CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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

MEDICAL REVIEW(S)

Review and Evaluation of Clinical Data
NDA 20-151

Sponsor:	Wyeth
Drug:	Effexor
Indication:	Depression
Material Submitted:	SLR-025: Final Printed Labeling
Correspondence Date:	December 20, 2002
Date Received:	December 23, 2002

Several supplements under this NDA provided for changes to the product labeling for Effexor: S-016, S-019, S-020, S-021, S-022, and S-023. These revisions are further described in the cover letter of this submission.

Approvable letters were forwarded on 1-10-02 (for S-016, S-019, S-020, and S-021) and on 7-2-02 (for S-022 and S-023). We requested specific revisions to the proposed changes in these supplements before a final approval action could be taken.

This submission contains Final Printed Labeling (FPL) which incorporates the revisions requested in the above two approvable letters.

The revisions, as reflected in the FPL, were reviewed by the undersigned and are acceptable. It is recommended that these supplements be approved.

Gregory M. Dubitsky, M.D.
December 27, 2002

cc: NDA 20-151
HFD-120 (Division File)
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/TLaughren
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/s/

Greg Dubitsky
12/27/02 08:35:43 PM
MEDICAL OFFICER

Thomas Laughren
12/28/02 11:51:32 AM
MEDICAL OFFICER

Review and Evaluation of Clinical Data
NDA #20-151

Sponsor:	Wyeth Pharmaceuticals
Drug:	Effexor (venlafaxine)
Indication:	Depression
Material Submitted:	SLR-023: Special Supplement-CBE
Correspondence Date:	May 31, 2002
Date Received:	June 3, 2002

I. Background

The sponsor is submitting this CBE (Changes Being Effected) supplement in accordance with 21 CFR 314.70(c)(2)(i) to add specific safety information to two sections of Effexor labeling:

1) PRECAUTIONS/General/Changes in Appetite and Weight and
2) ADVERSE REACTIONS/Postmarketing Reports.

It is anticipated that these changes will be implemented at the end of July 2002, at the earliest.

II. Review of Labeling Changes

A. PRECAUTIONS/General/Changes in Appetite and Weight

The sponsor proposes to add the following paragraph to this section:

> The safety and efficacy of venlafaxine therapy in combination with weight loss agents, including phentermine, have not been established. Co-administration of Effexor and weight loss agents is not recommended. Effexor is not indicated for weight loss alone or in combination with other products.

Wyeth states that they are adding this statement at this time because it has come to their attention that venlafaxine, alone or in combination with other drugs, is being advocated to produce weight loss. The information currently contained in this section suggests that anorexia

and weight loss are associated with venlafaxine treatment (e.g., treatment-emergent anorexia was reported in 11% of venlafaxine patients and 2% of placebo patients in short-term depression studies). The sponsor is concerned that this information is being used to endorse the use of venlafaxine as an anorexigenic agent.

A statement to warn against such use is felt to be necessary since venlafaxine is not approved as a weight loss agent and there has been no systematic evaluation of the safety or efficacy of the combined use of venlafaxine with weight loss agents. Additionally, there are theoretical reasons to expect that such combined use may be hazardous by virtue of augmented pharmacodynamic effects, such as blood pressure elevation possibly related to additive inhibition of norepinephrine reuptake or serotonin syndrome secondary to additive inhibition of serotonin reuptake. In fact, Meridia (sibutramine) labeling advises caution if this drug is used in combination with other CNS-active drugs, particularly serotonergic agents. Also, phentermine products carry a warning that they should not be co-administered with selective serotonin reuptake inhibitors.

Therefore, the sponsor wishes to add the above statement to discourage the use of Effexor as an anorexiant and the co-administration of Effexor with weight loss agents, such as phentermine.

B. ADVERSE REACTIONS/Postmarketing Reports

The sponsor proposes to add the adverse event term "pulmonary eosinophilia" to this listing.

This change is based on 3 spontaneous reports of pulmonary eosinophilia and 3 additional reports of pneumonia or pneumonitis with peripheral eosinophilia.

These cases were identified by searching for reports received by the company that contained the following MedDRA preferred terms: pulmonary eosinophilia, pneumonitis NOS, pneumonia NOS, or eosinophilia (exc pulmonary). The sponsor provided the MedWatch reports for these 6 cases.

