CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

NDA 20-699/S-012

Name:	Effexor XR Extended-Release Capsules
Generic Name:	venlafaxine hydrochloride
Sponsor:	Wyeth Pharmaceuticals Inc.
Approval Date:	06/12/00
Indications:	For the treatment of depression and generalized anxiety disorder.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-699/S-012

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-699/S-012

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville MD 20857

JUN 12 2000

NDA 20-699/S-012/S-014

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 applications dated December 20, 1999 (S-012) and April 25, 2000 (S-014), submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Effexor XR (venlafaxine hydrochloride) Extended Release Capsules.

Supplemental application S-012 provides for the following revisions to product labeling:

1. The addition of the following new inactive ingredients under the **DESCRIPTION** section: D&C Red #28, D&C Yellow #10, and FD&C Blue #1).
2. An editorial change to the last sentence of the first paragraph in the **WARNINGS-Sustained Hypertension** section to clarify the meaning of the statement.
3. The addition of a new subsection under the **PRECAUTIONS** section entitled **Mydriasis**.
4. The addition of a new subsection under the **PRECAUTIONS-Drug Interactions** section entitled **Indinavir**.
5. The revision of the **OVERDOSAGE-Human Experience** section.
6. The reformatting of the **HOW SUPPLIED** section.

We have completed our review of this supplemental application, and it is approved effective as of the date of this letter. Additionally, we note that this supplemental application was submitted under "Special Supplement – Changes Being Effected", and these changes to product labeling have already taken place.

Supplemental application S-014 provides for 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

   [ ]

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**:

   "'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. [ ]

   [ ]

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

We note that this labeling supplement, S-014, 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,

6/12/03

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

cc:
Archival NDA 20-243
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

Rd:5/19/00
Ft:06/02/00
filename:EFFEXOR XR AP LETTER S-012 AE LETTER S-014.DOC

APPROVED (NDA 20-699/S-012)
APPROVABLE (NDA 20-699/S-014)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-699/S-012

LABELING

APPROVED

JUN 12 2000

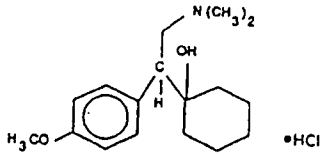
Effexor® XR
(venlafaxine hydrochloride)
Extended-Release Capsules
CI 4876-5

CODE
INSERTED
HERE

Effexor® XR
(venlafaxine hydrochloride)
Extended-Release Capsules
CI 4876-5

Effexor® XR
(venlafaxine hydrochloride)
Extended-Release Capsules

DESCRIPTION
Effexor XR is an extended-release capsule for oral administration that contains venlafaxine hydrochloride, a structurally novel antidepressant. Venlafaxine hydrochloride is chemically unrelated to tricyclic, tetracyclic, and other available antidepressants and to other agents used to treat Generalized Anxiety Disorder. It is designated (R/S)-1-[2-(dimethylamino)-1-(4-methoxyphenyl)ethyl] cyclohexanol hydrochloride or (±)-1-[α- [(dimethylamino)methyl]-p-methoxybenzyl] cyclohexanol hydrochloride and has the empirical formula of $C_{17}H_{27}NO_2$ hydrochloride. Its molecular weight is 313.87. The structural formula is shown below.



venlafaxine hydrochloride

Venlafaxine hydrochloride is a white to off-white crystalline solid with a solubility of 572 mg/mL in water (adjusted to ionic strength of 0.2 M with sodium chloride). Its octanol:water (0.2 M sodium chloride) partition coefficient is 0.43.

Effexor XR is formulated as an extended-release capsule for once-a-day oral administration. Drug release is controlled by diffusion through the coating membrane on the spheroids and is not pH dependent. Capsules contain venlafaxine hydrochloride equivalent to 37.5 mg, 75 mg, or 150 mg venlafaxine. Inactive ingredients consist of cellulose, ethylcellulose, gelatin, hydroxypropyl methylcellulose, iron oxide, and titanium dioxide. The 37.5 mg capsule also contains D&C Red #28, D&C Yellow #10, and FD&C Blue #1.

CLINICAL PHARMACOLOGY

Pharmacodynamics
The mechanism of the antidepressant action of venlafaxine in humans is believed to be associated with its potentiation of neurotransmitter activity in the CNS. Preclinical studies have shown that venlafaxine and its active metabolite, O-desmethylvenlafaxine (ODV), are potent inhibitors of neuronal serotonin and norepinephrine reuptake and weak inhibitors of dopamine reuptake. Venlafaxine and ODV

have no significant affinity for muscarinic cholinergic, H_1-histaminergic, or α_1-adrenergic receptors in vitro. Pharmacologic activity at these receptors is hypothesized to be associated with the various anticholinergic, sedative, and cardiovascular effects seen with other psychotropic drugs. Venlafaxine and ODV do not possess monoamine oxidase (MAO) inhibitory activity.

Pharmacokinetics

Steady-state concentrations of venlafaxine and ODV in plasma are attained within 3 days of oral multiple dose therapy. Venlafaxine and ODV exhibited linear kinetics over the dose range of 75 to 450 mg/day. Mean±SD steady-state plasma clearance of venlafaxine and ODV is 1.3±0.6 and 0.4±0.2 L/h/kg, respectively; apparent elimination half-life is 5±2 and 11±2 hours, respectively; and apparent (steady-state) volume of distribution is 7.5±3.7 and 5.7±1.8 L/kg, respectively. Venlafaxine and ODV are minimally bound at therapeutic concentrations to plasma proteins (27 and 30%, respectively).

Absorption

Venlafaxine is well absorbed and extensively metabolized in the liver. O-desmethylvenlafaxine (ODV) is the only major active metabolite. On the basis of mass balance studies, at least 92% of a single oral dose of venlafaxine is absorbed. The absolute bioavailability of venlafaxine is about 45%.

Administration of Effexor XR (150 mg q24 hours) generally resulted in lower C_{max} (150 ng/mL for venlafaxine and 260 ng/mL for ODV) and later T_{max} (5.5 hours for venlafaxine and 9 hours for ODV) than for immediate release venlafaxine tablets ($C_{max's}$ for immediate release 75 mg q12 hours were 225 ng/mL for venlafaxine and 290 ng/mL for ODV; $T_{max's}$ were 2 hours for venlafaxine and 3 hours for ODV). When equal daily doses of venlafaxine were administered as either an immediate release tablet or the extended-release capsule, the exposure to both venlafaxine and ODV was similar for the two treatments, and the fluctuation in plasma concentrations was slightly lower with the Effexor XR capsule. Effexor XR, therefore, provides a slower rate of absorption, but the same extent of absorption compared with the immediate release tablet.

Food did not affect the bioavailability of venlafaxine or its active metabolite, ODV. Time of administration (AM vs PM) did not affect the pharmacokinetics of venlafaxine and ODV from the 75 mg Effexor XR capsule.

Metabolism and Excretion

Following absorption, venlafaxine undergoes extensive presystemic metabolism in the liver, primarily to ODV, but also to N-desmethylvenlafaxine, N,O-didesmethylvenlafaxine, and other minor metabolites. *In vitro* studies indicate that the formation of ODV is catalyzed by CYP2D6; this has been confirmed in a clinical study showing that patients with low CYP2D6 levels ("poor metabolizers") had increased levels of venlafaxine and reduced levels of ODV compared to people with normal CYP2D6 ("extensive metabolizers"). The differences between the CYP2D6 poor and extensive metabolizers, however, are not expected to be clinically important because the sum of venlafaxine and ODV is similar in the two groups and venlafaxine and ODV are pharmacologically approximately equiactive and equipotent.

Approximately 87% of a venlafaxine dose is recovered in the urine within 48 hours as unchanged venlafaxine (5%), unconjugated ODV (29%), conjugated ODV (26%), or other minor inactive metabolites (27%). Renal elimination of venlafaxine and its metabolites is thus the primary route of excretion.

Special Populations

Age and Gender: A population pharmacokinetic analysis of 404 venlafaxine-treated patients from two studies involving both b.i.d. and t.i.d. regimens showed that dose-normalized trough plasma levels of either venlafaxine or ODV were unaltered by age or gender differences. Dosage adjustment based on the age or gender of a patient is generally not necessary (see "**DOSAGE AND ADMINISTRATION**").

Extensive/Poor Metabolizers: Plasma concentrations of venlafaxine were higher in CYP2D6 poor metabolizers than extensive metabolizers. Because the total exposure (AUC) of venlafaxine and ODV was similar in poor and extensive metabolizer groups, however, there is no need for different venlafaxine dosing regimens for these two groups.

Liver Disease: In 9 patients with hepatic cirrhosis, the pharmacokinetic disposition of both venlafaxine and ODV was significantly altered after oral administration of venlafaxine. Venlafaxine elimination half-life was prolonged by about 30%, and clearance decreased by about 50% in cirrhotic patients compared to normal subjects. ODV elimination half-life was prolonged by about 60%, and clearance decreased by about 30% in cirrhotic patients compared to normal subjects. A large degree of intersubject variability was noted. Three patients with more severe cirrhosis had a more substantial decrease in venlafaxine clearance (about 90%) compared to normal subjects. Dosage adjustment is necessary in these patients (see "**DOSAGE AND ADMINISTRATION**").

Renal Disease: In a renal impairment study, venlafaxine elimination half-life after oral administration was prolonged by about 50% and clearance was reduced by about 24% in renally impaired patients (GFR=10-70 mL/min), compared to normal subjects. In dialysis patients, venlafaxine elimination half-life was prolonged by about 180% and clearance was reduced by about 57% compared to normal subjects. Similarly, ODV elimination half-life was prolonged by about 40% although clearance was unchanged in patients with renal impairment (GFR=10-70 mL/min) compared to normal subjects. In dialysis patients, ODV elimination half-life was prolonged by about 142% and clearance was reduced by about 56% compared to normal subjects. A large degree of intersubject variability was noted. Dosage adjustment is necessary in these patients (see "**DOSAGE AND ADMINISTRATION**").

Clinical Trials

Depression

The efficacy of Effexor XR (venlafaxine hydrochloride) extended-release capsules as a treatment for depression was established in two placebo-controlled, short-term, flexible-dose studies in adult outpatients meeting DSM-III-R or DSM-IV criteria for major depression.

