CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:
20-699/S-022

Trade Name: Effexor XR Extended-release Capsules

Generic Name: venlafaxine hydrochloride

Sponsor: Wyeth-Ayerst Laboratories

Approval Date: February 11, 2003

Indications: Provides for the treatment of social anxiety disorder.

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APPLICATION NUMBER:

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APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-699/S-022

Wyeth-Ayerst Laboratories
Attention: Kenneth R. Bonk
Associate Director II, Worldwide Regulatory Affairs
P.O. Box 8299
Philadelphia, PA 19101

Dear Mr. Bonk:

Please refer to your supplemental new drug application dated September 10, 2001, received September 12, 2001, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Effexor® XR (venlafaxine hydrochloride) Extended-release Capsules.

We acknowledge receipt of your amendments dated August 29, September 5 and December 5, 2002.

Your submission of August 29, 2002, constituted a complete response to our July 9, 2002, action letter.

This supplemental new drug application provides for the use of Effexor® XR (venlafaxine hydrochloride) Extended-release Capsules for the treatment of social anxiety disorder as a new indication.

We also refer to the January 22, 2003, telephone conversation during which the enclosed labeling text was agreed upon.

We have completed the review of this supplemental application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed upon enclosed labeling text. Accordingly, the supplemental application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the enclosed labeling.

Please submit the copies of final printed labeling (FPL) electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA* (January 1999). Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved supplement NDA 20-699/S-022." Approval of this submission by FDA is not required before the labeling is used.

FDA's Pediatric Rule [at 21 CFR 314.55/21 CFR 601.27] was challenged in court. On October 17, 2002,

the court ruled that FDA did not have the authority to issue the Pediatric Rule and has barred FDA from enforcing it. Although the government decided not to pursue an appeal in the courts, it will work with Congress in an effort to enact legislation requiring pharmaceutical manufacturers to conduct appropriate pediatric clinical trials. In addition, third party interveners have decided to appeal the court's decision striking down the rule. Therefore, we encourage you to submit a pediatric plan that describes development of your product in the pediatric population where it may be used. Please be aware that whether or not this pediatric plan and subsequent submission of pediatric data will be required depends upon passage of legislation or the success of the third party appeal. In any event, we hope you will decide to submit a pediatric plan and conduct the appropriate pediatric studies to provide important information on the safe and effective use of this drug in the relevant pediatric populations.

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

If you should have any questions, please call Ms. Anna Marie H. Weikel, R.Ph., Senior Regulatory Project Manager, at (301) 594-5535.

Sincerely,

{See appended electronic signature page}

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

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

/s/

Russell Katz
2/11/03 12:46:17 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-699/S-022

APPROVED LABELING

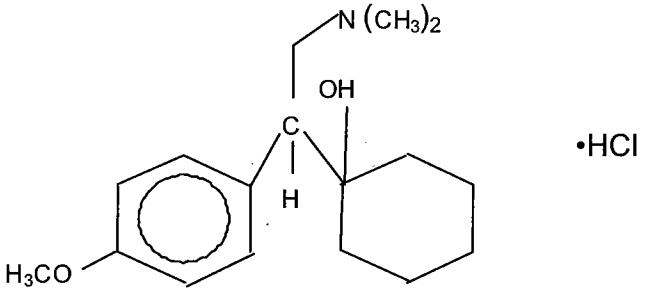
FDA approved labeling for NDA 20-699/S-022
Attachment to FDA approval letter

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. 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

Major Depressive Disorder

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

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 depressive disorder 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.

In one longer-term study, outpatients meeting DSM-IV criteria for major depressive disorder who had responded during an 8-week open trial on Effexor XR (75, 150, or 225 mg, qAM) were randomized to continuation of their same Effexor XR dose or to placebo, for up to 26 weeks of observation for relapse. Response during the open phase was defined as a CGI Severity of Illness item score of ≤ 3 and a HAM-D-21 total score of ≤ 10 at the day 56 evaluation. Relapse during the double-blind phase was defined as follows: (1) a reappearance of major depressive disorder as defined by DSM-IV criteria and a CGI Severity of Illness item score of ≥ 4 (moderately ill), or (2) 2 consecutive CGI Severity of Illness item scores of ≥ 4, or (3) a final CGI Severity of Illness item score of ≥ 4 for any patient who withdrew from the study for any reason. Patients receiving continued Effexor XR treatment experienced significantly lower relapse rates over the subsequent 26 weeks compared with those receiving placebo.

In a second longer-term trial, outpatients meeting DSM-III-R criteria for major depressive disorder, recurrent type, who had responded (HAM-D-21 total score ≤ 12 at the day 56 evaluation) and continued to be improved [defined as the following criteria being met for days 56 through 180: (1) no HAM-D-21 total score ≥ 20, (2) no more than 2 HAM-D-21 total scores > 10, and (3) no single CGI Severity of Illness item score ≥ 4 (moderately ill)] during an initial 26 weeks of treatment on Effexor (100-200 mg/day, on a bid schedule) were randomized to continuation of their same Effexor dose or to placebo. The follow-up period to observe patients for relapse, defined as a CGI Severity of Illness item score ≥ 4, was for up to 52 weeks. Patients receiving continued Effexor treatment experienced significantly lower relapse rates over the subsequent 52 weeks compared with those receiving placebo.

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, one 6-month, placebo-controlled,

fixed-dose study, and one 6-month, placebo-controlled, flexible-dose study in outpatients meeting DSM-IV criteria for GAD.

One 8-week 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 8-week 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.

Two 6-month studies, one evaluating Effexor XR doses of 37.5, 75, and 150 mg/day and the other evaluating Effexor XR doses of 75-225 mg/day, showed that daily doses of 75 mg or higher were more effective than placebo on the HAM-A total, both the HAM-A anxiety and tension items, and the CGI scale during 6 months of treatment. While there was also evidence for superiority over placebo for the 37.5 mg/day dose, this dose was not as consistently effective as the higher doses.

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

Social Anxiety Disorder (Social Phobia)

The efficacy of Effexor XR capsules as a treatment for Social Anxiety Disorder (also known as Social Phobia) was established in two double-blind, parallel group, 12-week, multicenter, placebo-controlled, flexible-dose studies in adult outpatients meeting DSM-IV criteria for Social Anxiety Disorder. Patients received doses in a range of 75-225 mg/day. Efficacy was assessed with the Liebowitz Social Anxiety Scale (LSAS). In these two trials, Effexor XR was significantly more effective than placebo on change from baseline to endpoint on the LSAS total score.

Examination of subsets of the population studied did not reveal any differential responsiveness on the basis of gender. There was insufficient information to determine the effect of age or race on outcome in these studies.

INDICATIONS AND USAGE

Major Depressive Disorder

Effexor XR (venlafaxine hydrochloride) extended-release capsules is indicated for the treatment of major depressive disorder.

The efficacy of Effexor XR in the treatment of major depressive disorder 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 major depressive disorder 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 efficacy of Effexor XR in maintaining a response in major depressive disorder for up to 26 weeks following 8 weeks of acute treatment was demonstrated in a placebo-controlled trial. The efficacy of Effexor in maintaining a response in patients with recurrent major depressive disorder who had responded and continued to be improved during an initial 26 weeks of treatment and were then followed for a period of up to 52 weeks was demonstrated in a second placebo-controlled trial (see "**Clinical Trials**"). Nevertheless, the physician who elects to use Effexor/Effexor XR for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient.

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 and 6-month 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.

Although the effectiveness of Effexor XR has been demonstrated in 6-month clinical trials in patients with GAD, 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**").

Social Anxiety Disorder

Effexor XR is indicated for the treatment of Social Anxiety Disorder, also known as Social Phobia, as defined in DSM-IV (300.23).