Wyeth concludes that there is reasonable suspicion that venlafaxine may be associated with pulmonary eosinophilia.

III. Conclusions and Recommendations

I feel that there is an adequate theoretical basis for a hazardous pharmacodynamic interaction between venlafaxine and many weight loss agents to support the sponsor's statement discouraging such combined use. Furthermore, it is worth emphasizing, as this statement does, that venlafaxine itself is not indicated for weight loss.

I have no objection to the addition of the adverse event term "pulmonary eosinophilia" to the listing of postmarketing adverse event reports. A search by the undersigned of the FDA AERS DataMart on 6-19-02 for reports of "acute eosinophilic pneumonia" or "pulmonary eosinophilia" with any venlafaxine product revealed only 3 reports, all of which are included among the reports identified by the sponsor. Given the small number of reports relative to the large patient exposure to venlafaxine products over the past several years, no further action is deemed necessary at this time.

In sum, these revisions to Effexor labeling are acceptable and it is recommended that this supplement be approved.

Gregory M. Dubitsky, M.D.
June 19, 2002

cc: NDA 20-151
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Greg Dubitsky
6/19/02 03:21:09 PM
MEDICAL OFFICER

Thomas Laughren
6/20/02 12:20:09 PM
MEDICAL OFFICER

Review and Evaluation of Clinical Data
NDA #20-151

Sponsor:	Wyeth Pharmaceuticals
Drug:	Effexor (venlafaxine)
Indication:	Depression
Material Reviewed:	Consultative Response from the DNDP Safety Team dated 5-3-02.
Related NDA's:	NDA 20-699 (Effexor XR)

I. Background

The sponsor had submitted CBE labeling supplements on 4-25-00 for both Effexor and Effexor XR to add new safety information to the labeling for these two products (NDA 20-151/SLR-016 and NDA 20-699/SLR-014, respectively). Labeling changes included, among other things, the addition of data related to increases in serum cholesterol observed during long-term Effexor treatment to the "ADVERSE REACTIONS/Laboratory Changes" section of labeling for both drugs.

Following my review of this change, I did not feel that the added language was adequate. Specifically, I felt that these observations warranted more prominent placement in labeling (i.e., under PRECAUTIONS) [ ]

[ ]

The sponsor disagreed with this position. Over the next several months, Wyeth and the Division attempted to reach some agreement on how this information should be labeled.

To provide additional perspective, the Division Safety Team was consulted on 1-11-02 to evaluate the data and provide an opinion on the appropriate labeling of these data.

Also, the sponsor, after further considering this issue, proposed labeling changes to accomodate our concerns in a 3-22-02 letter, to include adding a PRECAUTIONS statement that contained a suggestion to consider cholesterol levels during long-term treatment.

Dr. Gerard Boehm, M.D., M.P.H., of the Safety Team, reviewed all submissions and reviews pertinent to this issue and completed a response on 5-3-02. This response is summarized below.

II. Summary of the Safety Team Consultative Response

Dr. Boehm described high levels of LDL (low density lipoprotein) cholesterol and low levels of HDL (high density lipoprotein) as risk factors for coronary heart disease. He acknowledged that, although venlafaxine treatment appears to elevate total cholesterol levels, we do not know the effects of venlafaxine on LDL and HDL levels. Hence, the clinical implications of this finding are not entirely clear.

Nonetheless, he did opine that it seemed reasonable to describe the observed changes associated with venlafaxine and corresponding placebo treatment in product labeling. Additionally, he recommended some minor changes to the sponsor's proposal contained in their 3-22-02 letter.

III. Recommendations

Based on my consideration of Dr. Boehm's recommendations, I recommend the following language to describe this observation in Effexor and Effexor XR 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

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 ≥50 mg/dL from baseline and to a value ≥261 mg/dL or 2) an average on-therapy increase in serum cholesterol ≥50 mg/dL from baseline and to a value ≥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

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 ≥50 mg/dL from baseline and to a value ≥261 mg/dL or 2) an average on-therapy increase in serum cholesterol ≥50 mg/dL from baseline and to a value ≥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).