A 12-week study utilizing Effexor XR doses in a range 75-150 mg/day (mean dose for completers was 136 mg/day) and an 8-week study utilizing Effexor XR doses in a range 75-225 mg/day (mean dose for completers was 177 mg/day) both demonstrated superiority of Effexor XR over placebo on the HAM-D total score, HAM-D Depressed Mood Item, the MADRS total score, the Clinical Global Impressions (CGI) Severity of Illness item, and the CGI Global Improvement item. In both studies, Effexor XR was also significantly better than placebo for certain factors of the HAM-D, including the anxiety/somatization factor, the cognitive disturbance factor, and the retardation factor, as well as for the psychic anxiety score.

A 4-week study of inpatients meeting DSM-III-R criteria for major depression with melancholia utilizing Effexor (the immediate release form of venlafaxine) in a range of 150 to 375 mg/day (t.i.d. schedule) demonstrated superiority of Effexor over placebo. The mean dose in completers was 350 mg/day.

Examination of gender subsets of the population studied did not reveal any differential responsiveness on the basis of gender.

Generalized Anxiety Disorder

The efficacy of Effexor XR capsules as a treatment for Generalized Anxiety Disorder (GAD) was established in two 8-week, placebo-controlled, fixed-dose studies in outpatients meeting DSM-IV criteria for GAD.

One study evaluating Effexor XR doses of 75, 150, and 225 mg/day, and placebo showed that the 225 mg/day dose was more effective than placebo on the Hamilton Rating Scale for Anxiety (HAM-A) total score, both the HAM-A anxiety and tension items, and the Clinical Global Impressions (CGI) scale. While there was also evidence for superiority over placebo for the 75 and 150 mg/day doses, these doses were not as consistently effective as the highest dose. A second study evaluating Effexor XR doses of 75 and 150 mg/day and placebo showed that both doses were more effective than placebo on some of these same outcomes, however, the 75 mg/day dose was more consistently effective than the 150 mg/day dose. A dose-response relationship for effectiveness in GAD was not clearly established in the 75-225 mg/day dose range utilized in these two studies.

Examination of gender subsets of the population studied did not reveal any differential responsiveness on the basis of gender.

INDICATIONS AND USAGE

Depression

Effexor XR (venlafaxine hydrochloride) extended-release capsules is indicated for the treatment of depression

The efficacy of Effexor XR in the treatment of depression was established in 8- and 12-week controlled trials of outpatients whose diagnoses corresponded most closely to the DSM-III-R or DSM-IV category of major depressive disorder (see "**Clinical Trials**").

A major depressive episode (DSM-IV) implies a prominent and relatively persistent (nearly every day for at least 2 weeks) depressed mood or the loss of interest or pleasure in nearly all activities, representing a change from previous functioning, and includes the presence of at least five of the following nine symptoms during the same two-week period: depressed mood, markedly diminished interest or pleasure in usual activities, significant change in weight and/or appetite, insomnia or hypersomnia, psychomotor agitation or retardation, increased fatigue, feelings of guilt or worthlessness, slowed thinking or impaired concentration, a suicide attempt or suicidal ideation.

The efficacy of Effexor (the immediate release form of venlafaxine) in the treatment of depression in inpatients meeting diagnostic criteria for major depressive disorder with melancholia was established in a 4-week controlled trial (see "**Clinical Trials**"). The safety and efficacy of Effexor XR in hospitalized depressed patients have not been adequately studied.

The effectiveness of Effexor XR in long-term use, that is, for more than 12 weeks, has not been systematically evaluated in controlled trials. The physician who elects to use Effexor XR for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient (see "**DOSAGE AND ADMINISTRATION**").

Generalized Anxiety Disorder

Effexor XR is indicated for the treatment of Generalized Anxiety Disorder (GAD) as defined in DSM-IV. Anxiety or tension associated with the stress of everyday life usually does not require treatment with an anxiolytic.

The efficacy of Effexor XR in the treatment of GAD was established in 8-week placebo-controlled trials in outpatients diagnosed with GAD according to DSM-IV criteria (See **"Clinical Trials"**).

Generalized Anxiety Disorder (DSM-IV) is characterized by excessive anxiety and worry (apprehensive expectation) that is persistent for at least 6 months and which the person finds difficult to control. It must be associated with at least 3 of the following 6 symptoms: restlessness or feeling keyed up or on edge, being easily fatigued, difficulty concentrating or mind going blank, irritability, muscle tension, sleep disturbance.

The effectiveness of Effexor XR in the long-term treatment of GAD, that is, for more than 8 weeks, has not been systematically evaluated in controlled trials. The physician who elects to use Effexor XR for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient (See **"DOSAGE AND ADMINISTRATION"**).

CONTRAINDICATIONS

Effexor XR (venlafaxine hydrochloride) extended-release capsules is contraindicated in patients known to be hypersensitive to venlafaxine hydrochloride.

Concomitant use in patients taking monoamine oxidase inhibitors (MAOIs) is contraindicated (see **"WARNINGS"**).

WARNINGS

Potential for Interaction with Monoamine Oxidase Inhibitors

Adverse reactions, some of which were serious, have been reported in patients who have recently been discontinued from a monoamine oxidase inhibitor (MAOI) and started on venlafaxine, or who have recently had venlafaxine therapy discontinued prior to initiation of an MAOI. These reactions have included tremor, myoclonus, diaphoresis, nausea, vomiting, flushing, dizziness, hyperthermia with features resembling neuroleptic malignant syndrome, seizures, and death. In patients receiving antidepressants with pharmacological properties similar to venlafaxine in combination with an MAOI, there have also been reports of serious, sometimes fatal, reactions. For a selective serotonin reuptake inhibitor, these reactions have included hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital

signs, and mental status changes that include extreme agitation progressing to delirium and coma. Some cases presented with features resembling neuroleptic malignant syndrome. Severe hyperthermia and seizures, sometimes fatal, have been reported in association with the combined use of tricyclic antidepressants and MAOIs. These reactions have also been reported in patients who have recently discontinued these drugs and have been started on an MAOI. The effects of combined use of venlafaxine and MAOIs have not been evaluated in humans or animals. Therefore, because venlafaxine is an inhibitor of both norepinephrine and serotonin reuptake, it is recommended that Effexor XR (venlafaxine hydrochloride) extended-release capsules not be used in combination with an MAOI, or within at least 14 days of discontinuing treatment with an MAOI. Based on the half-life of venlafaxine, at least 7 days should be allowed after stopping venlafaxine before starting an MAOI.

Sustained Hypertension

Venlafaxine is associated with sustained increases in blood pressure in some patients. Among patients treated with 75-375 mg per day of Effexor XR in premarketing depression studies, 3% (19/705) experienced sustained hypertension [defined as treatment-emergent supine diastolic blood pressure (SDBP) ≥ 90 mm Hg and ≥ 10 mm Hg above baseline for 3 consecutive on-therapy visits]. Among patients treated with 75-225 mg per day of Effexor XR in premarketing GAD studies, 0.4% (2/476) experienced sustained hypertension. Experience with the immediate-release venlafaxine showed that sustained hypertension was dose-related, increasing from 3-7% at 100-300 mg per day to 13% at doses above 300 mg per day. An insufficient number of patients received mean doses of Effexor XR over 300 mg/day to fully evaluate the incidence of sustained increases in blood pressure at these higher doses.

In placebo-controlled premarketing depression studies with Effexor XR 75-225 mg/day, a final on-drug mean increase in supine diastolic blood pressure (SDBP) of 1.2 mm Hg was observed for Effexor XR-treated patients compared with a mean decrease of 0.2 mm Hg for placebo-treated patients. In placebo-controlled premarketing GAD studies with Effexor XR 75-225 mg/day, a final on-drug mean increase in SDBP of 1.1 mm Hg was observed for Effexor XR-treated patients compared with a mean decrease of 0.9 mm Hg for placebo-treated patients.

In premarketing depression and GAD studies, 0.7% (5/705) and 0.4% (2/476) of the Effexor XR-treated patients, respectively, discontinued treatment because of elevated blood pressure. Among these patients, most of the blood pressure increases were in a modest range (12-16 mm Hg, SDBP in depression studies; 22 mm Hg for the two patients discontinuing for hypertension in GAD studies).

Sustained increases of SDBP could have adverse consequences. Therefore, it is recommended that patients receiving Effexor XR have regular monitoring of blood pressure. For patients who experience a sustained increase in blood pressure while receiving venlafaxine, either dose reduction or discontinuation should be considered.

PRECAUTIONS

General

Insomnia and Nervousness

Treatment-emergent insomnia and nervousness were more commonly reported for patients treated with Effexor XR (venlafaxine hydrochloride) extended-release capsules than with placebo in pooled analyses of short-term depression and GAD studies, as shown in Table 1.

Table 1
Incidence of Insomnia and Nervousness in Placebo-Controlled Depression and GAD Trials

	Depression		GAD	
Symptom	Effexor XR n = 357	Placebo n = 285	Effexor XR n = 476	Placebo n = 201
Insomnia	17%	11%	22%	11%
Nervousness	10%	5%	12%	5%

Insomnia and nervousness each led to drug discontinuation in 0.9% of the patients treated with Effexor XR in Phase 3 depression studies.

In Phase 3 GAD trials, insomnia and nervousness led to drug discontinuation in 5% and 3%, respectively, of the patients treated with Effexor XR.

Changes in Appetite and Weight

Treatment-emergent anorexia was more commonly reported for Effexor XR-treated (8%) than placebo-treated patients (4%) in the pool of short-term depression studies. Significant weight loss, especially in underweight depressed patients, may be an undesirable result of Effexor XR treatment. A loss of 5% or more of body weight occurred in 7% of Effexor XR-treated and 2% of placebo-treated patients in placebo-controlled depression trials. Discontinuation rates for anorexia and weight loss associated with Effexor XR were low (1.0% and 0.1%, respectively, of Effexor XR-treated patients in Phase 3 depression studies).

In the pool of short-term GAD studies, treatment-emergent anorexia was reported in 13% and 2% of patients receiving Effexor XR and placebo, respectively. A loss of 7% or more of body weight occurred in 3% of the Effexor XR-treated and 0% of the placebo-treated patients in these trials. Discontinuation rates for anorexia and weight loss were low (1.7% and 0.2% respectively, of Effexor XR-treated patients).