Social Anxiety Disorder (DSM-IV) is characterized by a marked and persistent fear of 1 or more social or performance situations in which the person is exposed to unfamiliar people or to possible scrutiny by others. Exposure to the feared situation almost invariably provokes anxiety, which may approach the intensity of a panic attack. The feared situations are avoided or endured with intense anxiety or distress. The avoidance, anxious anticipation, or distress in the feared situation(s) interferes significantly with the person's normal routine, occupational or academic functioning, or social activities or relationships, or there is a marked distress about having the phobias. Lesser degrees of performance anxiety or shyness generally do not require psychopharmacological treatment.

The efficacy of Effexor XR in the treatment of Social Anxiety Disorder was established in two 12-week placebo-controlled trials in adult outpatients with Social Anxiety Disorder (DSM-IV). Effexor XR has not been studied in children or adolescents with Social Anxiety Disorder (See "**Clinical Trials**").

The effectiveness of Effexor XR in the long-term treatment of Social Anxiety Disorder, i.e., for more than 12 weeks, has not been systematically evaluated in adequate and well-controlled trials. Therefore, 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

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

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 studies in patients with major depressive disorder, 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 37.5-225 mg per day of Effexor XR in premarketing GAD studies, 0.5% (5/1011) experienced sustained hypertension. Among patients treated with 75-225 mg per day of Effexor XR in premarketing Social Anxiety Disorder studies, 1.4% (4/277) 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 studies in patients with major depressive disorder 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 37.5-225 mg/day up to 8 weeks or up to 6 months, a final on-drug mean increase in SDBP of 0.3 mm Hg was observed for Effexor XR-treated patients compared with a mean decrease of 0.9 and 0.8 mm Hg, respectively, for placebo-treated patients. In placebo-controlled premarketing Social Anxiety Disorder studies with Effexor XR 75-225 mg/day up to 12 weeks, a final on-drug mean increase in SDBP of 1.6 mm Hg was observed for Effexor XR-treated patients compared with a mean decrease of 1.1 mm Hg for placebo-treated patients.

In premarketing major depressive disorder studies, 0.7% (5/705) of the Effexor XR-treated patients 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 premarketing GAD studies up to 8 weeks and up to 6 months, 0.7% (10/1381) and 1.3% (7/535) 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 (12-25 mm Hg, SDBP up to 8 weeks; 8-28 mm Hg up to 6 months). In premarketing Social Anxiety Disorder studies up to 12 weeks, 0.4% (1/277) of the Effexor XR-treated patients discontinued treatment because of elevated blood pressure. In this patient, the blood pressure increase was modest (13 mm Hg, SDBP).

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 major depressive disorder, GAD, and Social Anxiety Disorder studies, as shown in Table 1.

Table 1
Incidence of Insomnia and Nervousness in Placebo-Controlled Major Depressive Disorder, GAD, and Social Anxiety Disorder Trials

	Major Depressive Disorder		GAD		Social Anxiety Disorder	
Symptom	Effexor XR n = 357	Placebo n = 285	Effexor XR n = 1381	Placebo n = 555	Effexor XR n = 277	Placebo n=274
Insomnia	17%	11%	15%	10%	23%	7%
Nervousness	10%	5%	6%	4%	11%	3%

Insomnia and nervousness each led to drug discontinuation in 0.9% of the patients treated with Effexor XR in major depressive disorder studies.

In GAD trials, insomnia and nervousness led to drug discontinuation in 3% and 2%, respectively, of the patients treated with Effexor XR up to 8 weeks and 2% and 0.7%, respectively, of the patients treated with Effexor XR up to 6 months.

In Social Anxiety Disorder trials, insomnia and nervousness led to drug discontinuation in 3% and 0%, respectively, of the patients treated with Effexor XR up to 12 weeks.

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 studies in major depressive disorder. 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 major depressive disorder 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 major depressive disorder studies).

In the pool of GAD studies, treatment-emergent anorexia was reported in 8% and 2% of patients receiving Effexor XR and placebo up to 8 weeks, respectively. A loss of 7% or more of body weight occurred in 3% of the Effexor XR-treated and 1% of the placebo-treated patients up to 6 months in these trials. Discontinuation rates for anorexia and weight loss were low for patients receiving Effexor XR up to 8 weeks (0.9% and 0.3% respectively).

In the pool of Social Anxiety Disorder studies, treatment-emergent anorexia was reported in 20% and 2% of patients receiving Effexor XR and placebo up to 12 weeks, respectively. A loss of 7% or more of body weight occurred in none of the Effexor XR-treated or the placebo-treated patients up to 12 weeks in these trials. Discontinuation rates for anorexia and weight loss were low for patients receiving Effexor XR up to 12 weeks (0.4% and 0.0%, respectively).

Activation of Mania/Hypomania

During premarketing major depressive disorder 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 0.2% of placebo-treated patients experienced mania or hypomania. In premarketing Social Anxiety Disorder studies, no Effexor XR-treated patients and no placebo-treated patients experienced mania or hypomania. In all premarketing major depressive disorder 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 marketeddrugs to treat major depressive disorder. As with all

drugs effective in the treatment of major depressive disorder, Effexor XR should be used cautiously in patients with a history of mania.

Hyponatremia

Hyponatremia and/or the syndrome of inappropriate antidiuretic hormone secretion (SIADH) may occur with venlafaxine. This should be taken into consideration in patients who are, for example, volume-depleted, elderly, or taking diuretics.

Mydriasis

Mydriasis has been reported in association with venlafaxine; therefore patients with raised intraocular pressure or those 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 major depressive disorder studies, among 1381 Effexor XR-treated patients in GAD studies, or among 277 Effexor XR-treated patients in Social Anxiety Disorder studies. In all premarketing major depressive disorder 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.

Abnormal Bleeding

There have been reports of abnormal bleeding (most commonly ecchymosis) associated with venlafaxine treatment. While a causal relationship to venlafaxine is unclear, impaired platelet aggregation may result from platelet serotonin depletion and contribute to such occurrences.

Serum Cholesterol Elevation

Clinically relevant increases in serum cholesterol were recorded in 5.3% of venlafaxine-treated patients and 0.0% of placebo treated patients treated for at least 3 months in placebo-controlled trials (see ADVERSE REACTIONS-Laboratory Changes).

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

Suicide

The possibility of a suicide attempt is inherent in major depressive disorder 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 major depressive disorder should be observed when treating patients with GAD or Social Anxiety Disorder.

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 were analyzed for 275 patients who received Effexor XR and 220 patients who received placebo in 8- to 12-week double-blind, placebo-controlled trials inmajor depressive disorder, for 610 patients who received Effexor XR and 298 patients who received placebo in 8-week double-blind, placebo-controlled trials in GAD, and for 195 patients who received Effexor XR and 228 patients who received placebo in 12-week double-blind, placebo-controlled trials in Social Anxiety Disorder. The mean change from baseline in corrected QT interval (QT_c) for Effexor XR-treated patients in major depressive disorder 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 mean change from baseline in QT_c for Effexor XR-treated patients in the GAD studies did not differ significantly from that with placebo. The mean change from baseline in QT_c for Effexor XR-treated patients in the Social Anxiety Disorder studies was increased relative to that for placebo-treated patients (increase of 2.8 msec for Effexor XR and decrease of 2.0 msec for placebo).

In these same trials, the mean change from baseline in heart rate for Effexor XR-treated patients in the major depressive disorder 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 mean change from baseline in heart rate for Effexor XR-treated patients in the Social Anxiety Disorder studies

was significantly higher than that for placebo (a mean increase of 5 beats per minute for Effexor XR and no change for placebo).

In a flexible- dose study, with Effexor doses in the range of 200-375 mg/day and mean dose greater than 300 mg/day, Effexor treated patients had a mean increase in heart rate of 8.5 beats per minute compared with 1.7 beats per minute in the placebo group. As increases in heart rate were observed, caution should be exercised in patients whose underlying medical conditions might be compromised by increases in heart rate (e.g., patients with hyperthyroidism, heart failure, or recent myocardial infarction), particularly when using doses of Effexor above 200 mg/day.