Gregory M. Dubitsky, M.D.
June 15, 2002

cc: NDA 20-151
NDA 20-699
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Greg Dubitsky
6/15/02 05:51:44 PM
MEDICAL OFFICER

Thomas Laughren
6/19/02 11:03:05 AM
MEDICAL OFFICER

Review of Clinical Data

NDA:	20-151, 20-699
Drug Name:	Generic: Venlafaxine Trade name: Effexor™,EffexorXR™
Sponsor:	Wyeth Pharmaceuticals
Material Reviewed:	Sponsor's submissions dated 9/6/01, 9/20/01, 10/26/01, 3/22/02, Dr. Dubitsky's consult dated 11/6/01
Reviewer:	Gerard Boehm, MD, MPH
Date Completed:	5/3/2002

Background

On 4/25/00, Wyeth submitted a letter to the division with several Changes Being Effected (CBE) proposals for venlafaxine (Effexor/EffexorXR). One of the changes was a labeling update that described increased risk for serum cholesterol elevations among subjects treated with venlafaxine in long term trials. These findings were non-fasting total cholesterol results[1]. The sponsor's description of the cholesterol findings is located in the Adverse Events section of the current label and is provided in the following paragraph:

> *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 [redacted]

After reviewing the CBE submission, the division asked the sponsor to include the placebo data from these trials, requested more a prominent position in labeling, namely in the Precautions section [redacted]. The sponsor agreed to add the placebo data but rejected the proposal to move the information to the Precautions section of labeling [redacted]

In subsequent submissions, the sponsor recalculated risks for elevated cholesterol in a pooled analysis of long term data using a case definition suggested by their consultants that was designed to identify clinically important cholesterol increases. The sponsor explained that their studies collected non-fasting cholesterol, and that there is considerable intra-subject variability with cholesterol measurements. For these reasons, they felt that some of the elevations identified in their earlier analyses might not necessarily reflect clinically important changes. Their new case definition identified clinically important changes as final on therapy increases in serum cholesterol ≥50mg/dL from baseline and to a value ≥261mg/dL or an average on therapy increase in serum cholesterol ≥50mg/dL from baseline and to a value ≥261mg/dL. The sponsor felt this case definition considered intra-patient variability that could overestimate the proportion of patients with important changes.

[1] Described in the sponsor's 10/26/01 submission, p.3.

Using this case definition, the sponsor summarized their findings as follows:

- 3.3% (18/546) of the venlafaxine treated patients had final on-therapy values in the clinically important range.
- 1.6% (9/546) of the venlafaxine treated patients had average individual on-therapy values in the clinically important range.
- 1.3% (7/546) of the venlafaxine treated patients met both criteria.
- 0/73 placebo treated patients met the criteria.

In a memo on this subject (signed 11/6/01), Dr. Dubitsky wrote, "the submitted data suggest that venlafaxine treatment may be associated with a clinically relevant increase in serum cholesterol." He suggested limiting the analysis to subjects from 4 similarly designed long-term trials and not including data from relapse prevention trials where subjects in the "placebo" group had prior exposure to venlafaxine. In this group of 4 studies, the risk for a clinically relevant increase in cholesterol was 5.3% (9/169) in venlafaxine subjects and 0 (0/73) in placebo subjects. Dr. Dubitsky felt that "these findings merit prominent description in labeling..." Specifically, Dr. Dubitsky proposed placing a statement in the Precautions section of labeling [redacted]

Wyeth replied in a 3/22/02 letter that they would add the following wording to the Effexor/EffexorXR labeling:

PRECAUTIONS

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 long term trials (see ADVERSE REACTIONS- Laboratory Changes).

[redacted] serum cholesterol levels should be considered [redacted] long term treatment.

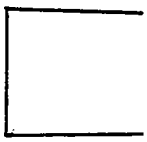
ADVERSE REACTIONS- Laboratory Changes

Effexor tablet text:

Patients treated with Effexor tablets for at least 3 months in placebo-controlled long-term trials had a mean final on-therapy increase in total cholesterol of 9.1mg/dL compared to a 7.1mg/dL decrease 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≥ 50mg/dL from baseline and to a value ≥ 261mg/dL or 2) an average on-therapy increase in serum cholesterol ≥ 50mg/dL from baseline and to a value ≥ 261mg/dL, were recorded in 5.3% of venlafaxine-treated patients and 0.0% of placebo-treated patients (see PRECAUTIONS- Serum Cholesterol Elevation).