Activation of Mania/Hypomania

During premarketing depression studies, mania or hypomania occurred in 0.3% of Effexor XR-treated patients and 0.0% placebo patients. In premarketing GAD studies, 0.0% of Effexor XR-treated patients and 0.5% of placebo-treated patients experienced mania or hypomania. In all premarketing depression trials with Effexor, mania or hypomania occurred in 0.5% of venlafaxine-treated patients compared with 0% of placebo patients. Mania/hypomania has also been reported in a small proportion of patients with mood disorders who were treated with other marketed antidepressants. As with all antidepressants, Effexor XR should be used cautiously in patients with a history of mania.

Mydriasis

Mydriasis has been reported in association with venlafaxine; therefore patients with raised intra-ocular pressure or at risk of acute narrow angle glaucoma should be monitored.

Seizures

During premarketing experience, no seizures occurred among 705 Effexor XR-treated patients in the depression studies or among 476 Effexor XR-treated patients in GAD studies. In all premarketing depression trials with Effexor, seizures were reported at various doses in 0.3% (8/3082) of venlafaxine-treated patients. Effexor XR, like many antidepressants, should be used cautiously in patients with a history of seizures and should be discontinued in any patient who develops seizures.

Suicide

The possibility of a suicide attempt is inherent in depression and may persist until significant remission occurs. Close supervision of high-risk patients should accompany initial drug therapy. Prescriptions for Effexor XR should be written for the smallest quantity of capsules consistent with good patient management in order to reduce the risk of overdose.

The same precautions observed when treating patients with depression should be observed when treating patients with GAD.

Use in Patients With Concomitant Illness

Premarketing experience with venlafaxine in patients with concomitant systemic illness is limited. Caution is advised in administering Effexor XR to patients with diseases or conditions that could affect hemodynamic responses or metabolism.

Venlafaxine has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were systematically excluded from many clinical studies during venlafaxine's premarketing testing. The electrocardiograms for 357 patients who received Effexor XR and 285 patients who received placebo in 8- to 12-week double-blind, placebo-controlled trials in depression and the electrocardiograms for 311 patients who received Effexor XR and 153 patients who received placebo in 8-week double-blind, placebo-controlled trials in GAD were analyzed. The mean change from baseline in corrected QT interval (QT_c) for Effexor XR-treated patients in depression studies was increased relative to that for placebo-treated patients (increase of 4.7 msec for Effexor XR and decrease of 1.9 msec for placebo). The clinical significance of these changes is unknown. The mean change from baseline in corrected QT interval (QT_c) for Effexor XR-treated patients in the GAD studies did not differ significantly from that with placebo.

In these same trials, the mean change from baseline in heart rate for Effexor XR-treated patients in the depression studies was significantly higher than that for placebo (a mean increase of 4 beats per minute for Effexor XR and 1 beat per minute for placebo). The mean change from baseline in heart rate for Effexor XR-treated patients in the GAD studies was significantly higher than that for placebo (a mean increase of 3 beats per minute for Effexor XR and no change for placebo). The clinical significance of these changes is unknown.

Evaluation of the electrocardiograms for 769 patients who received immediate release Effexor in 4- to 6-week double-blind, placebo-controlled trials showed that the incidence of trial-emergent conduction abnormalities did not differ from that with placebo.

In patients with renal impairment (GFR=10-70 mL/min) or cirrhosis of the liver, the clearances of venlafaxine and its active metabolites were decreased, thus prolonging the elimination half-lives of these substances. A lower dose may be necessary (see **"DOSAGE AND ADMINISTRATION"**). Effexor XR, like all antidepressants, should be used with caution in such patients.

Information for Patients

Physicians are advised to discuss the following issues with patients for whom they prescribe Effexor XR (venlafaxine hydrochloride) extended-release capsules:

Interference with Cognitive and Motor Performance

Clinical studies were performed to examine the effects of venlafaxine on behavioral performance of healthy individuals. The results revealed no clinically significant impairment of psychomotor, cognitive, or complex behavior performance. However, since any psychoactive drug may impair judgment, thinking, or motor skills, patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that venlafaxine therapy does not adversely affect their ability to engage in such activities.

Concomitant Medication

Patients should be advised to inform their physicians if they are taking, or plan to take, any prescription or over-the-counter drugs, since there is a potential for interactions.

Alcohol

Although venlafaxine has not been shown to increase the impairment of mental and motor skills caused by alcohol, patients should be advised to avoid alcohol while taking venlafaxine.

Allergic Reactions

Patients should be advised to notify their physician if they develop a rash, hives, or a related allergic phenomenon.

Pregnancy

Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy.

Nursing

Patients should be advised to notify their physician if they are breast-feeding an infant.

Laboratory Tests

There are no specific laboratory tests recommended.

Drug Interactions

As with all drugs, the potential for interaction by a variety of mechanisms is a possibility.

Alcohol

A single dose of ethanol (0.5 g/kg) had no effect on the pharmacokinetics of venlafaxine or O-desmethylvenlafaxine (ODV) when venlafaxine was administered at 150 mg/day in 15 healthy male subjects. Additionally, administration of venlafaxine in a stable regimen did not exaggerate the psychomotor and psychometric effects induced by ethanol in these same subjects when they were not receiving venlafaxine.

Cimetidine

Concomitant administration of cimetidine and venlafaxine in a steady-state study for both drugs resulted in inhibition of first-pass metabolism of venlafaxine in 18 healthy subjects. The oral clearance of venlafaxine was reduced by about 43%, and the exposure (AUC) and maximum concentration (C_{max}) of the drug were increased by about 60%. However, co-administration of cimetidine had no apparent effect on the pharmacokinetics of ODV, which is present in much greater quantity in the circulation than venlafaxine. The overall pharmacological activity of venlafaxine plus ODV is expected to increase only slightly, and no dosage adjustment should be necessary for most normal adults. However, for patients with pre-existing hypertension, and for elderly patients or patients with hepatic dysfunction, the interaction associated with the concomitant use of venlafaxine and cimetidine is not known and potentially could be more pronounced. Therefore, caution is advised with such patients.

Diazepam

Under steady-state conditions for venlafaxine administered at 150 mg/day, a single 10 mg dose of diazepam did not appear to affect the pharmacokinetics of either venlafaxine or ODV in 18 healthy male subjects. Venlafaxine also did not have any effect on the pharmacokinetics of diazepam or its active metabolite, desmethyldiazepam, or affect the psychomotor and psychometric effects induced by diazepam.

Haloperidol

Venlafaxine administered under steady-state conditions at 150 mg/day in 24 healthy subjects decreased total oral-dose clearance (Cl/F) of a single 2 mg dose of haloperidol by 42%, which resulted in a 70% increase in haloperidol AUC. In addition, the haloperidol C_{max} increased 88% when coadministered with venlafaxine, but the haloperidol elimination half-life ($t_{1/2}$) was unchanged. The mechanism explaining this finding is unknown.

Lithium

The steady-state pharmacokinetics of venlafaxine administered at 150 mg/day were not affected when a single 600 mg oral dose of lithium was administered to 12 healthy male subjects. ODV also was unaffected. Venlafaxine had no effect on the pharmacokinetics of lithium.

Drugs Highly Bound to Plasma Proteins

Venlafaxine is not highly bound to plasma proteins; therefore, administration of Effexor XR to a patient taking another drug that is highly protein bound should not cause increased free concentrations of the other drug.

Drugs that Inhibit Cytochrome P450 Isoenzymes

CYP2D6 Inhibitors: *In vitro* and *in vivo* studies indicate that venlafaxine is metabolized to its active metabolite, ODV, by CYP2D6, the isoenzyme that is responsible for the genetic polymorphism seen in the metabolism of many antidepressants. Therefore, the potential exists for a drug interaction between drugs that inhibit CYP2D6-mediated metabolism of venlafaxine, reducing the metabolism of venlafaxine to ODV, resulting in increased plasma concentrations of venlafaxine and decreased concentrations of the active metabolite. CYP2D6 inhibitors such as quinidine would be expected to do this, but the effect would be similar to what is seen in patients who are genetically CYP2D6 poor metabolizers (See "*Metabolism and Excretion*" under **"CLINICAL PHARMACOLOGY"**). Therefore, no dosage adjustment is required when venlafaxine is coadministered with a CYP2D6 inhibitor.

The concomitant use of venlafaxine with drug treatment(s) that potentially inhibits both CYP2D6 and CYP3A4, the primary metabolizing enzymes for venlafaxine, has not been studied. Therefore, caution is advised should a patient's therapy include venlafaxine and any agent(s) that produce simultaneous inhibition of these two enzymes systems.

Drugs Metabolized by Cytochrome P450 Isoenzymes

CYP2D6: *In vitro* studies indicate that venlafaxine is a relatively weak inhibitor of CYP2D6. These findings have been confirmed in a clinical drug interaction study comparing the effect of venlafaxine with that of fluoxetine on the CYP2D6-mediated metabolism of dextromethorphan to dextrorphan.

Imipramine - Venlafaxine did not affect the pharmacokinetics of imipramine and 2-OH-imipramine. However, desipramine AUC, C_{max}, and C_{min} increased by about 35% in the presence of venlafaxine. The 2-OH-desipramine AUC's increased by at least 2.5 fold (with venlafaxine 37.5 mg q12h) and by 4.5 fold (with venlafaxine 75 mg q12h). Imipramine did not affect the pharmacokinetics of venlafaxine and ODV. The clinical significance of elevated 2-OH-desipramine levels is unknown.

Risperidone - Venlafaxine administered under steady-state conditions at 150 mg/day slightly inhibited the CYP2D6-mediated metabolism of risperidone (administered as a single 1 mg oral dose) to its active metabolite, 9-hydroxyrisperidone, resulting in an approximate 32% increase in risperidone AUC. However, venlafaxine coadministration did not significantly alter the pharmacokinetic profile of the total active moiety (risperidone plus 9-hydroxyrisperidone.)

CYP3A4: Venlafaxine did not inhibit CYP3A4 *in vitro*. This finding was confirmed *in vivo* by clinical drug interaction studies in which venlafaxine did not inhibit the metabolism of several CYP3A4 substrates, including alprazolam, diazepam, and terfenadine.