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 alldrugs effective in the treatment of major depressive disorder, 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, including herbal preparations, 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 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 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.

Non-teratogenic Effects

If venlafaxine is used until or shortly before birth, discontinuation effects in the newborn should be considered.

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), 6% (77/1381), and 2% (6/277) of Effexor XR-treated patients in placebo-controlled premarketing major depressive disorder, GAD, and Social Anxiety Disorder trials, respectively, were 65 years of age or over. Of 2,897 Effexor-treated patients in premarketing phase major depressive disorder 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 major depressive disorder (includes two U.S. trials and one European trial), on data up to 8 weeks from a pool of five controlled clinical trials in GAD with Effexor XR, and on data up to 12 weeks from a pool of two controlled clinical trials in Social Anxiety Disorder. 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 major depressive disorder discontinued treatment due to an adverse experience, compared with 6% of the 285 placebo-treated patients in those studies. Approximately 18% of the 1381 patients who received Effexor XR capsules in placebo-controlled clinical trials for GAD discontinued treatment due to an adverse experience, compared with 12% of the 555 placebo-treated patients in those studies. Approximately 17% of the 277 patients who received Effexor XR capsules in placebo-controlled clinical trials for Social Anxiety Disorder discontinued treatment due to an adverse experience, compared with 5% of the 274 placebo-treated patients in those studies. The most common events leading to discontinuation and considered 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					
	Major Depressive Disorder Indication[2]		GAD Indication[3,4]		Social Anxiety Disorder Indication	
	Effexor XR n=357	Placebo n=285	Effexor XR n=1381	Placebo n=555	Effexor XR n=277	Placebo n=274
Body as a Whole						
Asthenia	--	--	3%	<1%	1%	<1%
Headache	--	--	--	--	2%	<1%
Digestive System						
Nausea	4%	<1%	8%	<1%	4%	0%
Anorexia	1%	<1%	--	--	--	--
Dry Mouth	1%	0%	2%	<1%	--	--
Vomiting	--	--	1%	<1%	--	--
Nervous System						
Dizziness	2%	1%	--	--	2%	0%
Insomnia	1%	<1%	3%	<1%	3%	<1%
Somnolence	2%	<1%	3%	<1%	2%	<1%
Nervousness	--	--	2%	<1%	--	--
Tremor	--	--	1%	0%	--	--
Anxiety	--	--	--	--	1%	<1%
Skin						
Sweating	--	--	2%	<1%	1%	0%
Urogenital System						
Impotence[5]	--	--	--	--	3%	0%

[1] Two of the major depressive disorder studies were flexible dose and one was fixed dose. Four of the GAD studies were fixed dose and one was flexible dose. Both of the Social Anxiety Disorder studies were flexible dose.

[2] In U.S. placebo-controlled trials for major depressive disorder, 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%).

[3] In two short-term U.S. placebo-controlled trials for GAD, the following were also common events leading to discontinuation and were considered to be drug-related for Effexor XR-treated patients (% Effexor XR [n = 476], % Placebo [n = 201]): headache (4%, <1%); vasodilatation (1%, 0%); anorexia (2%, <1%); dizziness (4%, 1%); thinking abnormal (1%, 0%); and abnormal vision (1%, 0%).

[4] In long-term placebo-controlled trials for GAD, the following was also a common event leading to discontinuation and was considered to be drug-related for Effexor XR-treated patients (% Effexor XR [n = 535], % Placebo [n = 257]): decreased libido (1%, 0%).

[5] Incidence is based on the number of men (Effexor XR = 158, placebo = 153).

Adverse Events Occurring at an Incidence of 2% or More Among Effexor XR-Treated Patients
Tables 3, 4, and 5 enumerate the incidence, rounded to the nearest percent, of treatment-emergent adverse events that occurred during acute therapy of major depressive disorder (up to 12 weeks; dose range of 75 to 225 mg/day), of GAD (up to 8 weeks; dose range of 37.5 to 225 mg/day), and of Social Anxiety Disorder (up to 12 weeks; dose range of 75 to 225 mg/day),respectively, in 2% or more of patients treated with Effexor XR 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, 4, and 5:
Major Depressive 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 major depressive disorder 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),

gastrointestinal complaints (nausea, dry mouth, anorexia, and constipation), problems of special senses (abnormal vision), and sweating.

Social 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 the 2 placebo-controlled trials for the Social Anxiety Disorder indication (Table 5): Asthenia, gastrointestinal complaints (anorexia, dry mouth, nausea), CNS complaints (anxiety, insomnia, libido decreased, nervousness, somnolence, dizziness), abnormalities of sexual function (abnormal ejaculation, orgasmic dysfunction, impotence), yawn, sweating, and abnormal vision.

TABLE 3
Treatment-Emergent Adverse Event Incidence in Short-Term Placebo-Controlled Effexor XR Clinical Trials in Patients with Major Depressive Disorder[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 (male)[6,7]	16%	<1%
Impotence[7]	4%	<1%
Anorgasmia (female)[8,9]	3%	<1%

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

	% Reporting Event	
Body System	**Effexor XR**	**Placebo**
Preferred Term	(n=357)	(n=285)

[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]

Body System Preferred Term	% Reporting Event Effexor XR (n=1381)	 Placebo (n=555)
Body as a Whole		
Asthenia	12%	8%
Cardiovascular System		
Vasodilatation[3]	4%	2%
Digestive System		
Nausea	35%	12%
Constipation	10%	4%
Anorexia	8%	2%
Vomiting	5%	3%
Nervous System		
Dizziness	16%	11%
Dry Mouth	16%	6%
Insomnia	15%	10%
Somnolence	14%	8%
Nervousness	6%	4%
Libido Decreased	4%	2%
Tremor	4%	<1%
Abnormal Dreams[4]	3%	2%
Hypertonia	3%	2%
Paresthesia	2%	1%
Respiratory System		
Yawn	3%	<1%
Skin		
Sweating	10%	3%
Special Senses		
Abnormal Vision[5]	5%	<1%
Urogenital System		
Abnormal Ejaculation[6,7]	11%	<1%
Impotence[7]	5%	<1%
Orgasmic Dysfunction (female)[8,9]	2%	0%

[1] Adverse events for which the Effexor XR reporting rate was less than or equal to the placebo rate are not included. These events are: abdominal pain, accidental injury, anxiety, back pain, diarrhea, dysmenorrhea, dyspepsia, flu syndrome, headache, infection, myalgia, pain, palpitation, pharyngitis, rhinitis, tinnitus, and urinary frequency.
[2] <1% means 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] Includes "delayed ejaculation" and "anorgasmia."
[7] Percentage based on the number of males (Effexor XR = 525, placebo = 220).
[8] Includes "delayed orgasm," "abnormal orgasm," and "anorgasmia."
[9] Percentage based on the number of females (Effexor XR = 856, placebo = 335).