Effexor XR text:

[redacted]



Discussion
Elevated LDL cholesterol and low levels of HDL are risk factors for coronary heart disease. Large observation cohort studies have observed a continuous, linear and graded relationship between coronary heart disease events and increasing LDL levels and decreasing HDL levels. A large US cohort study found that after adjusting for other risk factors, 27% of CHD events in men and 34% in women were attributable to total cholesterol levels >200mg/dL. Total excess risk for CHD from lipid disorders depends on the presence of other CHD risk factors including hypertension and tobacco use. [1]

The sponsor's most recent labeling proposal includes cholesterol result comparisons using placebo data. The placebo data provide important comparative information that allows interpretation of the changes observed in the Effexor group and appear appropriate.

The implications of the observed elevated total cholesterol results among subjects treated with Effexor are not completely clear. It seems that the sponsor's interest in including information about the effect of Effexor on total cholesterol is to disclose for prescribers and patients a potential for increased CHD risk. While Effexor appears to increase total cholesterol, we do not know the effect of Effexor on LDL or HDL cholesterol levels since these results have not been submitted to the division. In the absence of this information, it seems reasonable to describe the observed changes in labeling.

Recommendations
I propose the following changes to the sponsor's latest proposal:

- Labeling Text
  I recommend changing the text in the PRECAUTIONS section as follows:

  Measurement of[ ]serum cholesterol levels should be considered[ ]during long term treatment.

  ...a mean final on-therapy increase in total cholesterol of 9.1mg/dL compared[ ]a decrease of 7.1mg/dL[ ]among placebo treated patients.

- Uniform references to product name
  The ADVERSE REACTIONS section for Effexor seems appropriate although I would suggest that to avoid confusion, the drug be referred to by its generic or trade name uniformly throughout the statement (the proposed language uses Effexor in the beginning and venlafaxine towards the end).

- Additional Placebo Data
  The ADVERSE REACTIONS section for Effexor XR should include the placebo data for the controlled trial mean cholesterol changes that the sponsor reported.

- Effexor XR Format

The cholesterol data from the immediate release studies that appears in the Effexor XR label should be placed in a separate paragraph to better distinguish the source of these data.

[1] Pignone MP, Phillips CJ, Atkins D, Teutsch SM, Mulrow CD, Lohr, KN. Screening and treating adults for lipid disorders. *Am J Prev Med* 2001;20 (3S):77-89 (http://www.elsevier.com/locate/ajpmonline).

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/s/

Jerry Boehm
5/3/02 06:46:29 AM
MEDICAL OFFICER

Judith Racoosin
5/8/02 01:31:21 PM
MEDICAL OFFICER

Review and Evaluation of Clinical Data
NDA #20-151

Sponsor:	Wyeth Pharmaceuticals
Drug:	Effexor (venlafaxine)
Indication:	Depression
Material Submitted:	SLR-022: Special Supplement-CBE
Correspondence Date:	March 8, 2002
Date Received:	March 11, 2002

I. Background

The sponsor is submitting this CBE (Changes Being Effected) supplement in accordance with 21 CFR 314.70(c)(2)(i) to add specific safety information to two sections of Effexor labeling:

1) WARNINGS/Sustained Hypertension and
2) ADVERSE REACTIONS/Postmarketing Reports.

It was anticipated that these changes would be implemented in the second quarter of 2002.

II. Review of Labeling Changes

A. WARNINGS/Sustained Hypertension

The sponsor proposes to amend the first sentence in this section to indicate that venlafaxine treatment is associated with sustained increases in blood pressure <u>in some patients</u> (added text underlined).

B. ADVERSE REACTIONS/Postmarketing Reports

The sponsor proposes to add the adverse event terms "neutropenia" and "pancytopenia" to this listing.

These changes are based on 34 spontaneous post-marketing reports of neutropenia and 18 reports of pancytopenia and aplastic anemia.