Indinavir - In a study of 9 healthy volunteers, venlafaxine administered under steady-state conditions at 150 mg/day resulted in a 28% decrease in the AUC of a single 800 mg oral dose of indinavir and a 36% decrease in indinavir C_{max}. Indinavir did not affect the pharmacokinetics of venlafaxine and ODV. The clinical significance of this finding is unknown.

CYP1A2: Venlafaxine did not inhibit CYP1A2 *in vitro*. This finding was confirmed *in vivo* by a clinical drug interaction study in which venlafaxine did not inhibit the metabolism of caffeine, a CYP1A2 substrate.

CYP2C9: Venlafaxine did not inhibit CYP2C9 *in vitro*. The clinical significance of this finding is unknown.

CYP2C19: Venlafaxine did not inhibit the metabolism of diazepam, which is partially metabolized by CYP2C19 (see "Diazepam" above.)

Monoamine Oxidase Inhibitors
See **"CONTRAINDICATIONS"** and **"WARNINGS"**.

CNS-Active Drugs
The risk of using venlafaxine in combination with other CNS-active drugs has not been systematically evaluated (except in the case of those CNS-active drugs noted above). Consequently, caution is advised if the concomitant administration of venlafaxine and such drugs is required.

Electroconvulsive Therapy
There are no clinical data establishing the benefit of electroconvulsive therapy combined with Effexor XR (venlafaxine hydrochloride) extended-release capsules treatment.

Postmarketing Spontaneous Drug Interaction Reports
See **"ADVERSE REACTIONS," "Postmarketing Reports."**

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis
Venlafaxine was given by oral gavage to mice for 18 months at doses up to 120 mg/kg per day, which was 1.7 times the maximum recommended human dose on a mg/m^2 basis. Venlafaxine was also given to rats by oral gavage for 24 months at doses up to 120 mg/kg per day. In rats receiving the 120 mg/kg dose, plasma concentrations of venlafaxine at necropsy were 1 times (male rats) and 6 times (female rats) the plasma concentrations of patients receiving the maximum recommended human dose. Plasma levels of the O-desmethyl metabolite were lower in rats than in patients receiving the maximum recommended dose. Tumors were not increased by venlafaxine treatment in mice or rats.

Mutagenesis
Venlafaxine and the major human metabolite, O-desmethylvenlafaxine (ODV), were not mutagenic in the Ames reverse mutation assay in Salmonella bacteria or the Chinese hamster ovary/HGPRT mammalian cell forward gene mutation assay. Venlafaxine was also was not mutagenic or clastogenic in the *in vitro* BALB/c-3T3 mouse cell transformation assay, the sister chromatid exchange assay in cultured Chinese hamster ovary cells, or in the *in vivo* chromosomal aberration assay in rat bone marrow. ODV was not clastogenic in the *in vitro* Chinese hamster ovary cell chromosomal aberration assay, but elicited a clastogenic response in the *in vivo* chromosomal aberration assay in rat bone marrow.

Impairment of Fertility
Reproduction and fertility studies in rats showed no effects on male or female fertility at oral doses of up to 2 times the maximum recommended human dose on a mg/m^2 basis.

Pregnancy

Teratogenic Effects - Pregnancy Category C
Venlafaxine did not cause malformations in offspring of rats or rabbits given doses up to 2.5 times (rat) or 4 times (rabbit) the maximum recommended human daily dose on a mg/m^2 basis. However, in rats, there was a decrease in pup weight, an increase in stillborn pups, and an increase in pup deaths during the first 5 days of lactation, when dosing began during pregnancy and continued until weaning. The cause of these deaths is not known. These effects occurred at 2.5 times (mg/m^2) the maximum human daily dose. The no effect dose for rat pup mortality was 0.25 times the human dose on a mg/m^2 basis. There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Labor and Delivery
The effect of venlafaxine on labor and delivery in humans is unknown.

Nursing Mothers
Venlafaxine and ODV have been reported to be excreted in human milk. Because of the potential for serious adverse reactions in nursing infants from Effexor XR, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use
Safety and effectiveness in pediatric patients have not been established.

Geriatric Use
Approximately 4% (14/357) and 3% (14/476) of Effexor XR-treated patients in placebo-controlled premarketing depression and GAD trials, respectively, were 65 years of age or over. Of 2,897 Effexor-treated patients in premarketing phase depression studies, 12% (357) were 65 years of age or over. No overall differences in effectiveness or safety were observed between geriatric patients and younger patients, and other reported clinical experience generally has not identified differences in response between the elderly and younger patients. However, greater sensitivity of some older individuals cannot be ruled out. As with other antidepressants, several cases of hyponatremia and syndrome of inappropriate antidiuretic hormone secretion (SIADH) have been reported, usually in the elderly.

The pharmacokinetics of venlafaxine and ODV are not substantially altered in the elderly (see **"CLINICAL PHARMACOLOGY"**). No dose adjustment is recommended for the elderly on the basis of age alone, although other clinical circumstances, some of which may be more common in the elderly, such as renal or hepatic impairment, may warrant a dose reduction (see **"DOSAGE AND ADMINISTRATION"**).

ADVERSE REACTIONS

The information included in the Adverse Findings Observed in Short-Term, Placebo-Controlled Studies with Effexor® XR subsection is based on data from a pool of three 8- and 12-week controlled clinical trials in depression (includes two U.S. trials and one European trial) and from a pool of two 8-week controlled clinical trials in GAD with Effexor XR. Information on additional adverse events associated with Effexor XR in the entire development program for the formulation and with Effexor (the immediate release formulation of venlafaxine) is included in the **"Other Adverse Events Observed During the Premarketing Evaluation of Effexor and Effexor XR"** subsection (See also **"WARNINGS"** and **"PRECAUTIONS"**).

Adverse Findings Observed in Short-Term, Placebo-Controlled Studies with Effexor XR

Adverse Events Associated with Discontinuation of Treatment

Approximately 11% of the 357 patients who received Effexor XR (venlafaxine hydrochloride) extended-release capsules in placebo-controlled clinical trials for depression discontinued treatment due to an adverse experience, compared with 6% of the 285 placebo-treated patients in those studies. Approximately 23% of the 476 patients who received Effexor XR capsules in placebo-controlled clinical trials for GAD discontinued treatment due to an adverse experience, compared with 10% of the 201 placebo-treated patients in those studies. The most common events leading to discontinuation and considered to be drug-related (i.e., leading to discontinuation in at least 1% of the Effexor XR-treated patients at a rate at least twice that of placebo for either indication) are shown in Table 2.

Table 2
Common Adverse Events Leading to Discontinuation of Treatment in Placebo-Controlled Trials[1]

Adverse Event	Percentage of Patients Discontinuing Due to Adverse Event			
	Depression Indication[2]		GAD Indication	
	Effexor XR n=357	Placebo n=285	Effexor XR n=476	Placebo n=201
Body as a Whole				
Headache	--	--	4%	<1%
Asthenia	--	--	3%	<1%
Cardiovascular System				
Vasodilatation	--	--	1%	0%
Digestive System				
Nausea	4%	<1%	10%	<1%
Anorexia	1%	<1%	2%	<1%
Dry Mouth	1%	0%	2%	<1%
Nervous System				
Dizziness	2%	1%	4%	1%
Insomnia	1%	<1%	5%	2%
Nervousness	--	--	3%	<1%
Somnolence	2%	<1%	4%	<1%
Thinking abnormal	--	--	1%	0%
Tremor	--	--	1%	0%
Special Senses				
Abnormal Vision	--	--	1%	0%

[1] Two of the depression studies were flexible dose and one was fixed dose. The two GAD studies were fixed dose.
[2] In U.S. placebo-controlled trials for depression, the following were also common events leading to discontinuation and were considered to be drug-related for Effexor XR-treated patients (% Effexor XR [n = 192], % Placebo [n = 202]: hypertension (1%, <1%); diarrhea (1%, 0%); paresthesia (1%, 0%); tremor (1%, 0%); abnormal vision, mostly blurred vision (1%, 0%); and abnormal, mostly delayed, ejaculation (1%, 0%).

Adverse Events Occurring at an Incidence of 2% or More Among Effexor XR-Treated Patients

Tables 3 and 4 enumerate the incidence, rounded to the nearest percent, of treatment-emergent adverse events that occurred during acute therapy of depression (up to 12 weeks) and of GAD (up to 8 weeks), respectively, in 2% or more of patients treated with Effexor XR (dose range of 75 to 225 mg/day) where the incidence in patients treated with Effexor XR was greater than the incidence for the respective placebo-treated patients. The table shows the percentage of patients in each group who had at least one episode of an event at some time during their treatment. Reported adverse events were classified using a standard COSTART-based Dictionary terminology.

The prescriber should be aware that these figures cannot be used to predict the incidence of side effects in the course of usual medical practice where patient characteristics and other factors differ from those which prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and nondrug factors to the side effect incidence rate in the population studied.

