and 1-10-02
20-151	S-019	9-29-00	Approvable letter dated 1-10-02
20-151	S-020	6-26-01	Approvable letter dated 1-10-02
20-151	S-021	9-27-01	Approvable letter dated 1-10-02
20-151	S-022	3-8-02	Approvable letter dated 7-2-02
20-151	S-023	5-31-02	Approvable letter dated 7-2-02
Effexor XR (venlafaxine hydrochloride) Extended Release Capsules (NDA 20-699)			
20-699	S-014	4-25-00, and amended on 12-8-00, 9-6-00, and 10-26-01	Approvable letters dated 6-12-00, 3-20-01, and 1-10-02
20-699	S-018	9-29-00	Approvable letter dated 1-10-02
20-699	S-021	6-26-01	Approvable letter dated 1-10-02
20-699	S-023	9-13-01	Approvable letter dated 1-10-02
20-699	S-026	3-12-02	Approvable letter dated 7-2-02
20-699	S-027	5-31-02	Approvable letter dated 7-2-02

The above supplemental applications provide for the following revisions to product labeling:

20-151/S-016
20-699/S-014
These supplements propose 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.

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, 2999, and June 14, 2000.

20-151/S-020
20-699/S-021
These supplements provide 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 provide 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 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).

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

These supplements provide for the following revisions:

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

These supplements provide for the following revisions:

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.

Additionally, we acknowledge receipt of your correspondences dated December 20, 2002 (NDA 20-151/S-025 and December 19, 2002 (NDA 20-699/S-034). These correspondences, administratively coded by the Agency as "Changes Being Effected" labeling supplements, provide for a consolidation of all of the above labeling changes and address all of the requests for labeling revisions made by the Agency in letters dated June 12, 2000, July 20, 2000, March 20, 2001, January 10, 2002, and July 2, 2002.

We have completed our review of supplemental applications 20-151/S-025 & 20-699/S-034, and have concluded that adequate information has been presented to demonstrate that the drug products are safe and effective for use as recommended in the submitted final printed labeling (package insert submitted December 19, 2992/20-151 S-025/Label Code CI 6027-9 and December 20, 2002/20-699 S-034/Label Code CI 7786-1), which incorporates all of the revisions made in the above supplements. Accordingly, these supplemental applications are approved effective on the date of this letter.

Additionally, since supplemental applications 20-151/S-016/S-019/S-020/S-021/S-022/S-023 and 20-699/S-014/S-018/S-021/S-023/S-026/S-027 are superceded by the approval of 20-151/S-025 and 20-699/S-034, these supplemental applications will be retained in our files.

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 Mr. 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

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Russell Katz
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