TABLE 5
Treatment-Emergent Adverse Event Incidence in Short-Term Placebo-Controlled Effexor XR Clinical Trials in Social Anxiety Disorder Patients[1,2]

Body System Preferred Term	% Reporting Event Effexor XR (n=277)	 Placebo (n=274)
Body as a Whole		
Headache	34%	33%
Asthenia	17%	8%
Flu syndrome	6%	5%
Accidental injury	5%	3%
Abdominal pain	4%	3%
Cardiovascular System		
Hypertension	5%	4%
Vasodilatation[3]	3%	1%
Palpitation	3%	1%
Digestive system		
Nausea	29%	9%
Anorexia[4]	20%	1%
Constipation	8%	4%
Diarrhea	6%	5%
Vomiting	3%	2%
Eructation	2%	0
Metabolic and nutritional		
Weight loss	4%	0
Nervous System		
Insomnia	23%	7%
Dry mouth	17%	4%
Dizziness	16%	8%
Somnolence	16%	8%
Nervousness	11%	3%
Libido decreased	9%	<1%
Anxiety	5%	3%
Agitation	4%	1%
Tremor	4%	<1%
Abnormal dreams[5]	4%	<1%
Paresthesia	3%	<1%
Twitching	2%	0
Respiratory System		
Yawn	5%	<1%
Sinusitis	2%	1%
Skin		
Sweating	13%	2%
Special Senses		
Abnormal vision[6]	6%	3%
Urogenital System		
Abnormal ejaculation[7,8]	16%	1%
Impotence[8]	10%	1%
Orgasmic dysfunction[9,10]	8%	0

TABLE 5
Treatment-Emergent Adverse Event Incidence in Short-Term Placebo-Controlled Effexor XR Clinical Trials in Social Anxiety Disorder Patients [1,2]

	% Reporting Event	
Body System Preferred Term	**Effexor XR** (n=277)	**Placebo** (n=274)

[1] Adverse events for which the Effexor XR reporting rate was less than or equal to the placebo rate are not included. These events are: back pain, depression, dysmenorrhea, dyspepsia, infection, myalgia, pain, pharyngitis, rash, rhinitis, and upper respiratory infection.
[2] <1% means greater than zero but less than 1%.
[3] Mostly "hot flashes."
[4] Mostly "decreased appetite" and "loss of appetite."
[5] Mostly "vivid dreams," "nightmares," and "increased dreaming."
[6] Mostly "blurred vision."
[7] Includes "delayed ejaculation" and "anorgasmia."
[8] Percentage based on the number of males (Effexor XR = 158, placebo = 153).
[9] Includes "abnormal orgasm," and "anorgasmia."
[10] Percentage based on the number of females (Effexor XR = 119, placebo = 121).

Vital Sign Changes

Effexor XR (venlafaxine hydrochloride) extended-release capsules treatment for up to 12 weeks in premarketing placebo-controlled major depressive disorder 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. Effexor XR treatment for up to 12 weeks in premarketing placebo-controlled Social Anxiety Disorder trials was associated with mean final on-therapy increase in pulse rate of approximately 4 beats per minute, compared with no change for placebo. (See the "**Sustained Hypertension**" section of **"WARNINGS"** for effects on blood pressure).

In a flexible-dose study, with Effexor doses in the range of 200-375 mg/day and mean dose greater than 300 mg/day, the mean pulse was increased by about 2 beats per minute compared with a decrease of about 1 beat per minute for placebo.

Laboratory Changes

Effexor XR (venlafaxine hydrochloride) extended-release capsules treatment for up to 12 weeks in premarketing placebo-controlled trials for major depressive disorder was associated with a mean final on-therapy increase in serum cholesterol concentration of approximately 1.5 mg/dL compared with a mean final decrease of7.4 mg/dL for placebo. Effexor XR treatment for up to 8 weeks and up to 6 months in premarketing placebo-controlled GAD trials was associated with mean final on-therapy increases in serum cholesterol concentration of approximately 1.0 mg/dL and 2.3 mg/dL, respectively

while placebo subjects experienced mean final decreasesof 4.9 mg/dL and 7.7 mg/dL, respectively. Effexor XR treatment for up to 12 weeks in premarketing placebo-controlled Social Anxiety Disorder trials was associated with mean final on-therapy increases in serum cholesterol concentration of approximately 11.4 mg/dL compared with a mean final decrease of 2.2 mg/dL for placebo.

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 with a decrease of 7.1 mg/dl among placebo treated patients. This increase was duration dependent over the study period and tended to be greater with higher doses. Clinically relevant increases in serum cholesterol, defined as 1) a final on-therapy increase in serum cholesterol $\geq$50 mg/dL from baseline and to a value $\geq$261 mg/dL or 2) an average on-therapy increase in serum cholesterol $\geq$50 mg/dL from baseline and to a value $\geq$261 mg/dL, were recorded in 5.3% of venlafaxine-treated patients and 0.0% of placebo-treated patients (see **PRECAUTIONS-General/Serum Cholesterol Elevation**).

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 major depressive disorder studies and Effexor was administered to 96 patients. During its premarketing assessment, multiple doses of Effexor XR were also administered to 1381 patients in phase 3 GAD studies and 277 patients in phase 3 Social Anxiety Disorder studies. In addition, in premarketing assessment of Effexor, multiple doses were administered to 2897 patients in phase 2-3 studies for major depressive disorder. 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 5356 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, 4, and 5 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, chills, fever, neck pain; **Infrequent**: face edema, intentional injury, malaise, moniliasis, neck rigidity, pelvic pain, photosensitivity reaction, suicide attempt, withdrawal syndrome; **Rare**: appendicitis, bacteremia, carcinoma, cellulitis.

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

Digestive system - **Frequent**: increased appetite; **Infrequent**: bruxism, colitis, dysphagia, tongue edema, esophagitis, gastritis, gastroenteritis, gastrointestinal ulcer, gingivitis, glossitis, rectal hemorrhage, hemorrhoids, melena, oral moniliasis, stomatitis, mouth ulceration; **Rare**: cheilitis, cholecystitis, cholelithiasis, esophageal spasms, duodenitis, hematemesis, gastrointestinal hemorrhage, gum hemorrhage, hepatitis, ileitis, jaundice, intestinal obstruction, parotitis, periodontitis, 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, bleeding time increased, cyanosis, eosinophilia, lymphocytosis, multiple myeloma, purpura.

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

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

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

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

Skin and appendages - **Frequent**: pruritus; **Infrequent**: acne, alopecia, brittle nails, contact dermatitis, dry skin, eczema, skin hypertrophy, maculopapular rash, psoriasis, urticaria; **Rare**: erythema nodosum, exfoliative dermatitis, lichenoid dermatitis, hair discoloration, skin discoloration, furunculosis, hirsutism, leukoderma, petechial rash, 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, eye pain, hyperacusis, otitis media, parosmia, photophobia, taste loss, visual field defect; **Rare**: blepharitis, chromatopsia, conjunctival edema, deafness, exophthalmos, glaucoma, retinal hemorrhage, subconjunctival hemorrhage, keratitis, labyrinthitis, miosis, papilledema, decreased pupillary reflex, otitis externa, scleritis, uveitis.

Urogenital system - **Frequent**: metrorrhagia,* prostatic disorder (prostatitis and enlarged prostrate),* urination impaired, vaginitis*; **Infrequent**: albuminuria, amenorrhea,* cystitis, dysuria, hematuria, leukorrhea,* menorrhagia,* nocturia, bladder pain, breast pain, polyuria, pyuria, urinary incontinence, urinary retention, urinary urgency, vaginal hemorrhage*; **Rare**: abortion,* anuria, breast discharge, breast engorgement, balanitis,* breast enlargement, endometriosis,* female lactation,* fibrocystic breast, calcium crystalluria, cervicitis,* orchitis,* ovarian cyst,* prolonged erection,* gynecomastia (male),* hypomenorrhea,* kidney calculus, kidney pain, kidney function abnormal, mastitis, menopause,* pyelonephritis, oliguria, salpingitis,* urolithiasis, uterine hemorrhage,* uterine spasm,* vaginal dryness.*

*Based on the number of men and women as appropriate.

[The proposed revisions, submitted in S-023, are acceptable.]

Postmarketing Reports

Voluntary reports of other adverse events temporally associated with the use of venlafaxine that have been received since market introduction and that may have no causal relationship with the use of venlafaxine include the following: agranulocytosis, anaphylaxis, aplastic anemia, catatonia, congenital anomalies, CPK increased, deep vein thrombophlebitis, delirium; EKG abnormalities such as QT prolongation; cardiac arrhythmias including atrial fibrillation, supraventricular tachycardia, ventricular extrasystoles, and rare reports of ventricular fibrillation and ventricular tachycardia, including torsades de pointes; 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), night sweats, pancreatitis, panic, prolactin increased, renal failure, serotonin syndrome, shock-like electrical sensations (in some cases, subsequent to the discontinuation of venlafaxine 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.