Commonly Observed Adverse Events from Tables 3 and 4:

Depression

Note in particular the following adverse events that occurred in at least 5% of the Effexor XR patients and at a rate at least twice that of the placebo group for all placebo-controlled trials for the depression indication (Table 3): Abnormal ejaculation, gastrointestinal complaints (nausea, dry mouth, and anorexia), CNS complaints (dizziness, somnolence, and abnormal dreams), and sweating. In the two U.S. placebo-controlled trials, the following additional events occurred in at least 5% of Effexor XR-treated patients (n = 192) and at a rate at least twice that of the placebo group: Abnormalities of sexual function (impotence in men, anorgasmia in women, and libido decreased), gastrointestinal complaints (constipation and flatulence), CNS complaints (insomnia, nervousness, and tremor), problems of special senses (abnormal vision), cardiovascular effects (hypertension and vasodilatation), and yawning

Generalized Anxiety Disorder

Note in particular the following adverse events that occurred in at least 5% of the Effexor XR patients and at a rate at least twice that of the placebo group for all placebo-controlled trials for the GAD indication (Table 4): Abnormalities of sexual function (abnormal ejaculation and impotence in men, and libido decreased), gastrointestinal complaints (nausea, dry mouth, anorexia, constipation, and vomiting), CNS complaints (insomnia and nervousness), problems of special senses (abnormal vision), cardiovascular complaints (vasodilatation), yawning, and sweating

TABLE 3
Treatment-Emergent Adverse Event Incidence in Short-Term Placebo-Controlled Effexor XR Clinical Trials in Depressed Patients[1,2]

Body System Preferred Term	% Reporting Event Effexor XR (n=357)	 Placebo (n=285)
Body as a Whole		
Asthenia	8%	7%
Cardiovascular System		
Vasodilatation[3]	4%	2%
Hypertension	4%	1%
Digestive System		
Nausea	31%	12%
Constipation	8%	5%
Anorexia	8%	4%
Vomiting	4%	2%
Flatulence	4%	3%
Metabolic/Nutritional		
Weight Loss	3%	0%
Nervous System		
Dizziness	20%	9%
Somnolence	17%	8%
Insomnia	17%	11%
Dry Mouth	12%	6%
Nervousness	10%	5%
Abnormal Dreams[4]	7%	2%
Tremor	5%	2%
Depression	3%	<1%
Paresthesia	3%	1%
Libido Decreased	3%	<1%
Agitation	3%	1%
Respiratory System		
Pharyngitis	7%	6%
Yawn	3%	0%
Skin		
Sweating	14%	3%
Special Senses		
Abnormal Vision[5]	4%	<1%
Urogenital System		
Abnormal Ejaculation	16%	<1%
(male)[6,7]	4%	<1%

Impotence[7]	3%	<1%
Anorgasmia (female)[8,9]		

[1] Incidence, rounded to the nearest %, for events reported by at least 2% of patients treated with Effexor XR, except the following events which had an incidence equal to or less than placebo: abdominal pain, accidental injury, anxiety, back pain, bronchitis, diarrhea, dysmenorrhea, dyspepsia, flu syndrome, headache, infection, pain, palpitation, rhinitis, and sinusitis.
[2] <1% indicates an incidence greater than zero but less than 1%.
[3] Mostly "hot flashes."
[4] Mostly "vivid dreams," "nightmares," and "increased dreaming."
[5] Mostly "blurred vision" and "difficulty focusing eyes."
[6] Mostly "delayed ejaculation."
[7] Incidence is based on the number of male patients.
[8] Mostly "delayed orgasm" or "anorgasmia."
[9] Incidence is based on the number of female patients.

TABLE 4
Treatment-Emergent Adverse Event Incidence in Short-Term Placebo-Controlled Effexor XR Clinical Trials in GAD Patients[1,2]

	% Reporting Event	
Body System Preferred Term	**Effexor XR** (n=476)	**Placebo** (n=201)
Body as a Whole		
Asthenia	16%	9%
Infection[3]	10%	9%
Abdominal Pain	6%	5%
Fever	3%	<1%
Neck Pain	3%	2%
Chills	3%	<1%
Cardiovascular System		
Vasodilatation[4]	6%	2%
Tachycardia	3%	2%
Digestive System		
Nausea	43%	11%
Anorexia	13%	2%
Diarrhea	12%	10%
Constipation	12%	5%
Vomiting	6%	2%
Flatulence	3%	1%
Musculoskeletal System		
Myalgia	4%	3%
Nervous System		
Dry Mouth	23%	5%
Insomnia	22%	11%
Dizziness	20%	11%
Somnolence	20%	11%
Nervousness	12%	5%
Libido Decreased	6%	2%
Abnormal Dreams[5]	4%	2%
Tremor	4%	<1%
Paresthesia	3%	<1%
Thinking Abnormal[6]	2%	1%
Trismus	2%	0%
Twitching	2%	<1%
Respiratory System		
Rhinitis	8%	6%
Yawn	6%	<1%
Cough Increased	3%	2%
Skin		
Sweating	11%	<1%
Special Senses		
Abnormal Vision[7]	8%	0%
Urogenital System		
Abnormal Ejaculation (male)[8,9]	17%	0%
Impotence[9]	6%	1%
Dysmenorrhrea[10]	6%	5%
Orgasmic Dysfunction (female)[10,11]	4%	0%
Urinary Frequency	3%	2%

[1] Incidence, rounded to the nearest %, for events reported by at least 2% of patients treated with Effexor XR, except the following events which had an incidence equal to or less than placebo: accidental injury, agitation, back pain, depression, dyspepsia, flu syndrome, headache, hypertonia, pain, palpitation, pharyngitis, sinusitis, and tinnitus.
[2] <1% indicates an incidence greater than zero but less than 1%.
[3] Mostly upper respiratory infections.
[4] Mostly "hot flashes."
[5] Mostly "vivid dreams," "nightmares," and "increased dreaming."
[6] Mostly "difficulty concentrating."
[7] Mostly "blurred vision" and "difficulty focusing eyes."
[8] Mostly "delayed ejaculation," includes "anorgasmia."
[9] Incidence is based on the number of male patients.
[10] Incidence is based on the number of female patients.
[11] Mostly "delayed orgasm" and includes "abnormal orgasm" and "anorgasmia "

Vital Sign Changes
Effexor XR (venlafaxine hydrochloride) extended-release capsules treatment for up to 12 weeks in premarketing placebo-controlled depression trials was associated with a mean final on-therapy increase in pulse rate of approximately 2 beats per minute, compared with 1 beat per minute for placebo. Effexor XR treatment for up to 8 weeks in premarketing placebo-controlled GAD trials was associated with a mean final on-therapy increase in pulse rate of approximately 2 beats per minute, compared with less than 1 beat per minute for placebo. (See the **"Sustained Hypertension"** section of **"WARNINGS"** for effects on blood pressure).

Laboratory Changes
Effexor XR (venlafaxine hydrochloride) extended-release capsules treatment for up to 12 weeks in premarketing placebo-controlled depression trials and for up to 8 weeks in premarketing placebo-controlled GAD trials was associated with a mean final on-therapy increases in serum cholesterol concentration of approximately 1.5 mg/dL and 2.5 mg/dL, respectively. These changes are of unknown clinical significance.

ECG Changes
(See the "*Use in Patients with Concomitant Illnesses*" section of **"PRECAUTIONS"**).

Other Adverse Events Observed During the Premarketing Evaluation of Effexor and Effexor XR

During its premarketing assessment, multiple doses of Effexor XR were administered to 705 patients in phase 3 depression studies and Effexor was administered to 96 patients. During its premarketing assessment, multiple doses of Effexor XR were administered to 476 patients in phase 3 GAD studies. In addition, in premarketing assessment of Effexor, multiple doses were administered to 2897 patients in phase 2-3 depression studies. The conditions and duration of exposure to venlafaxine in both development programs varied greatly, and included (in overlapping categories) open and double-blind studies, uncontrolled and controlled studies, inpatient (Effexor only) and outpatient studies, fixed-dose, and titration studies. Untoward events associated with this exposure were recorded by clinical investigators using terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of untoward events into a smaller number of standardized event categories.

In the tabulations that follow, reported adverse events were classified using a standard COSTART-based Dictionary terminology. The frequencies presented, therefore, represent the proportion of the 4174 patients exposed to multiple doses of either formulation of venlafaxine who experienced an event of the type cited on at least one occasion while receiving venlafaxine. All reported events are included except those already listed in Tables 3 and 4 and those events for which a drug cause was remote. If the COSTART term for an event was so general as to be uninformative, it was replaced with a more informative term. It is important to emphasize that, although the events reported occurred during treatment with venlafaxine, they were not necessarily caused by it.

Events are further categorized by body system and listed in order of decreasing frequency using the following definitions: **frequent** adverse events are defined as those occurring on one or more occasions in at least 1/100 patients; **infrequent** adverse events are those occurring in 1/100 to 1/1000 patients; **rare** events are those occurring in fewer than 1/1000 patients.

Body as a whole - **Frequent**: chest pain substernal; **Infrequent**: face edema, intentional injury, malaise, moniliasis, neck rigidity, pelvic pain, photosensitivity reaction, suicide attempt; **Rare**: appendicitis, carcinoma, cellulitis, withdrawal syndrome.

Cardiovascular system - **Frequent**: migraine, postural hypotension; **Infrequent**: angina pectoris, arrhythmia, extrasystoles, hypotension, peripheral vascular disorder (mainly cold feet and/or cold hands), syncope, thrombophlebitis; **Rare**: arteritis, first-degree atrioventricular block, bigeminy, bradycardia, bundle branch block, cerebral ischemia, coronary artery disease, congestive heart failure, heart arrest, mitral valve disorder, mucocutaneous hemorrhage, myocardial infarct, pallor.

Digestive system - **Frequent**: eructation, increased appetite; **Infrequent**: bruxism, colitis, dysphagia, tongue edema, esophagitis, gastritis, gastroenteritis, gastrointestinal ulcer, gingivitis, glossitis, rectal hemorrhage, hemorrhoids, melena, stomatitis, mouth ulceration; **Rare**: cheilitis, cholecystitis, cholelithiasis, hematemesis, gastrointestinal hemorrhage, gum hemorrhage, hepatitis, ileitis, jaundice, intestinal obstruction, oral moniliasis, proctitis, increased salivation, soft stools, tongue discoloration.

Endocrine system - **Rare**: goiter, hyperthyroidism, hypothyroidism, thyroid nodule, thyroiditis.

Hemic and lymphatic system - **Frequent**: ecchymosis; **Infrequent**: anemia, leukocytosis, leukopenia, lymphadenopathy, thrombocythemia, thrombocytopenia; **Rare**: basophilia, cyanosis, eosinophilia, lymphocytosis.

Metabolic and nutritional - **Frequent**: edema, weight gain; **Infrequent**: alkaline phosphatase increased, glycosuria, hypercholesteremia, hyperglycemia, hyperuricemia, hypoglycemia, hypokalemia, SGOT increased, thirst; **Rare**: alcohol intolerance, bilirubinemia, BUN increased, creatinine increased, diabetes mellitus, dehydration, gout, hemochromatosis, hypercalcinuria, hyperkalemia, hyperlipemia, hyperphosphatemia, hyponatremia, hypophosphatemia, hypoproteinemia, SGPT increased, uremia.

Musculoskeletal system - **Frequent**: arthralgia; **Infrequent**: arthritis, arthrosis, bone pain, bone spurs, bursitis, leg cramps, myasthenia, tenosynovitis; **Rare**: pathological fracture, myopathy, osteoporosis, osteosclerosis, rheumatoid arthritis, tendon rupture.