These cases were identified by searching for reports received by the company that contained the following MedDRA terms: leucopenia NOS, neutropenia, agranulocytosis, white blood cell disorder NOS, white blood cell abnormality, white blood cell count decreased, bone marrow depression NOS, and pancytopenia NOS. The sponsor provided a few representative case reports for these events, which were examined by the undersigned. Some of these are difficult to interpret due to lack of clinical details but there are a few remarkable cases, such as this one:

Mfr. Report # 8-98303-023A - a 90 y.o. female experienced pancytopenia (hemoglobin=8.2 g/dL, platelets=12,000/cmm, and WBC=80/cmm) with the development of bronchopneumonia after 5 days of venlafaxine therapy. The patient received leukocyte transfusions and antibiotics but subsequently died. The CBC was reportedly normal 5 months prior to the event. Concomitant medication consisted of moclobemide, which had been taken for over 7 months.

Wyeth concludes that there is reasonable suspicion that venlafaxine may be associated with neutropenia, aplastic anemia, and pancytopenia.

III. Conclusions and Recommendations

These revisions to Effexor labeling are acceptable and it is recommended that this supplement be approved.

However, the addition of the terms "neutropenia" and "pancytopenia" to labeling and the sponsor's statement that there is reasonable suspicion that these events may be associated with venlafaxine beg the question, which is not addressed, of whether venlafaxine treatment confers a substantially increased risk of these events.

Judith A. Racoosin, M.D., M.P.H., of the Division Safety Team, reviewed the incidence of aplastic anemia with recently approved antidepressant agents in February 1998, over four years ago. At that time, there were no cases of bone marrow biopsy-confirmed reports of aplastic anemia associated with venlafaxine. Since that time, more experience with Effexor has accumulated and Effexor XR, the extended-release formulation of venlafaxine, has accrued substantial use in treating depression as well as generalized anxiety disorder. Additionally, that review

focused only on aplastic anemia and excluded cases of severe neutropenia and agranulocytosis.

Therefore, it is recommended that the Division Safety Team be consulted to evaluate the current risk of severe neutropenia, to include agranulocytosis, and severe pancytopenia, to include aplastic anemia, with venlafaxine.

Gregory M. Dubitsky, M.D.
June 18, 2002

cc: NDA 20-151
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/s/

Greg Dubitsky
6/18/02 01:55:37 PM
MEDICAL OFFICER

Thomas Laughren
6/18/02 04:02:06 PM
MEDICAL OFFICER
I agree a consult to the safety group regarding neutropenia would be useful.-TPL

Review and Evaluation of Clinical Data
NDA #20-151

Sponsor:	Wyeth-Ayerst Research
Drug:	Effexor
Indication:	Depression
Material Submitted:	SLR-021: Special Supplement-CBE
Correspondence Date:	September 27, 2001
Date Received:	September 27, 2001

I. Background

The sponsor (W-A) is submitting this CBE (Changes Being Effected) supplement in accordance with 21 CFR 314.70(c)(2)(i) to provide for the addition of specific safety information to three sections of Effexor labeling:

1) PRECAUTIONS/General,

2) PRECAUTIONS/Information for Patients, and

3) ADVERSE REACTIONS/Postmarketing Reports.

Additionally, this submission contains FPL (Final Printed Labeling) for S-017 and S-018 (prevention of relapse and recurrence of depression). W-A anticipates that this FPL will be used in production in the fourth quarter of 2001, at the earliest.

Finally, the sponsor has proposed several editorial changes to Effexor labeling.

II. Review of Changes to Labeling

A. PRECAUTIONS/General

The following new subsection is proposed:

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.

An identical change was proposed for Effexor XR labeling in SLR-023 to NDA 20-699 which was submitted on 9-13-01. I reviewed this change on 10-10-01 and had no objection to this revision to Effexor XR labeling. Similarly, I have no objection to making this change to Effexor labeling.

B. PRECAUTIONS/Information for Patients

The subsection entitled "Concomitant Medication" was revised to explicitly indicate that patients should advise their physicians if they are taking, or plan to take, any herbal preparations.

An identical change was proposed for Effexor XR labeling in SLR-023 to NDA 20-699. This change was reviewed by the undersigned on 10-10-01 and I had no objection to this revision to Effexor XR labeling. Similarly, there is no objection to making this change to Effexor labeling.