Discontinuation effects have been reported in patients receiving venlafaxine (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 major depressive disorder 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.

There were no reports of acute overdose with Effexor XR in Social Anxiety Disorder trials.

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

Major Depressive Disorder

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

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

Social Anxiety Disorder (Social Phobia)

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 Social Anxiety Disorder, the initial dose of Effexor XR was 75 mg/day and the maximum dose was 225 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 patients with Social Anxiety Disorder 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. (See the 'Use in Patients with Concomitant Illnesses' section of PRECAUTIONS).

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 major depressive disorder, Generalized Anxiety Disorder, or Social 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 Treatment

There is no body of evidence available from controlled trials to indicate how long patients withmajor depressive disorder, Generalized Anxiety Disorder, or Social Anxiety Disorder should be treated with Effexor XR.

It is generally agreed that acute episodes of major depressive disorder require several months or longer of sustained pharmacological therapy beyond response to the acute episode. In one study, in which patients responding during 8 weeks of acute treatment with Effexor XR were assigned randomly to placebo or to the same dose of Effexor XR (75, 150, or 225 mg/day, qAM) during 26 weeks of maintenance treatment as they had received during the acute stabilization phase, longer-term efficacy was demonstrated. A second longer-term study has demonstrated the efficacy of Effexor in maintaining a response in patients with recurrent major depressive disorder who had responded and continued to be improved during an initial 26 weeks of treatment and were then randomly assigned to placebo or Effexor for a period of up to 52 weeks on the same dose (100-200 mg/day, on a bid schedule) (see "**Clinical Trials**" under "**CLINICAL PHARMACOLOGY**"). Based on these limited data, it is not known whether or not the dose of Effexor/Effexor XR needed for maintenance treatment is identical to the dose needed to achieve an initial response. Patients should be periodically reassessed to determine the need for maintenance treatment and the appropriate dose for such treatment.

In patients with Generalized Anxiety Disorder, Effexor XR has been shown to be effective in 6-month clinical trials. The need for continuing medication in patients with GAD who improve with Effexor XR treatment should be periodically reassessed.

In patients with Social Anxiety Disorder, there are no efficacy data beyond 12 weeks of treatment with Effexor XR. The need for continuing medication in patients with Social Anxiety Disorder 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. Patients who have received Effexor XR for 6 weeks or more should have their dose tapered over at least a 2-week period. 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.

Discontinuation symptoms have been systematically evaluated in patients taking venlafaxine, to include prospective analyses of clinical trials in Generalized Anxiety Disorder and retrospective surveys of trials ofmajor depressive disorder. Abrupt discontinuation or dose reduction of venlafaxine at various doses has been found to be associated with the appearance of new symptoms, the frequency of which increased with increased dose level and with longer duration of treatment. Reported symptoms include agitation, anorexia, anxiety, confusion, coordination impaired, diarrhea, dizziness, dry mouth, dysphoric mood, fasciculation, fatigue, headaches, hypomania, insomnia, nausea, nervousness, nightmares, sensory disturbances (including shock-like electrical sensations), somnolence, sweating, tremor, vertigo, and vomiting. It is therefore recommended that the dosage of Effexor XR be tapered gradually and the patient monitored. The period required for tapering may depend on the dose, duration of therapy and the individual patient. Discontinuation effects are well known to occur with antidepressants.

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).

The appearance of these capsules is a trademark ofWyeth Pharmaceuticals.

Wyeth Laboratories
A Wyeth-Ayerst Company
Philadelphia, PA 19101

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On Original

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-699/S-022

APPROVABLE LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-699/S-022

Wyeth-Ayerst Laboratories
Attention: Kenneth R. Bonk
Associate Director II, Worldwide Regulatory Affairs
P.O. Box 8299
Philadelphia, PA 19101

Dear Mr. Bonk:

Please refer to your supplemental new drug application dated September 10, 2001, received September 12, 2001, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Effexor XR (venlafaxine HCl) Extended-release Capsules.

We acknowledge receipt of your amendments dated December 26, 2001, and February 28, 2002.

This supplemental new drug application provides for the use of Effexor XR (venlafaxine HCl) Extended-release Capsules for the treatment of social anxiety disorder.

We have completed the review of this application, as submitted with the draft labeling, and it is approvable. Before this application may be approved, however, it will be necessary for you to address the following:

Labeling

Accompanying this letter as an attachment is our proposal for the labeling for Effexor XR Extended-release Capsules for the social anxiety disorder indication. Please submit revised draft labeling identical in content to the enclosed labeling (text for the package insert). Explanations for our proposed changes are provided in the bracketed comments embedded within the proposed text. We would be happy to discuss these proposed changes in more detail through a teleconference if you wish.

Safety Update

Under 21 CFR 314.50(d)(vi)(b), we request that you provide a final safety update for Effexor XR Extended-release Capsules for social anxiety disorder.

Regulatory Status Update

Please provide any new information on the worldwide regulatory status of Effexor XR Extended-release capsules for social anxiety disorder, including the status of all actions either taken or pending before foreign regulatory authorities.

World Literature Update

Prior to approval, we will require an updated report on the world archival literature pertaining to the safety of this product for this indication.

In addition, all previous revisions as reflected in the most recently approved labeling must be included. To facilitate review of your submission, please provide a highlighted or marked-up copy that shows the changes that are being made.

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

Within 10 days after the date of this letter, you are required to amend the supplemental application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of any such action FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

Under 21 CFR 314.102(d) of the new drug regulations, you may request an informal meeting or telephone conference with this division to discuss what further steps need to be taken before the application may be approved.

This product may be considered to be misbranded under the Federal Food, Drug, and Cosmetic Act if it is marketed with these changes prior to approval of this supplemental application.

If you should have any questions, please call Ms. Anna Marie H. Weikel, R.Ph., Regulatory Health Project Manager, at (301) 594-5535.

Sincerely,

{See appended electronic signature page}

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

Enclosure

42 page(s) of draft labeling has been removed from this portion of the review.

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/s/

Russell Katz
7/9/02 10:58:45 AM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-699/S-022

MEDICAL REVIEW

REVIEW AND EVALUATION OF CLINICAL DATA
Approvable Response Submission

NDA:	20-699 SE1-022 (AZ)
Sponsor:	Wyeth Ayerst
Drug	
Generic Name:	Venlafaxine hydrochloride (extended release capsules) (R/S)-1-[2-(dimethylamino)-1-(4-methoxyphenyle)ethyl] cyclohexanol hydrochloride
Chemical Name:	
Brand Name:	Effexor® XR 75 mg Venlafaxine ER capsules and placebo
Formulation:	
Indication:	Social Anxiety Disorder
Dates of Submission:	August 29, 2002
Materials Reviewed:	Response to 7/9/02 Approvable Letter: Proposed Labeling, Safety Update, Regulatory Status Update and World Literature Update (52 volumes)
Clinical Reviewer:	Karen L. Brugge, M.D.
Review Completion Date:	10/4/02

I. Background. The purpose of this review is to assist the Team Leader and Division Director in the regulatory processing of this submission. A 7/9/02 Approvable letter was sent to the sponsor for Effexor® XR (EXR) for treating Social Anxiety disorder (SAD). The present submission is a response to the Approvable Letter.

II. Sponsor's Response.

A. Safety Update. The sponsor provides a safety update of 3 SAD trials (Studies 388, 390 and 392) that were completed since their original sNDA submission. All 3 trials were parallel group, placebo controlled, multicenter, double-blind, randomized trials. These studies employed a flexible dose (75-225 mg/day) design except for one study that also had a fixed dose (75 mg/day) EXR group. Two trials (Studies 388 and 392) employed an 11 week treatment phase, while the third trial (Study 390) employed a 28 week treatment phase. All three studies had an optional 2-week taper phase. Each trial had approximately 120 to 140 subjects in each treatment group.