Nervous system - **Frequent**: amnesia, confusion, depersonalization, emotional lability, hypesthesia, vertigo; **Infrequent**: apathy, ataxia, circumoral paresthesia, CNS stimulation, euphoria, hallucinations, hostility, hyperesthesia, hyperkinesia, hypotonia, incoordination, libido increased, manic reaction, myoclonus, neuralgia, neuropathy, paranoid reaction, psychosis, seizure, abnormal speech, stupor; **Rare**: akathisia, akinesia, alcohol abuse, aphasia, bradykinesia, buccoglossal syndrome, cerebrovascular accident, loss of consciousness, delusions, dementia, dystonia, facial paralysis, abnormal gait, Guillain-Barre Syndrome, hypokinesia, neuritis, nystagmus, psychotic depression, reflexes decreased, reflexes increased, suicidal ideation, torticollis.

Respiratory system - **Frequent**: dyspnea; **Infrequent**: asthma, chest congestion, epistaxis, hyperventilation, laryngismus, laryngitis, pneumonia, voice alteration; **Rare**: atelectasis, hemoptysis, hypoventilation, hypoxia, pleurisy, pulmonary embolus, sleep apnea.

Skin and appendages - **Frequent**: rash, pruritus; **Infrequent**: acne, alopecia, brittle nails, contact dermatitis, dry skin, eczema, skin hypertrophy, maculopapular rash, psoriasis, urticaria; **Rare**: erythremia nodosum, exfoliative dermatitis, lichenoid dermatitis, hair discoloration, skin discoloration, furunculosis, hirsutism, leukoderma, pustular rash, vesiculobullous rash, seborrhea, skin atrophy, skin striae.

Special senses - **Frequent**: abnormality of accommodation, mydriasis, taste perversion; **Infrequent**: cataract, conjunctivitis, corneal lesion, diplopia, dry eyes, exophthalmos, eye pain, hyperacusis, otitis media, parosmia, photophobia, taste loss, visual field defect; **Rare**: blepharitis, chromatopsia, conjunctival edema, deafness, glaucoma, retinal hemorrhage, subconjunctival hemorrhage, keratitis, labyrinthitis, miosis, papilledema, decreased pupillary reflex, otitis externa, scleritis, uveitis.

Urogenital system - **Frequent**: metrorrhagia,* prostatitis,* urination impaired, vaginitis*; **Infrequent**: albuminuria, amenorrhea,* cystitis, dysuria, hematuria, female lactation,* leukorrhea,* menorrhagia,* nocturia, bladder pain, breast pain, polyuria, pyuria, urinary incontinence, urinary retention, urinary urgency, vaginal hemorrhage*; **Rare**: abortion,* anuria, breast engorgement, breast enlargement, fibrocystic breast, calcium crystalluria, cervicitis,* ovarian cyst,* prolonged erection,* gynecomastia (male),* hypomenorrhea,* kidney calculus, kidney pain, kidney function abnormal, mastitis, menopause,* pyelonephritis, oliguria, salpingitis,* urolithiasis, uterine hemorrhage,* uterine spasm.*
*Based on the number of men and women as appropriate.

Postmarketing Reports
Voluntary reports of other adverse events temporally associated with the use of Effexor (the immediate release form of venlafaxine) that have been received since market introduction and that may have no causal relationship with the use of Effexor include the following: agranulocytosis, anaphylaxis, aplastic anemia, catatonia, congenital anomalies, CPK increased, deep vein thrombophlebitis, delirium, EKG abnormalities (such as atrial fibrillation, supraventricular tachycardia, ventricular extrasystoles, ventricular tachycardia), epidermal necrosis/Stevens-Johnson Syndrome, erythema multiforme, extrapyramidal symptoms (including tardive dyskinesia), hemorrhage (including eye and gastrointestinal bleeding), hepatic events (including GGT elevation; abnormalities of unspecified liver function tests; liver damage, necrosis, or failure; and fatty liver), involuntary movements, LDH increased, neuroleptic malignant syndrome-like events (including a case of a 10-year-old who may have been taking methylphenidate, was treated and recovered), pancreatitis, panic, prolactin increased, renal failure, serotonin syndrome, shock-like electrical sensations (in some cases, subsequent to the discontinuation of Effexor or tapering of dose), and syndrome of inappropriate antidiuretic hormone secretion (usually in the elderly).

There have been reports of elevated clozapine levels that were temporally associated with adverse events, including seizures, following the addition of venlafaxine. There have been reports of increases in prothrombin time, partial thromboplastin time, or INR when venlafaxine was given to patients receiving warfarin therapy.

DRUG ABUSE AND DEPENDENCE

Controlled Substance Class
Effexor XR (venlafaxine hydrochloride) extended-release capsules is not a controlled substance.

Physical and Psychological Dependence
In vitro studies revealed that venlafaxine has virtually no affinity for opiate, benzodiazepine, phencyclidine (PCP), or N-methyl-D-aspartic acid (NMDA) receptors.

Venlafaxine was not found to have any significant CNS stimulant activity in rodents. In primate drug discrimination studies, venlafaxine showed no significant stimulant or depressant abuse liability.

The discontinuation effects of Effexor XR have not been systematically evaluated in controlled clinical trials (See "**DOSAGE AND ADMINISTRATION**").

While venlafaxine has not been systematically studied in clinical trials for its potential for abuse, there was no indication of drug-seeking behavior in the clinical trials. However, it is not possible to predict on the basis of premarketing experience the extent to which a CNS active drug will be misused, diverted, and/or abused once marketed. Consequently, physicians should carefully evaluate patients for history of drug abuse and follow such patients closely, observing them for signs of misuse or abuse of venlafaxine (e.g., development of tolerance, incrementation of dose, drug-seeking behavior).

OVERDOSAGE

Human Experience

Among the patients included in the premarketing evaluation of Effexor XR, there were 2 reports of acute overdosage with Effexor XR in depression trials, either alone or in combination with other drugs. One patient took a combination of 6 g of Effexor XR and 2.5 mg of lorazepam. This patient was hospitalized, treated symptomatically, and recovered without any untoward effects. The other patient took 2.85 g of Effexor XR. This patient reported paresthesia of all four limbs but recovered without sequelae.

There were 2 reports of acute overdose with Effexor XR in GAD trials. One patient took a combination of 0.75 g of Effexor XR and 200 mg of paroxetine and 50 mg of zolpidem. This patient was described as being alert, able to communicate, and a little sleepy. This patient was hospitalized, treated with activated charcoal, and recovered without any untoward effects. The other patient took 1.2 g of Effexor XR. This patient recovered and no other specific problems were found. The patient had moderate dizziness, nausea, numb hands and feet, and hot-cold spells 5 days after the overdose. These symptoms resolved over the next week.

Among the patients included in the premarketing evaluation with Effexor, there were 14 reports of acute overdose with venlafaxine, either alone or in combination with other drugs and/or alcohol. The majority of the reports involved ingestion in which the total dose of venlafaxine taken was estimated to be no more than several-fold higher than the usual therapeutic dose. The 3 patients who took the highest doses were estimated to have ingested approximately 6.75 g, 2.75 g, and 2.5 g. The resultant peak plasma levels of venlafaxine for the latter 2 patients were 6.24 and 2.35 µg/mL, respectively, and the peak plasma levels of O-desmethylvenlafaxine were 3.37 and 1.30 µg/mL, respectively. Plasma venlafaxine levels were not obtained for the patient who ingested 6.75 g of venlafaxine. All 14 patients recovered without sequelae. Most patients reported no symptoms. Among the remaining patients, somnolence was the most commonly reported symptom. The patient who ingested 2.75 g of venlafaxine was observed to have 2 generalized convulsions and a prolongation of QTc to 500 msec, compared with 405 msec at baseline. Mild sinus tachycardia was reported in 2 of the other patients.

In postmarketing experience, overdose with venlafaxine has occurred predominantly in combination with alcohol and/or other drugs. Electrocardiogram changes (e.g. prolongation of QT interval, bundle branch block, QRS prolongation), sinus and ventricular tachycardia, bradycardia, hypotension, altered level of consciousness (ranging from somnolence to coma), seizures, vertigo, and death have been reported.

Management of Overdosage

Treatment should consist of those general measures employed in the management of overdosage with any antidepressant.

Ensure an adequate airway, oxygenation, and ventilation. Monitor cardiac rhythm and vital signs. General supportive and symptomatic measures are also recommended. Induction of emesis is not recommended. Gastric lavage with a large bore orogastric tube with appropriate airway protection, if needed, may be indicated if performed soon after ingestion or in symptomatic patients.

Activated charcoal should be administered. Due to the large volume of distribution of this drug, forced diuresis, dialysis, hemoperfusion, and exchange transfusion are unlikely to be of benefit. No specific antidotes for venlafaxine are known.

In managing overdosage, consider the possibility of multiple drug involvement. The physician should consider contacting a poison control center for additional information on the treatment of any overdose. Telephone numbers for certified poison control centers are listed in the *Physicians' Desk Reference* (PDR).

DOSAGE AND ADMINISTRATION

Effexor XR should be administered in a single dose with food either in the morning or in the evening at approximately the same time each day. Each capsule should be swallowed whole with fluid and not divided, crushed, chewed, or placed in water.

Initial Treatment

Depression

For most patients, the recommended starting dose for Effexor XR is 75 mg/day, administered in a single dose. In the clinical trials establishing the efficacy of Effexor XR in moderately depressed outpatients, the initial dose of venlafaxine was 75 mg/day. For some patients, it may be desirable to start at 37.5 mg/day for 4 to 7 days, to allow new patients to adjust to the medication before increasing to 75 mg/day. While the relationship between dose and antidepressant response for Effexor XR has not been adequately explored, patients not responding to the initial 75 mg/day dose may benefit from dose increases to a maximum of approximately 225 mg/day. Dose increases should be in increments of up to 75 mg/day, as needed, and should be made at intervals of not less than 4 days, since steady state plasma levels of venlafaxine and its major metabolites are achieved in most patients by day 4. In the clinical trials establishing efficacy, upward titration was permitted at intervals of 2 weeks or more; the average doses were about 140-180 mg/day (see **"Clinical Trials"** under **"CLINICAL PHARMACOLOGY"**).

