CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-151/

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

ADMINISTRATIVE

REGULATORY PROJECT MANAGER
LABELING REVIEW

Date: January 27, 2003
DRUG/NDA: Effexor (venlafaxine hydrochloride) Immediate Release Tablets (NDA 20-151) and Effexor XR (venlafaxine hydrochloride) Extended Release Capsules (NDA 20-699)
Sponsor: Wyeth
Indication: Major Depressive Disorder/Panic Disorder

NDA	Supplement	Dated	Action
Effexor (venlafaxine hydrochloride) Immediate Release Tablets (NDA 20-151)			
20-151	SLR-015	12-29-99	AP Letter dated 6-12-00 Label Code: CI 6027-2
20-151	SLR-016	4-25-00, and amended on 10-26-01	AE Letter Dated 7-20-00 and 1-10-02
20-151	SE8-017	5-5-00	AP Letter dated 5-2-01 Approved on draft labeling
20-151	SE8-018	5-5-00	AP Letter dated 5-2-01 Approved on draft labeling
20-151	SLR-019	9-29-00	AE Letter Dated 1-10-02
20-151	SLR-020	6-26-01	AE Letter Dated 1-10-02
20-151	SLR-021	9-27-01	AE Letter Dated 1-10-02
20-151	SLR-022	3-8-02	AE Letter Dated 7-2-02
20-151	SLR-023	5-31-02	AE Letter Dated 7-2-02
20-151	SLR-025	12-20-02	Open
Effexor XR (venlafaxine hydrochloride) Extended Release Capsules (NDA 20-699)			
20-699	SLR-012	12-20-99	AP Letter Dated 6-12-00 Label Code CI 4876-4
20-699	SLR-014	4-25-00, and amended on 12-8-00, 9-6-00, and 10-26-01	AE Letters Dated 6-12-00, 3-20-01, and 1-10-02 Label Code: CI 5044-5
20-699	SE8-015	5-5-00	AP Letter Dated 5-2-01 Approved on draft labeling
20-699	SE8-016	5-5-00	AP Letter Dated 5-2-01 Approved on draft labeling
20-699	SLR-018	9-29-00	AE Letter Dated 1-10-02
20-699	SLR-021	6-26-01	AE Letter Dated 1-10-02
20-699	SLR-023	9-13-01	AE Letter Dated 1-10-02
20-699	SLR-026	3-12-02	AE Letter Dated 7-2-02
20-699	SLR-027	5-31-02	AE Letter Dated 7-2-02
20-699	SLR-029	7-9-02, and amended on 7-26-02	AP Letter Dated 10-22-02 (approved on draft labeling)
20-699	SLR-034	12-19-02	Open

Notes of interest:

1. See previous labeling review signed off on 11-16-01.

2. The labeling for Effexor and Effexor XR are separate and not combined formulation labeling. Although, as may be expected, many sections are identical. Therefore, this labeling review encompasses both product formulations. Additionally, all labeling revisions for both the Effexor and Effexor XR products are identical since these were all safety related revisions.

3. Although all of the above labeling supplements were submitted under CBE regulations, and an approvable action has issued for all of these supplements except the most recent supplements, the Agency has been unable to take a final approval action due to a couple points of contention regarding new subsections under the **PRECAUTIONS-General** section entitled **Serum Cholesterol Elevation** and revisions to **ADVERSE REACTIONS-Laboratory** section of labeling.

4. Wyeth has agreed to our requested changes in submissions dated December 19, and 20, 2002, and, in lieu of opening up all of the supplements, I have administratively coded these submissions as new supplements (NDAs 20-151/SLR-025 & 20-699/SLR-034) which encompasses all of the changes requested in Agency letters dated 6-12-00, 6-14-00, 7-20-00, 3-20-01, 1-10-02, and 7-2-02.

REVIEW

20-151/SLR-016
Date: 4-25-00, and amended on 10-26-01
20-699/SLR-014
Date: 4-25-00, and amended on 12-8-00, 9-6-00, and 10-26-01
CBE: Yes
Reviewed by Medical Officer: See review of NDAs 20-151/SLR-025 & 20-699/SLR-034

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/SLR-019
20-699/SLR-018
Date: 9-29-01
CBE: Yes
Reviewed by Medical Officer: See review of NDAs 20-151/SLR-025 & 20-699/SLR-034

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 as requested in Agency letters dated September 13, 2999, and June 14, 2000.