Deaths. One completed suicide occurred in one S (39005-167) who had a history of two previous suicide attempts and suicidal ideation.

Serious Adverse Events. A listing of serious adverse events (SAEs) is provided in the appendix as Table 1 (as provided by the sponsor). This list does not reveal any new or unexpected SAEs in EXR treated subjects (Ss). Most of the SAEs appear to be due to underlying and/or pre-existing conditions.

Adverse Dropouts. A review of a summary table of the incidence rate of adverse dropouts by Preferred Term for each treatment group of each of the three trials was conducted. This review failed to reveal any remarkable or new adverse events not already described in the Approvable version of proposed labeling (the version sent to the sponsor with the Approvable Letter). One EXR adverse dropout was due to hyperlipemia. Sections of labeling currently describe hypercholesterolemia (in the Approvable Letter version).

B. Regulatory Status Update. Applications for marketing EXR for the SAD indication were submitted to the following countries (submission dates provided):

- Canada on 11/6/01
- Mexico on 6/27/02-approved
- Philippines on 1/27/02-approved
- Venezuela on 2/13/02

No EXR SAD applications were rejected in any country and EXR has not been withdrawn from the market in any country for any reason.

C. World-Literature Update. The sponsor conducted a literature search between the dates of 1/11/01 and 7/17/02 on EXR for treatment of SAD using search methods similar to that employed for the original sNDA submission. The search yielded a total of 27 review articles and 2 case reports. No new safety findings were reported.

D. Proposed Labeling. For the purpose of this review the sponsor's proposed labeling (provided in Attachment 1 in volume 1 of the hard copy submission) was reviewed as described in the following. Any changes noted on page 3 in Attachment 1 of the submission or in proposed labeling (as indicated by strike through or double underline) were compared to the Approvable version of labeling (the version sent to the sponsor with the Approvable Letter). Additionally, any changes in the Approvable version were compared to corresponding sections of the sponsor's response version of labeling.

Based on the above review, the sponsor's proposed labeling generally reflects that submitted in the Approvable version with only a few minor editorial changes and the insertion or correction of numbers or values, as requested in the Approvable version. These corrected numbers correspond to values that appear in copies of summary tables in the present submission, of data that the sponsor provided in previous submissions under this NDA. In conclusion the sponsor generally agrees with the Approvable version of labeling and proposed changes appear to be acceptable.

III. Conclusions and Recommendations

The sponsor does not report any new or unexpected safety findings. Also, the proposed labeling appears to generally be in agreement with the Approvable version with a few minor editorial changes that appear to be acceptable.

Karen Brugge, M.D., Date 10/4/02
Medical Reviewer,
FDA CDER ODE1 DNDP HFD 120

cc: IND/HFD 120/HFD 120/K Brugge/A Homonnay/T Laughren

Table 1. Listing of Serious Adverse Events Reported in Studies 388, 390 and 392

Treatment Patient Number	Age[a] (y)	Sex	Mean Daily Dose (mg)	Days on Therapy at Onset	Adverse Event Preferred Term (Verbatim)	Discontinuation Because of Identified Adverse Event	Drug Relationship	Outcome	Duration (days)
					Study 0600B4-388-EU				
Placebo									
388011-408[b]	30	F	–	Poststudy	Suicide attempt	No	NR	Resolved	1
Venlafaxine ER									
388012-441[b]	32	M	188.7	29	Accidental injury (Faciocranial trauma)	No	NR	Resolved	1
388022-859[b]	32	M	75.0	Poststudy	Suicide attempt (*Attempted suicide with a blade*)	No	NR	Resolved	1
388034-1326[b]	34	F	198.2	Poststudy	Unintended pregnancy (Pregnancy)	No	NR	Resolved	246
					Study 0600B4-390-US				
Placebo									
390007-271[b]	20	F	–	33	Intentional overdose - Prozac (intentional suicidal gesture)	Yes	NR	Resolved	2
	20	F	–	26	Intentional overdose - Xanax (intentional suicidal gesture)	No	NR	Resolved	2
Venlafaxine ER 75 mg									
390010-362[b]	35	M	72.3	39	Abdominal syndrome acute (Appendicitis)	No	NR	Resolved	2
390005-167[b]	22	M	176.8	86	Suicide (Completed suicide)	Yes	NR	Death	1
390007-255[b]	28	M	197.3	35	Dehydration	No	NR	Resolved	2
				35	Ketosis (Ketoacidosis with elevated anion gap)	No	NR	Resolved	2
				34	Vomiting (Vomiting secondary to food poisoning)	No	NR	Resolved	2
				173	Flu syndrome (Acute diabetic ketoacidosis secondary to influenza)[c]	No	NR	Resolved	3
				173	Ketosis (Acute diabetic ketoacidosis secondary to influenza)[c]	No	NR	Resolved	3
				168	Infection (Viral infection)	No	NR	Resolved	3
390007-269[b]	36	F	74.1	167	Unintended pregnancy (Pregnancy)	Yes	NR	Resolved	Persisted
390016-631[b]	65	F	208.6	133	Paranoid reaction (Schizophrenia, paranoid type)	Yes	NR	Persists	Ongoing
				133	Schizophrenic reaction (Schizophrenia, *paranoid type*)	Yes	NR	Persists	Ongoing
390019-769[b]	49	F	176.6	43, 87	Hypertension (Worsening hypertension; Uncontrolled hypertension)	Yes	NR	Resolved	15
					Study 0600B4-392-US				
Placebo									
392015-561[b]	53	M	–	26	Skin carcinoma (basal cell carcinoma of nose)	No	NR	Resolved	1
392023-882[b]	27	F	–	49	Unintended pregnancy (pregnancy)	Yes	NR	Resolved	19
392025-0970[b,d]	45	M	–	Placebo lead-in	Abdominal syndrome acute (appendicitis)	Yes	NR	Resolved	2
Venlafaxine ER									
392021-820[b]	30	F	75	20	Unintended pregnancy (pregnancy)	No	NR	Resolved	227
Paroxetine									
392015-570[b]	41	F	34.5	28	Deep thrombophlebitis (deep venous thrombosis left upper leg)	Yes	NR	Resolved	8
392025-976[b]	46	M	33.8	34	Accidental injury (fractured left hip)	Yes	NR	Unknown	1

a: Age at study entry.
b: An IND safety report was filed for this patient.
c: The verbatim term for both the events 'flu syndrome' and 'ketosis' was 'acute diabetic ketoacidosis secondary to influenza.'
d: The patient had received 1 dose of placebo in the prestudy lead-in period at the time of this adverse event. He returned the remainder of the prestudy drug supply and was lost to follow-up. He was never randomized to a double-blind treatment group, was considered to be a screen failure, and is not part of the safety population of this report. This serious adverse event resulted in an IND safety report.

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/s/

Karen Brugge
10/4/02 04:36:53 PM
MEDICAL OFFICER

Thomas Laughren
12/6/02 02:45:54 PM
MEDICAL OFFICER
I agree that this supplement can now be approved; see memo to file for more detailed comments.--TPL

REVIEW AND EVALUATION OF CLINICAL DATA

NDA:	20-699 S-022
Sponsor:	Wyeth Ayerst
Drug	
Generic Name:	Venlafaxine hydrochloride (extended release capsules) (R/S)-1-[2-(dimethylamino)-1-(4-methoxyphenyle)ethyl] cyclohexanol hydrochloride
Chemical Name:	
Brand Name:	Effexor® XR 75 mg Venlafaxine ER capsules and placebo
Formulation:	
Indication:	Social Anxiety Disorder
Dates of Submission:	September 10, 2001
Materials Reviewed:	Efficacy Supplement of Clinical Trials 387 and 393 (see Section IVA for complete listing)
Clinical Reviewer:	Karen L. Brugge, M.D.
Review Completion Date:	4/25/02

EXECUTIVE SUMMARY

Purpose of this review: The purpose of this summary and review are to assist the Team Leader and Director of the Division of Neuropharmacological Drug Products in the regulatory processing of this supplemental NDA 20-699, S-022 submission. The summary provides a brief overview of the Clinical review.