It should be noted that, while the maximum recommended dose for moderately depressed outpatients is also 225 mg/day for Effexor (the immediate release form of venlafaxine), more severely depressed inpatients in one study of the development program for that product responded to a mean dose of 350 mg/day (range of 150 to 375 mg/day). Whether or not higher doses of Effexor XR are needed for more severely depressed patients is unknown; however, the experience with Effexor XR doses higher than 225 mg/day is very limited.

Generalized Anxiety Disorder
For most patients, the recommended starting dose for Effexor XR is 75 mg/day, administered in a single dose. In clinical trials establishing the efficacy of Effexor XR in outpatients with Generalized Anxiety Disorder (GAD), the initial dose of venlafaxine was 75 mg/day. For some patients, it may be desirable to start at 37.5 mg/day for 4 to 7 days, to allow new patients to adjust to the medication before increasing to 75 mg/day. Although a dose-response relationship for effectiveness in GAD was not clearly established in fixed-dose studies, certain patients not responding to the initial 75 mg/day dose may benefit from dose increases to a maximum of approximately 225 mg/day. Dose increases should be in increments of up to 75 mg/day, as needed, and should be made at intervals of not less than 4 days.

Switching Patients from Effexor Tablets
Depressed patients who are currently being treated at a therapeutic dose with Effexor may be switched to Effexor XR at the nearest equivalent dose (mg/day), e.g., 37.5 mg venlafaxine two-times-a-day to 75 mg Effexor XR once daily. However, individual dosage adjustments may be necessary.

Patients with Hepatic Impairment
Given the decrease in clearance and increase in elimination half-life for both venlafaxine and ODV that is observed in patients with hepatic cirrhosis compared with normal subjects (see **"CLINICAL PHARMACOLOGY"**), it is recommended that the starting dose be reduced by 50% in patients with moderate hepatic impairment. Because there was much individual variability in clearance between patients with cirrhosis, individualization of dosage may be desirable in some patients.

Patients with Renal Impairment
Given the decrease in clearance for venlafaxine and the increase in elimination half-life for both venlafaxine and ODV that is observed in patients with renal impairment (GFR = 10-70 mL/min) compared with normal subjects (see **"CLINICAL PHARMACOLOGY"**), it is recommended that the total daily dose be reduced by 25%-50%. In patients undergoing hemodialysis, it is recommended that the total daily dose be reduced by 50% and that the dose be withheld until the dialysis treatment is completed (4 hrs). Because there was much individual variability in clearance between

patients with renal impairment, individualization of dosage may be desirable in some patients.

Elderly Patients
No dose adjustment is recommended for elderly patients solely on the basis of age. As with any drug for the treatment of depression or generalized anxiety disorder, however, caution should be exercised in treating the elderly. When individualizing the dosage, extra care should be taken when increasing the dose.

Maintenance/Extended Treatment
There is no body of evidence available from controlled trials to indicate how long patients with depression or generalized anxiety disorder should be treated with Effexor XR.

It is generally agreed, however, that pharmacological treatment for acute episodes of depression should continue for up to six months or longer. Whether the dose of antidepressant needed to induce remission is identical to the dose needed to maintain euthymia is unknown.

In patients with Generalized Anxiety Disorder, there are no efficacy data beyond eight weeks of treatment with Effexor XR. The need for continuing medication in patients with GAD who improve with Effexor XR treatment should be periodically reassessed.

Discontinuing Effexor XR
When discontinuing Effexor XR after more than 1 week of therapy, it is generally recommended that the dose be tapered to minimize the risk of discontinuation symptoms. In clinical trials with Effexor XR, tapering was achieved by reducing the daily dose by 75 mg at 1 week intervals. Individualization of tapering may be necessary. While the discontinuation effects of Effexor XR have not been systematically evaluated in controlled clinical trials, retrospective surveys of new events occurring during taper or following discontinuation revealed the following six events that occurred at an incidence of at least 3% and for which the incidence for Effexor XR was at least twice the placebo incidence in depression trials: dizziness, dry mouth, insomnia, nausea, nervousness, and sweating. The following nine events occurred at an incidence of at least 3% and had an incidence for Effexor XR that was at least twice the placebo incidence in GAD trials: anorexia, diarrhea, dizziness, dry mouth, insomnia, nausea, nervousness, somnolence, and sweating.

Switching Patients To or From a Monoamine Oxidase Inhibitor
At least 14 days should elapse between discontinuation of an MAOI and initiation of therapy with Effexor XR. In addition, at least 7 days should be allowed after stopping Effexor XR before starting an MAOI (see "**CONTRAINDICATIONS**" and "**WARNINGS**").

HOW SUPPLIED
Effexor® XR (venlafaxine hydrochloride) extended-release capsules are available as follows:

37.5 mg, grey cap/peach body with "**W**" and "Effexor XR" on the cap and "37.5" on the body.

NDC 0008-0837-01, bottle of 100 capsules.
NDC 0008-0837-03, carton of 10 Redipak® blister strips of 10 capsules each.

Store at controlled room temperature, 20°C to 25°C (68°F to 77°F).
Bottles: Protect from light. Dispense in light-resistant container.
Blisters: Protect from light. Use blister carton to protect contents from light.

75 mg, peach cap and body with "**W**" and "Effexor XR" on the cap and "75" on the body.

NDC 0008-0833-01, bottle of 100 capsules.
NDC 0008-0833-03, carton of 10 Redipak® blister strips of 10 capsules each.

Store at controlled room temperature, 20°C to 25°C (68°F to 77°F).

150 mg, dark orange cap and body with "**W**" and "Effexor XR" on the cap and "150" on the body.

NDC 0008-0836-01, bottle of 100 capsules.
NDC 0008-0836-03, carton of 10 Redipak® blister strips of 10 capsules each.

Store at controlled room temperature, 20°C to 25°C (68°F to 77°F).

Wyeth Laboratories Inc.®
A Wyeth-Ayerst Company
Philadelphia, PA 19101

CI 4876-5 Revised December 9, 1999 Printed in USA

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-699/S-012

MEDICAL REVIEW(S)

MAR - 3 2000

34.1

Review and Evaluation of Clinical Data
NDA #20-699

Sponsor:	Wyeth-Ayerst Research
Drug:	Effexor XR Capsules
Proposed Indication:	Depression, GAD
Material Submitted:	SLR-012: Changes Being Effected
Correspondence Date:	December 20, 1999
Date Received:	December 22, 1999

I. Background

The sponsor (W-A) is proposing a number of modifications to Effexor XR labeling as "Changes Being Effected" (CBE) under the provisions of 21 CFR 314.70(c)(2)(i) and (ii). These changes were to be implemented on or before February 15, 2000. Many of these changes were proposed for the labeling for Effexor and were submitted in a CBE supplement (SLR-015) to NDA 20-151 on December 29, 1999.[1]

The modifications to Effexor XR labeling are reviewed below.

II. Proposed Labeling Changes

A. DESCRIPTION

A Special Supplement - Changes Being Effected submitted on 8-5-99 provided for a new capsule [ ] gray cap that contains [ ] dyes for the 37.5 mg Effexor XR Capsule product. These additional inactive ingredients have been added to this section of labeling (D&C Red #28, D&C Yellow #10, and FD&C Blue #1).

This change is pending review by the Office of New Drug Chemistry (ONDC) reviewer, Dr. Robert Seevers.

B. WARNINGS/Sustained Hypertension

An editorial change was made to the last sentence of the first paragraph to clarify the meaning of this statement

[1] See my Review and Evaluation of Clinical Data of NDA 20-151, SLR-015, dated 3-2-00.

(added wording underlined): "An insufficient number of patients received mean doses of Effexor XR over 300 mg/day to fully evaluate the incidence of sustained increases in blood pressure at these higher doses."

This change is acceptable.

C. PRECAUTIONS/General

A new subsection has been added:

"Mydriasis
Mydriasis has been reported in association with venlafaxine; therefore patients with raised intra-ocular pressure or at risk of acute narrow angle glaucoma should be monitored."

This additional information was reviewed in detail during the evaluation of corresponding labeling changes to Effexor labeling and was deemed to be acceptable.[1]

D. PRECAUTIONS/Drug Interactions

The sponsor proposes to add a new section under CYP3A4 describing an interaction study with indinavir (Crixivan®), a protease inhibitor used in the treatment of HIV infection:[2]

"Indinavir-In a study of 9 healthy volunteers, venlafaxine administered under steady-state conditions at 150 mg per day resulted in a 28% decrease in the AUC of a single 800 mg oral dose of indinavir and a 36% decrease in indinavir Cmax. Indinavir did not affect the pharmacokinetics of venlafaxine and ODV. The clinical significance of this finding is unknown."

This study description was reviewed during the evaluation of changes to Effexor labeling and was deemed to be acceptable.[1]

---

[2] Levin G, et al. Venlafaxine and Indinavir: Results of a Pharmacokinetic Interaction Study. Abstract #661 from the 39th Interscience Conference on Antimicrobial Agents and Chemotherapy, September 26-29, 1999; San Francisco, CA. (Attachment D, section 1)

E. OVERDOSAGE/Human Experience

The sponsor is proposing to state that overdose with venlafaxine has occurred predominantly in combination with alcohol and/or other drugs and to add the following adverse events to this section: electrocardiogram changes (e.g., prolongation of the QT interval, bundle branch block, QRS prolongation), sinus and ventricular tachycardia, bradycardia, hypotension, altered level of consciousness, seizures, and vertigo.

These changes were reviewed during the evaluation of changes to Effexor labeling and were deemed to be acceptable.[1]

F. HOW SUPPLIED

The sponsor has reformatted this section and the NDC numbers for each dosage strength for the carton of 10 Redipak® blister strips of 10 capsules have been added. Additionally, light protection statements for the 37.5 mg strength were added.

These changes are pending review by the ONDC reviewer.

III. Recommendations

Proposed changes to the clinical sections of Effexor XR labeling are acceptable and, from a clinical perspective, this supplement may be approved.

Changes to the DESCRIPTION and HOW SUPPLIED sections must be reviewed and found to be acceptable by the ONDC reviewer prior to final approval.