The sponsor submitted revisions to labeling identical to those as requested in the above Agency letters, and these changes were found to be acceptable to the medical officer.

20-151/SLR-020
20-699/SLR-021
Date: 6-26-01
CBE: Yes
Reviewed by Medical Officer: See review of NDAs 20-151/SLR-025 & 20-699/SLR-034

This supplement 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/SLR-021
Date: 9-21-01
20-699/SLR-023
Date: 9-13-01
CBE: Yes
Reviewed by Medical Officer: See review of NDAs 20-151/SLR-025 & 20-699/SLR-034

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).

20-151/SLR-022
Date: 3-8-02
20-699/SLR-026
Date: 3-12-02
CBE: Yes
Reviewed by Medical Officer: See review of NDAs 20-151/SLR-025 & 20-699/SLR-034

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/SLR-023
20-699/SLR-027
Date: 5-31-02
CBE: Yes
Reviewed by Medical Officer: See review of NDAs 20-151/SLR-025 & 20-699/SLR-034

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.

20-151/SLR-025
Date: 12-20-02
20-699/SLR-034
Date: 12-19-02
Label Code: CI 6027-9 (NDA 20-151) and CI 7786-1 (NDA 20-699)
CBE: Yes
Reviewed by Medical Officer: See review of NDAs 20-151/SLR-025 & 20-699/SLR-034

This correspondence, coded as a "Changes Being Effected" labeling supplement by the Agency, provides for a consolidation of all of the above labeling changes and addresses all of the requests for labeling revisions made by the Agency in letters dated 6-12-00, 6-14-00, 7-20-00, 3-20-01, 1-10-02, and 7-2-02.

CONCLUSIONS

1. The sponsor and the Agency have come to final agreement on all of the outstanding labeling issues, and the sponsor has implemented these revisions. The medical officer agrees that these supplements can be approved.

2. Therefore, I recommend that the open labeling supplements, NDAs 20-151/SLR-025 & 20-699/SLR-034, be approved, and the other supplements, NDAs 20-151/SLR-016/SLR-019/SLR-020/SLR-021/SLR-022/SLR-023 & 20-699/SLR-014/SLR-018/SLR-021/SLR-023/SLR-026/SLR-027 be superceded by the approval of NDAs 20-151/SLR-025 & 20-699/SLR-034.

{See appended electronic signature page}

Paul David, R.Ph., Senior Regulatory Project Manager

{See appended electronic signature page}

Robbin Nighswander, R.Ph., Supervisory Regulatory Health Project Officer

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/s/

Paul David
1/27/03 07:46:38 AM
CSO

Robbin Nighswander
1/27/03 02:04:53 PM
CSO

David, Paul A

From: David, Paul A
Sent: Thursday, June 27, 2002 8:08 AM
To: Pamela Swiggard (E-mail)
Cc: David, Paul A
Subject: Effexor IR/XR Labeling Supplements

Good Morning Pam.
The Division is in the process of completing its review of the labeling changes submitted to the Effexor, NDA 20-151/S-022, and Effexor XR, NDA 20-699/S-026, applications dated March 8, 2002, and March 12, 2002, respectively. These supplements, submitted as CBE changes, propose to add the terms "neutropenia" and "pancytopenia" to the Effexor IR/XR labeling.

We have consulted the changes to our safety team, and they are requesting that WA provide the following additional information:

The submissions did not include the original MedWatch reports, and just gave a "sampling" of the total reports. Therefore, please submit the original MedWatch/CIOMS reports for the sponsor-identified cases, as well as any other reports submitted to your postmarketing safety database describing a blood dyscrasia. We additionally request that you provide an estimate of drug use that would correspond to the period of exposure covered by the postmarketing AE reports.

If you have any questions, please contact me.