Background and Overview of Clinical Studies. Effexor® XR (EXR) is an extended release capsule formulation of an immediate release tablet formulation, Effexor® (venlafaxine hydrochloride). Venlafaxine HCl is believed to be a serotonin and norepinephrine reuptake inhibitor that is also a weak dopamine reuptake inhibitor. EXR is approved for treatment of major depressive disorder and generalized anxiety disorder. The sponsor is now requesting approval for a new indication of EXR, social anxiety disorder (SAD). The sponsor conducted two SAD trials (Studies 387 and 393) to support their claim.

Study Methods and Study Populations. Each study was a 12-week, multicenter, randomized, double-blind, placebo controlled, parallel group, flexible dose (75 to 225 mg/day of EXR) trial. A one-week single-blind placebo run-in phase was followed by a 12-week double-blind treatment phase of placebo or EXR treatment. The subjects (Ss) of Studies 387 and 393 consisted of 280 and 276 randomized (male and female) outpatients (≥18 years old), respectively, with DSM-IV SAD (generalized) and were otherwise generally healthy. These study populations were enriched by the use of a placebo run-in phase and requiring that Ss meet eligibility criteria on the basis of scores on SAD and anxiety rating scales (must exceed a minimum cut-off score). The study populations were further enriched by requiring that they scored less than a maximum cut-off score on rating scales for depressive symptoms.

Approximately 56% of the Ss in the two studies (pooled) were male and the majority of them were Caucasian (approximately 78%). Their mean age was approximately 39 ±13 years with only 5% of the Ss (25 Ss) 60 years of age or older (mean weight was approximately 79±18 kg.). Treatment groups were generally similar on demographic features and on mean baseline efficacy rating scores in each study. Exposure of Ss to EXR in the two studies, combined, was approximately 47.54 (N=277) mean patient years and the mean daily dose of the completers (N=165) was 184 mg of EXR.

Primary Efficacy Results. The EXR group of each study showed significantly greater improvement from baseline to treatment endpoint on the Leibowitz Social Anxiety Scale (LSAS total score) compared to the placebo group ($p \leq 0.01$). The EXR group showed a raw mean score improvement of approximately 18 score points compared to a raw mean score improvement of approximately 10 score points in the placebo group in each study. These primary efficacy results are based on an analysis of the last observation carried forward (LOCF) dataset of the Intent to Treat (ITT) Efficacy population (Ss with at least one dose of the study drug, who had both, a baseline LSAS assessment and at least one on-therapy LSAS assessment). An analysis of covariance (ANCOVA) with the baseline LSAS score as the covariate was conducted for the primary analysis. The sponsor also used nonparametric tests, which also yielded significant treatment group effects. Results of secondary analyses (OC dataset and results on additional efficacy variables) revealed results that were generally consistent with that of the primary analysis.

Safety Results. The safety profile of EXR generally appears similar to that observed in other patient populations and as described in EXR labeling. Clinically relevant findings included elevation in cholesterol and triglyceride levels (the latter was only observed in outlier safety results) in EXR Ss compared to controls, as well as small elevations in some of the liver enzyme

blood levels. The known hypertensive effects of EXR and a small prolongation in the mean QTc interval in EXR Ss compared to controls were also observed. The magnitude of these effects was similar to those previously observed in other patient populations and is also described in current EXR labeling.

Three additional safety observations are noted, but are considered preliminary and clinically unremarkable. One preliminary finding was a possible small signal for orthostatic hypotension in EXR Ss compared to controls in the SAD trials. Results of trials of other patient populations are also suggestive of a possible small signal, as described in previous reviews of EXR submissions. However, treatment group mean differences in orthostatic measures were only approximately 102 mmHg in the SAD trials, and therefore, do not appear to be clinically remarkable or significant. A second safety observation was of urinary pH results, together with small treatment group differences on chloride and bicarbonate blood levels that were suggestive of a small indirect or direct metabolic effect. These observations may be reflecting sudden inappropriate antidiuretic hormone secretion (SIADH). However, results on the treatment group mean blood sodium levels or incidence rates of outliers failed to show evidence for a treatment group SIADH-like effect. These chemistry results may also be due to artifact or a Type I error due to multiple comparisons. Current labeling describes SIADH and includes precautionary statements regarding volume-depleted patients, elderly patients and concomitant use of EXR with diuretics. Overall, these chemistry and orthostatic vital sign safety results are considered preliminary and unremarkable for several reasons. Observed treatment group differences were small, the chance of making a Type I error is likely given that multiple comparisons were conducted on multiple parameters, and finally these observations are based on a *post hoc* examination of the sponsor's results, among other reasons.

A third safety observation in the SAD trials was a possible gender effect on treatment group differences in the incidence rate of the following adverse events (AEs): nervousness, anxiety, sweating, decreased libido and impotence. These results may be reflecting other confounding variables, such as gender differences in reporting rate on a given AE, as well as the possibility for a Type I error due to multiple comparisons, among other possible considerations.

Conclusion. In conclusion, two adequately controlled 12-week multicenter trials (Study 387 and 393) revealed positive results that support the sponsor's efficacy claim for the new indication of EXR, SAD. The study results support a treatment regimen that uses a starting daily dose of 75 mg/day that is titrated up to a maximum dose of 225 mg/day. EXR treatment, as employed in the SAD trials, is also adequately safe for this patient population based on the safety results of these two trials, together with that already known about EXR in other patient populations. Furthermore, the safety profile of EXR in the SAD population is generally similar to that observed in previous clinical trials and to that described in current labeling. From a Clinical perspective and pending confirmation of the efficacy results by Biometrics, it is recommended that this supplemental NDA be given an approvable status.

I. Introduction and Background.

This review is to assist the Team Leader and Director of the Division of Neuropharmacological Drug Products in the regulatory processing of NDA20-699 S-022.

A. Indication and Proposed Direction of Use

Effexor® XR (EXR) is an extended release formulation of Effexor® (venlafaxine hydrochloride). The mechanism of action of venlafaxine HCl is believed to be as a serotonin and norepinephrine reuptake inhibitor that is also a weak dopamine reuptake inhibitor. The sponsor is requesting approval for a new indication of EXR, social anxiety disorder (SAD). The proposed recommended treatment for SAD is a starting oral daily dose of 75 mg followed by dose increments of up to 75 mg/day at intervals of no less than 4 days, as needed. The proposed labeling describes clinical trials as treating SAD patients with a maximum dose of up to 225 mg/day. It is recommended that some patients (venlafaxine HCl naïve patients) may be started on a lower dose of 37.5 mg/day for 4 to 7 days in order to adjust to the medication.

B. State of Armamentarium for Indication

Several classes of pharmacological drug products are currently approved for treatment of various types of DSM-IV Anxiety disorders, but are not approved specifically for SAD. However, paroxetine hydrochloride, a serotonin selective reuptake inhibitor is approved for the SAD indication.

C. Administrative History and Related Reviews

EXR is approved for treatment of major depressive disorder and generalized anxiety disorder. The original NDA submission for this drug (NDA 20-699) was approved on 10/20/97 and the Immediate release formulation of Effexor® was approved on 12/28/93 (NDA 20-151).

II. Clinically Relevant Findings from Chemistry, Animal Pharmacology and Toxicology, Microbiology, Biopharmaceutics, Statistics, and/or other Consultant Reviews.

This submission only contains Clinical and Biometric information for purpose of supporting a new efficacy claim. The statistical information is under review by Biometrics. At the time of this writing there are no biometric issues.

III. Human Pharmacokinetics and Pharmacodynamics

There is no new biopharmaceutical information in this submission. Refer to Section I (Background) section that describes pharmacodynamic properties of venlafaxine HCl. The pharmacokinetics (PK) of EXR, is described in labeling. For the convenience of the reader the PK properties of EXR are summarized as Attachment 1 in the appendix of this review.