Gregory M. Dubitsky, M.D.
March 2, 2000

cc: NDA #20-699
HFD-120 (Div. File)
HFD-120/GDubitsky
/TLaughren
/PDavid

3-3-00
T. Laughren

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-699/S-012

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

REGULATORY PROJECT MANAGER
LABELING REVIEW

NDA: 20-699
DRUG: Effexor XR (venlafaxine hydrochloride) Extended Release Tablets
Sponsor: Wyeth-Ayerst
Indication: Depression/GAD
Supplements: SLR-012 (dated 12-20-99)
SLR-014 (dated 4-25-00)

Notes of interest:

- The last approved FPL was SE1-001. The supplement was approved in an Agency letter dated 3-11-99, and FPL was submitted on 4-16-99.
- The last approved labeling supplement was SLR-008 (Agency approval letter dated 3-3-00) which provided for additions to the **DRUG ABUSE AND DEPENDENCE** and **DOSAGE AND ADMINISTRATION/Discontinuing Effexor** sections of labeling. This was approved on draft labeling. The Agency approval letter dated 3-3-00, requested 20 copies of FPL, however the FPL was submitted with CBE supplement SLR-014.

REVIEW

20-699/SLR-012
Dated: 12-20-99
CBE: Yes
Label Code: CI 4876-4
Reviewed by Medical Officer and Chemist: Yes, acceptable.

The supplement provides for the following additions:

1. The addition of the following new inactive ingredients under the **DESCRIPTION** section: D&C Red #28, D&C Yellow #10, and FD&C Blue #1)
2. An editorial change was made to the last sentence of the first paragraph in the **WARNINGS-Sustained Hypertension** section to clarify the meaning of the statement.
3. The addition of a new subsection under the **PRECAUTIONS** section entitled **Mydriasis**.
4. The addition of a new subsection under the **PRECAUTIONS-Drug Interactions** section entitled **Indinavir.**
5. The revision of the **OVERDOSAGE-Human Experience** section.
6. The reformatting of the **HOW SUPPLIED** section.

20-699/SLR-014
Dated: 4-25-00
CBE: Yes
Label Code: CI 5044-5
Reviewed by Medical Officer: Yes, approvable.

The supplement provides for the following:

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 tem[ ]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.

The clinical reviewer has found these changes to be approvable. However, the sponsor will need to submit additional data and agree to specific revisions to the labeling prior to the approval of this supplemental application.

CONCLUSIONS

1. These supplements only provide for the labeling revisions listed above. Please see attached documentation denoting the revisions made to labeling compared to the last approved FPL for Effexor XR (SE1-001; approval letter dated 3-11-99).

2. I recommend issuing an approval letter for supplement SLR-012 and an approvable letter for SLR-014.

Paul David. RPh
Regulatory Project Manager

John Purvis
Supervisory Consumer Safety Officer

NDA 20-699
HFD-120/Div File
HFD-120/T.Laughren/G.Dubitsky/P.David
Rd:5/19/00; ft:6/2/00pd
LABELING REVIEW

34.1

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-699/S-012

JAN -5 2000

Wyeth-Ayerst Laboratories
P.O. Box 8299
Philadelphia, PA 19101

Attention: Nanette Holston Associate Director
Global Brand Management
Worldwide Regulatory Affairs

Dear Mr. Holston:

We acknowledge receipt of your supplemental application for the following:

Name of Drug: Effexor XR (venlafaxine HCL) E-R Capsules

NDA Number: 20-699

Supplement Number: 012

Date of Supplement: 20-Dec-99

Date of Receipt: 22-Dec-99

Unless we find the application not acceptable for filing, this application will be filed under Section 505(b)(1) of the Act on 20-Feb-99 in accordance with 21 CFR 314.101(a).

All communications concerning this NDA should be addressed as follows:

Center for Drug Evaluation and Research
Division of Neuropharmacological Drug Products, HFD-120
Office of Drug Evaluation I
Attention: Document Control Room 4008
5600 Fishers Lane
Rockville, MD 20857

Sincerely,

1-5-00

John S. Purvis
Chief, Project Management Staff
Division of Neuropharmacological Drug Products, HFD-120
Office of Drug Evaluation I
Center for Drug Evaluation and Research

cc:
Original NDA 20-699/012
HFD-120/Div. Files
HFD-120/CSO/David

filename:

SUPPLEMENT ACKNOWLEDGEMENT

NDA SUPPLEMENT

WYETH-AYERST RESEARCH

P.O. BOX 8299 • PHILADELPHIA, PA 19101-8299 • (610) 902-3710
FAX: (610) 964-5973

Division of American Home Products Corporation

U.S. REGULATORY AFFAIRS

NDA NO. 20-699 REF NO. SLR-012
NDA SUPPL FOR Labeling

ORIGINAL

December 20, 1999

NDA 20-699
Effexor® XR (venlafaxine hydrochloride) Extended-Release Capsules

CENTER FOR DRUG EVALUATION AND RESEARCH

DEC 22 1999

RECEIVED HFD-120

Russell Katz, M.D., Acting Director
Division of Neuropharmacological Drug Products (HFD-120)
Center for Drug Evaluation and Research
Attn: Document Control Room 4008
Food and Drug Administration
1451 Rockville Pike
Rockville, MD 20852

"Special Supplement—Changes Being Effected"

Dear Dr. Katz:

Reference is made to our approved New Drug Application No. 20-699 for Effexor® XR (venlafaxine hydrochloride) Extended-Release Capsules.

We are submitting herewith a "Special Supplement - Changes Being Effected" under 21 CFR 314.70 (c)(2)(i) and (ii) to provide for revisions in the text of the physician's package insert to incorporate additional safety information under the **PRECAUTIONS/ General and Drug Interactions** and **OVERDOSAGE/Human Experience** sections. This additional information has been derived from published studies found in the medical literature and postmarketing adverse drug event reports (line listings).

Also, reference is made to the Special Supplement-Changes Being Effected (S-006) submitted on August 5, 1999, which provided for a new capsule [ ]cap colored gray with[ ] dyes for the 37.5 mg Effexor XR Capsule product (Refer to Attachment C). To address this issue, additional inactive ingredients have been added to the **DESCRIPTION** section of the package insert and light storage statements have been added to both the **HOW SUPPLIED** section of the package insert [ ]
[ ]

A summary of the labeling changes in the order in which they occur in the Effexor XR Capsules package insert is presented below.

DESCRIPTION
Added the statement, "The 37.5 mg capsule also contains D&C Red #28, D&C Yellow #10, and FD&C Blue #1".

WARNINGS/Sustained Hypertension
Added the words "increases in" to the last sentence of the first paragraph in order to clarify its meaning. The sentence now reads "An insufficient number of patients received mean doses of Effexor XR over 300 mg/day to fully evaluate the incidence of sustained increases in blood pressure at these higher doses."

PRECAUTIONS/ General
Added a new mydriasis subsection, which reads as follows:

Mydriasis has been reported in association with venlafaxine; therefore patients with raised intra-ocular pressure or at risk of acute narrow angle glaucoma should be monitored.

PRECAUTIONS/ Drug Interactions
Added a new indinavir subsection, which summarizes a study that examined the drug interactions between venlafaxine and indinavir in healthy volunteers.

This section reads as follows:

> In a study of 9 healthy volunteers, venlafaxine administered under steady-state conditions at 150 mg per day resulted in a 28% decrease in the AUC of a single 800 mg oral dose of indinavir and a 36 % decrease in indinavir Cmax. Indinavir did not affect the pharmacokinetics of venlafaxine and ODV. The clinical significance of this finding is unknown.

OVERDOSAGE/Human Experience

In addition to premarketing evaluation with venlafaxine, postmarketing experience has suggested the inclusion of new adverse event terms. Therefore, based on new spontaneous adverse event reports and published medical literature, the overdosage section was strengthened by the addition of the following new adverse event terms: electrocardiogram changes (e.g. bundle branch, QRS prolongation), ventricular tachycardia, bradycardia, hypotension, altered level of consciousness, seizures and vertigo.

The last paragraph of this section now reads.

> In postmarketing experience, overdose with venlafaxine has occurred predominantly in combination with alcohol and/or other drugs. Electrocardiogram changes (e.g. prolongation of QT interval, bundle branch block, QRS prolongation), sinus and ventricular tachycardia, bradycardia, hypotension, altered level of consciousness (ranging from somnolence to coma), seizures, vertigo, and death have been reported.

HOW SUPPLIED

This section has been reformatted and the NDC numbers for each dosage strength for the carton of 10 Redipak® blister strips of 10 capsules have been added. Also, the following light protection statements were added for the 37.5 mg capsule:

Bottles: Protect from light. Dispense in light- resistant container.
Blisters: Protect from light. Use blister carton to protect contents from light.

The following material is enclosed in support of this supplementation application:

Attachment A: Four copies of the text used to prepare the final printed labeling (FLP). Shaded areas indicate additional text and strike-outs indicate deleted text.

Attachment B: Revised FPL distributed as nineteen mounted copies in the Review copy one mounted copy in the Archival copy.

Attachment C: Special Supplement-Changes Being Effected (S-006) cover letter submitted on August 5, 1999.

Attachment D: Mydriasis Supporting Documentation

1. Line listings of postmarketing adverse drug event reports.
2. Reprint of published medical literature

Attachment E: Indinavir Supporting Documentation

1. Published abstract: Venlafaxine and Indinavir: Results of a Pharmacokinectic Study. G.M. Levin et al. Presented at the 39th Interscience Conference on Antimicrobial Agents and Chemotherapy, September 26-29, 1999, San Francisco, CA.
2. Telephone contact report between Dr. Sharon Popik (Wyeth-Ayerst) and Dr. Gary Levin (University of Florida).

Attachment F: Overdosage Supporting Documentation

1. Line listings of postmarketing adverse drug event reports.
2. Reprints of published medical literature

Attachment G: Two copies of package insert currently in use for Effexor XR Capsules (CI 4876-4)

These labeling changes will be implemented on or before February 15, 2000. We trust that you will find the enclosed labeling acceptable and that this "Special Supplement -Changes Being Effected" will be approved at your earliest convenience. If you have any questions regarding this submission, please contact the undersigned at (610) 902-3775 or Ms. Deborah Holloway at (610) 902-5243.

Sincerely,

WYETH-AYERST LABORATORIES

Nanette Holston
Associate Director
Global Brand Management
Worldwide Regulatory Affairs

NH:DH:jad:effexorcbe2
Attachment