C. ADVERSE REACTIONS/Postmarketing Reports

The sponsor proposes to add the following adverse event terms to the list of postmarketing reports:

- QT prolongation.
- "cardiac arrhythmias" to describe a class of events.
- rare reports of ventricular fibrillation, including torsade de pointes.
- night sweats.

The addition of identical terms to the corresponding subsection of Effexor XR labeling was proposed in SLR-023 to NDA 20-699. These changes were examined by the undersigned on 10-10-01 and I had no objection to these

revisions to Effexor XR labeling. Similarly, there is no objection to adding these terms to Effexor labeling.

Also, the sponsor proposes to delete the term [ ] from this subsection as we had previously requested for Effexor XR labeling in a 6-12-00 letter. This is acceptable for Effexor labeling as well.

D. Labeling Changes Pursuant to Approved Efficacy Supplements

Revisions pursuant to previously approved efficacy supplements (S-017 and S-018) and depicted in the sponsor's annotated labeling under Tab A were compared to the labeling attached to our most recent approval letter for Effexor, dated 5-2-01.

The noted revisions were identical to the corresponding sections of the approval labeling except for two parts of labeling:

1) under ADVERSE REACTIONS/Incidence in Controlled Trials/Laboratory Changes, the sponsor has added information from longer-term studies with Effexor regarding increases in serum cholesterol. This paragraph was not included in our approval labeling.

2) under DOSAGE AND ADMINISTRATION in the subsection entitled [ ], the title of the subsection should read "Maintenance Treatment." Also, 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."

E. Editorial Changes to Labeling

The sponsor has proposed approximately 45 editorial changes to Effexor labeling which are indicated on the annotated labeling under Tab A of this submission. These include such revisions as removing italicized font and quotation marks, correction of misspelled words, and changing "e.g." to "eg."

Each indicated change was reviewed by the undersigned and deemed to be acceptable.

III. Conclusions and Recommendations

The revisions to Effexor labeling contained in this supplement are acceptable except for the two subsections of labeling as described above. The sponsor should be requested to amend these parts to conform to the text contained in the labeling attached to our 5-2-01 approval letter. Upon making these changes, this supplement may be approved.

Gregory M. Dubitsky, M.D.

October 15, 2001

cc: NDA #20-151
HFD-120 (Div. File)
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/PDavid

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/s/

Greg Dubitsky
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Thomas Laughren
10/16/01 11:19:27 AM
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Review and Evaluation of Clinical Data
NDA #20-151

Sponsor:	Wyeth-Ayerst Research
Drug:	Effexor
Indication:	Depression
Material Submitted:	SLR-020: CBE Supplement
Correspondence Date:	June 26, 2001
Date Received:	June 28, 2001
Related Supplements:	NDA #20-699/SLR-021 (Effexor XR)

I. Background

These CBE supplements provide for the addition of identical safety information to the CONTRAINDICATIONS and PRECAUTIONS/Pregnancy sections of Effexor and Effexor XR labeling. The proposed changes are reviewed below.

II. Labeling Changes

A. Contraindications

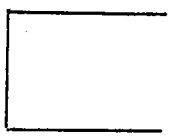
The first sentence of this section is revised to include excipient hypersensitivity:

"Hypersensitivity to venlafaxine hydrochloride or to any excipients in the formulation."

No data are provided to support this change.

B. Precautions/Pregnancy

The sponsor plans to add a subsection under PRECAUTIONS entitled "Non-teratogenic Effects" that will read as follows:



In support of this labeling change, the sponsor provided a line listing of 17 spontaneous reports from their Global Safety Surveillance and Epidemiology database and from the medical literature, with a cutoff date of 12-11-00 (see Attachment 2). These reports describe abnormalities in neonates coincident with the mother taking venlafaxine up to the time of delivery.

Most of these mothers took concomitant drugs or substances, such as marijuana, cocaine, butalbutal, beclomethasone, lithium, alcohol, methadone, and fentanyl. Reported adverse events ranged from fussiness, hypotonia, and drowsiness to apnea and seizures. Many reports contained insufficient information.

Also, the sponsor presented a summary of a literature report of suspected neonatal withdrawal symptoms related to sertraline use in the mother.

Finally, they describe a study which demonstrated that selective serotonin reuptake inhibitor concentrations in fetal rat brains were as high as 85% of that in the maternal brain.