Regards,
Paul David, R.Ph.
Senior Regulatory Project Manager
Division of Neuropharmacological Drug Products, HFD-120
ODE1; CDER; FDA
Telephone: 301-594-5530
Fax: 301-594-2859
David@cder.fda.gov

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

/s/

Paul David
6/27/02 08:08:26 AM
CSO

REGULATORY PROJECT MANAGER
LABELING REVIEW

Date: November 2, 2001
DRUG/NDA: Effexor (venlafaxine hydrochloride) Immediate Release Tablets (NDA 20-151) and Effexor XR (venlafaxine hydrochloride) Extended Release Capsules (NDA 20-699)
Sponsor: Wyeth-Ayest
Indication: Major Depressive Disorder (MDD) for Immediate Release Tablets (20-151)
Major Depressive Disorder (MDD) and Generalized Anxiety Disorder (GAD) for the Extended Release Capsules (NDA 20-699)
Supplements:

NDA	Supplement	Dated	Action
Effexor (venlafaxine hydrochloride) Immediate Release Tablets (NDA 20-151)			
20-151	SLR-015	12-29-99	AP Letter dated 6-12-00 Label Code: CI 6027-2
20-151	SLR-016	4-25-00	AE Letter Dated 7-20-00 Label Code CI 6027-3
20-151	SE8-017	5-5-00	AP Letter dated 5-2-01 Approved on draft labeling
20-151	SE8-018	5-5-00	AP Letter dated 5-2-01 Approved on draft labeling
20-151	SLR-019	9-29-00	Open
20-151	SLR-020	6-26-01	Open
20-151	SLR-021	9-27-01	Open
Effexor XR (venlafaxine hydrochloride) Extended Release Capsules (NDA 20-699)			
20-699	SE8-007	9-15-99	AP Letter Dated 7-13-00
20-699	SLR-012	12-20-99	AP Letter Dated 6-12-00 Label Code CI 4876-4
20-699	SLR-014	4-25-00, and amended on 12-8-00, 9-6-01, 9-20-01, and 10-26-01	AE Letters Dated 6-12-00 and 3-20-01 Label Code: CI 5044-5
20-699	SE8-015	5-5-00	AP Letter Dated 5-2-01 Approved on draft labeling
20-699	SE8-016	5-5-00	AP Letter Dated 5-2-01 Approved on draft labeling
20-699	SLR-018	9-29-00	Open
20-699	SLR-021	6-26-01	Open
20-699	SLR-023	9-13-01	Open

Notes of interest:

1. The labeling for Effexor and Effexor XR are separate and not combined formulation labeling. Although, as may be expected, many sections are identical. Therefore, this labeling review encompasses both product formulations. Additionally, all labeling revisions, which are open, for both the Effexor and Effexor XR products are identical since these were all safety related revisions.
2. The labeling approved in an Agency letter dated 7-13-00 for supplemental application NDA 20-699/SE8-007, providing for longer-term use for the GAD indication was never implemented by WA because the AP letter dated 7-13-00 stated that WA had to use the labeling verbatim. Similarly, the labeling approved in an Agency letter dated 5-2-01 for supplemental applications NDAs 20-151/SE8-017/SE8-018 and 20-699/SE8-015/SE8-016, providing for the prevention of depression relapse/recurrence was never implemented by WA because the AP letter dated 5-2-01 stated that WA had to use the labeling verbatim. The labeling contained in the 7-13-00 and 5-2-01 letters did not incorporate the CBE labeling revisions submitted to 20-151/SLR-016 and 20-699/SLR-014 since there was disagreement regarding several issues. WA subsequently incorporated the labeling revisions approved in 20-151/SE8-017/SE8-018 and 20-699/SE8-007/SE8-015/SE8-016 in a bundled new labeling supplement coded as 20-151/SLR-021 and 20-699/SLR-023 dated 9-27-01 and 9-13-01, respectively.
3. The labeling revisions submitted under applications 20-151/SLR-016 and 20-699/SLR-014 are identical and these revisions were submitted as CBE supplemental applications. These supplemental applications provide for many safety related revisions. However, the biggest point of contention was the Agency's request to add a new subsection under the **PRECAUTIONS-General** section entitled **Serum Cholesterol Elevation**. Revisions in labeling regarding serum cholesterol were also requested in the **ADVERSE REACTIONS-Incidence in Controlled Trials-Laboratory Changes** section of labeling. The Agency's other requests related to these supplemental applications have been adequately addressed by the sponsor. Additionally, the Agency has issued 2 AE actions dated 6-12-00 and 3-20-01. Further clarification regarding the type of additional data for these labeling revisions was communicated by Dr. Dubitsky in a telecon with WA on 7-6-01. It was also decided that WA could submit FPL incorporating these changes for applications 20-151/SE8-017/SE8-018 and 20-699/SE8-007/SE8-015/SE8-016 until the Agency received additional information regarding cholesterol changes, and this was communicated to WA by me in a telecon dated 6-11-01. Although not considered a complete response, WA has subsequently submitted additional information to the 20-699/SLR-014 supplement in submissions dated 9-6-01, 9-20-01, and 10-26-01. These submissions have not been reviewed, as yet, by the medical officer.