The sponsor concludes that a causal association between maternal use of venlafaxine and discontinuation symptoms in the newborn cannot be ruled out.

III. Conclusions and Recommendations

I do not object to the sponsor's proposal to add a contraindication for patients who are hypersensitive to the excipients in Effexor or Effexor XR tablets.

With respect to the new subsection under PRECAUTIONS/ Pregnancy, it is not possible to draw any firm conclusions about neonatal withdrawal effects associated with venlafaxine from the submitted series of cases and literature reports.

However, it is reasonable to assume that venlafaxine does cross the placenta to some extent and, given that it does

seem to produce withdrawal symptoms in some adults who discontinue treatment, that it is likely to produce withdrawal symptoms in some infants who experience a cessation of drug exposure. By this reasoning, I do not object to adding this information to labeling.

It is recommended that the above supplements be approved.

Gregory M. Dubitsky, M.D.

July 20, 2001

cc: NDA #20-151
NDA #20-699
HFD-120 (Division Files)
HFD-120/GDubitsky
/TLaughren
/PDavid

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

/s/

Greg Dubitsky
7/20/01 06:20:45 PM
MEDICAL OFFICER

Thomas Laughren
7/28/01 04:49:19 PM
MEDICAL OFFICER
I agree that this supplement can be approved.--TPL

Review and Evaluation of Clinical Data
NDA # 20-151

Sponsor:	Wyeth-Ayerst Research
Drug:	Effexor (venlafaxine hydrochloride)
Proposed Indication:	Depression
Material Submitted:	Special Supplement-Changes Being Effected (SLR-019)
Correspondence Date:	September 29, 2000
Date Received:	October 2, 2000

In letters to the sponsor (W-A) dated 9-13-99 and 6-14-00, we requested that Effexor labeling be amended to include information concerning substantial increases in heartrate observed on ECG tracings in previously submitted trials using higher doses of Effexor (i.e., over 200 mg/day and up to 375 mg/day) in depressed patients.

This supplement, being submitted as "Changes Being Effected," incorporates the above information essentially as we had requested. Final Printed Labeling (FPL) is provided under Attachment D of the submission.

It is recommended that this supplement be approved.

Gregory M. Dubitsky, M.D.
October 12, 2000

cc: NDA# 20-151
HFD-120 (Div. File)
HFD-120/GDubitsky
/TLaughren
/PDavid

Review and Evaluation of Clinical Data
NDA #20-151

Sponsor:	Wyeth-Ayerst Research
Drug:	Effexor Tablets
Proposed Indication:	Depression
Material Submitted:	SLR-016: Changes Being Effected
Correspondence Date:	April 25, 2000
Date Received:	April 28, 2000

I. Background

The sponsor (W-A) is proposing a number of modifications to Effexor labeling as "Changes Being Effected" (CBE) under the provisions of 21 CFR 314.70(c)(2)(i).[1] These changes will be used in production in August 2000.

The proposed changes (and supporting data) are identical to those proposed for Effexor XR labeling, submitted to NDA 20-699 on the same date as SLR-014. My assessment of these modifications is conveyed in the Review and Evaluation of Clinical Data dated May 16, 2000. My recommendations are identical to those in that review and are repeated below for the convenience of the reader.

II. Recommendations

It is recommended that the sponsor be required to address the following issues before this supplement is approved:

1) Under PRECAUTIONS/General, the sponsor should present a more systematic overview of relevant clinical data to support the proposed section on [ ]. Specifically, the sponsor should evaluate their 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.

[1] Changes to add or strengthen a contraindication, warning, precaution, or adverse reaction.

2) Also under PRECAUTIONS/General, a new subsection should be created to address increases in serum cholesterol observed with longer-term venlafaxine treatment. The following is suggested:

"*Serum Cholesterol Elevation*

3) It is recommended 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:

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

The addition of a new "Hyponatremia" subsection under PRECAUTIONS/General and the modifications to the DRUG ABUSE AND DEPENDENCE and DOSAGE AND ADMINISTRATION sections regarding discontinuation effects with venlafaxine are acceptable.

Gregory M. Dubitsky, M.D.
May 21, 2000

cc: NDA #20-151
HFD-120 (Div. File)
HFD-120/GDubitsky
/TLaughren
/PDavid