REVIEW

20-151/SLR-019 Label Code No: CI 6027-4
20-699/SLR-018 Label Code No: CI 5044-6
Date: 9-29-00
CBE: Yes
Reviewed by Medical Officer: Yes, acceptable with one minor revision to the Effexor XR labeling

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.

The sponsor submitted revisions to labeling essentially as requested in the above Agency letters, and these changes were found to be acceptable to the medical officer with one minor revision. In the Effexor XR labeling, 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. The medical officer's review concludes that, since the information applies for to both patient populations, the reference should be added to the end of the latter section as well.

20-151/SLR-020 Label Code No: CI 6027-5
20-699/SLR-021 Label Code No: CI 5044-7
Date: 6-26-01
CBE: Yes
Reviewed by Medical Officer: Yes, acceptable

This supplement 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/SLR-021 Label Code No: CI 6027-6
20-699/SLR-023 Label Code No: CI 7509-1
Date: 9-13-01 (20-699/SLR-023) and 9-27-01 (20-151/SLR-021)
CBE: Yes
Reviewed by Medical Officer: Yes, acceptable with a few minor revisions.

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 [redacted] which was originally submitted under NDAs 20-151/SLR-016 and 20-699/SLR-014, and it incorporates most of the revisions 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 [redacted] 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/SE8-017/SE8-018 and 20-699/SE8-015/SE8-016 providing for the prevention of depression relapse/recurrence (approved in an Agency letter dated May 2, 2001) and NDA

20-699/SE8-007 providing for longer-term use for the Generalized Anxiety Disorder indication (approved in an Agency letter dated July 13, 2000).

The medical officer has concluded that all of the above changes are acceptable except for the following:

1. There is still general disagreement regarding the changes proposed by WA in the **ADVERSE REACTIONS- Laboratory Changes** section of labeling as well as WA's reluctance to add a new subsection under the **PRECAUTIONS-General** section entitled **Serum Cholesterol Elevation**. WA has submitted additional information to support their proposed changes and they have proposed to not include the additional subsection in amendments dated 9-6-01, 9-20-01, and 10-26-01. The medical officer has completed his review of the 9-6-01 and 9-20-01 submissions, and that has not changed the Agency's position regarding our proposed labeling. The 10-26-01 submission has not been reviewed as yet. It should be noted, as well, that these changes were only submitted to the Effexor XR labeling until there is general agreement between the Agency and WA regarding these changes. Once agreement is reached, the changes will be submitted in parallel to both formulations.
2. The subsection under the **DOSAGE AND ADMINISTRATION** section entitled [redacted] should be revised to state **Maintenance Treatment** as stated in the Agency letter dated 5-2-01.
3. For the immediate release formulation, 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...". WA needs to revise this section in accordance with the Agency letter dated 5-2-01.

CONCLUSIONS

1. The above labeling supplements only provide for those revisions as stated above for these open supplements as well as the labeling revisions approved for the prevention of depression relapse/recurrence and for the longer-term use for the Generalized Anxiety Disorder (applicable only to the extended release NDA) when compared to the last approved labeling 20-151/SLR-015 (Label Code CI 6027-2)and 20-699/SLR-012 (Label Code 4876-4). The only exception to this would be the revisions to labeling regarding serum cholesterol which were submitted to 20-151/SLR-016 and 20-699/SLR-014.

2. I recommend that an AE letter issue for these open labeling supplements stating that these supplements will be approved once the Agency and WA come to agreement regarding the information from longer term studies with venlafaxine in association with increases in serum cholesterol have been resolved.

3. WA should also be requested to revise their labeling with the revisions requested by the medical officer in his reviews of the open labeling supplements.

Paul David, R.Ph., Regulatory Project Manager

Robbin Nighswander, R.Ph., Regulatory Health Project Manager

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

/s/

Paul David
11/13/01 12:17:32 PM
CSO

Robbin Nighswander
11/16/01 03:06:31 PM
CSO