IV. Description of Clinical Data and Sources

A. Overall Data: Materials from NDA/IND

The following table itemizes materials utilized during the course of this clinical review.

Documents Utilized in Clinical Review	
DATE	DESCRIPTION
March 23, 2001	• NDA 20-699 S-022 Electronic version and hard desk copies of annotated labeling, study reports of studies 393 and 387 (not including supplemental volumes), Integrated Summary of Safety and Integrated Summary of Efficacy, CRT and CRF folders (20 total items). • 12/26/01 BZ submission: a response to questions (10/23/01 facsimile to the sponsor). • 2/28/02 BM submission: a response to questions (1/29/02 facsimile to the sponsor).

B. Tables Listing the Clinical Trials

Table IV.B.1. Clinical Studies Reviewed from this Submission

Protocol No	Study Design	Treatment Groups	N (Completers) per Treatment group (% of ITT Efficacy Pop.*)	N (ITT Efficacy Pop.) * per Treatment group	N (ITT Safety Pop.) ** per Treatment group	Randomized Population
387 Flexible Dose 12-Week Trial	Multicenter, Double blind, Randomized, Flexible dose, Parallel group (19 Canadian & U.S. sites)	75-225 mg/day venalafaxine extended release group Placebo group	88 (66%) 85 (62%) **Total: 173**	133 138 **Total: 271**	140 139 **Total: 279**	141 139 **Total: 280**
393 Flexible Dose 12-Week Trial	Multicenter, Double blind, Randomized, Flexible dose, Parallel group (17 U.S. sites)	75-225 mg/day venalafaxine extended release group Placebo group	77 (61%) 95 (70%) **Total: 172**	126 135 **Total: 261**	137 135 **Total: 272**	138 138 **Total: 276**

*ITT (Intent to Treat) Efficacy population: randomized subjects having at least one dose of double blind study drug and at least one baseline and one on-therapy Liebowitz Social Anxiety Scale assessments.
**ITT Safety Population: randomized subjects having at least one dose of double blind study drug.

C. Post-Marketing Experience

According to the sponsor, EXR is approved for marketing in 75 foreign countries and has not been withdrawn from the market "in any country for any reason." The sponsor has not submitted any foreign applications for authorization to market EXR for the indication of SAD. Effexor® IR and EXR have been marketed in the US for approximately 9 and 5 years, respectively (refer to previous section on Administrative History and Related Reviews, Section I C regarding US applications).

D. Literature Review

The sponsor conducted a literature search for EXR in social phobia (social anxiety disorder) populations using a number of databases, with adequate search methods as described elsewhere in this review (see Section VII M: Integrated Safety Information; Safety Results from Other Sources for details).

V. Clinical Review Methods

A. Materials Reviewed.

Refer to Section IV, above, regarding materials utilized for this review and for a summary of the clinical trials described in the submission.

B. Adequacy of Clinical Experience.

The sponsor makes their claim for the efficacy of EXR in the treatment of SAD in which they describe two multicenter, placebo controlled, flexible dose, randomized, parallel group, double-blind 12 week trials (878 and 393) in the proposed labeling. These included a total of approximately 432 subjects (Ss) in the Intent to Treat (ITT) Efficacy population and a total of over 500 randomized Ss (see previous Section IV for table of all clinical trials). The data from these two studies and safety information, as described in the submission are adequate to review, along with that already known regarding the safety of EXR, as described in current approved labeling.

C. Data Quality and Completeness

Based on the results of various comparisons made between listings, tables, Case Report Forms (CRFs), and/or narratives (as described in Attachment 2 of this review), the submission generally appears to show adequate accuracy, consistency and content of information. Therefore, the quality and completeness of the data described in the submission is considered to be adequate.

D. Evaluation of Financial Disclosure

The sponsor was able to contact most investigators for the two SAD trials (Studies 387 and 393) based on their listing of investigators in the Financial Disclosure section of the submission. Only a few could either not be reached or had financial arrangements that required disclosure, whereas the majority of investigators were listed as having no disclosable financial arrangement. A total of 6 investigators were reported as having financial arrangements that were primarily for reasons such as follows: participation in a Visiting Professor Program and other education programs, travel expenses, and consultations for amounts exceeding [redacted] One investigator [redacted] is described as a subinvestigator under a Principal Investigator, Dr. Michael Liebowitz who has equity interest in [redacted] exceeding [redacted] with a total of [redacted] However, this study site only had 14 randomized Ss in Study 387 and [redacted] was reported as not having any involvement with safety or efficacy data analyses and is not anticipated to "directly benefit from the sale" of the drug product. Studies were conducted in a manner to minimize any potential bias (e.g. were multicenter studies that used double-blind and randomized methods).

VI. Integrated Review of Efficacy

A. Review of Studies for Which Efficacy Claims Are Made

Studies 387 and 393 appear to be identical in methodology. Study 393 was conducted at US study sites, while Study 387 was conducted at Canadian and US sites. One investigator, Dr. Grosz, was involved with both studies and had 27 randomized Ss in Study 393 and 13 randomized Ss in Study 387. The two studies are summarized in Table IV.B.1 (see Section IV.B, above). These 12-week studies were multicenter, randomized, double-blind, placebo controlled, parallel group, flexible dose (75 to 225 mg/day of EXR) studies. The primary efficacy variable was the mean change from baseline to the last on-therapy total score on the Leibowitz Social Anxiety Scale (LSAS total score). The primary analysis was conducted using the last observation carried forward (LOCF) dataset of the ITT Efficacy population (Ss with at least one dose of the study drug, who had a baseline LSAS assessment and at least one on-therapy LSAS assessment). An analysis of covariance (ANCOVA) with the baseline LSAS score as the covariate was conducted to determine treatment group and study center main effects

and interaction effects on the primary efficacy variable. Nonparametric analysis were also conducted as well as a secondary analysis on the OC dataset. Additional efficacy variables and statistical analyses were also performed as a secondary analysis for treatment group effects on secondary variables. Each study had approximately 270 randomized Ss with approximately 170 Ss in each study who completed the trial (approximately 80 Ss who were completers in each treatment group of each study). The results of these studies showed significant treatment group effects on the primary efficacy variable in which greater improvement on the LSAS total score was observed in the EXR group compared to the placebo group if each study. Assumptions of normality of the efficacy data were not met, according to that described by the sponsor. Hence, nonparametric tests were also conducted which yielded positive results, similar to that revealed by the ANCOVA analyses. Other secondary analyses and on secondary variables, were generally consistent with those on the primary efficacy measure.

B. Studies 387 and 393, Double-blind, Placebo-controlled Studies of a Flexible Dose of Venlafaxine ER in Adult Outpatients with Generalized Social Anxiety Disorder.

1. Investigators and Sites
See Tables VI.B.1 and VI.B.2. in the appendix (as provided by the sponsor) are investigative site listings for Studies 387 (19 sites) and 393 (17 sites), respectively.

2. Objectives
The objective of each of the two studies was to determine the efficacy, safety and tolerability of EXR treatment (flexible dose of 75 to 225 mg/day) over 12 weeks in outpatients with SAD (generalized) compared to placebo treatment.

3. Study Population
The study populations of Studies 387 and 393 consisted of 280 and 276 randomized (male and female) Ss, respectively, who were generally healthy, at least 18 years old, and were outpatients with DSM-IV SAD (generalized). See Table IV.B.1 (in section IV B, above) and Section VIB.7 (below) for a further breakdown and disposition of Ss. The submission lists inclusion and exclusion criteria with some of the key criteria described below. The sponsor described specifications regarding permitted and prohibited use of medications (including herbal supplements). Psychiatric comorbidity and the use of concomitant medications in the study population are described in later sections.

Key Inclusion Criteria (not a complete list).
Ss were required to have the following:

- SAD, generalized (DSM-IV) for at least 6 months prior to study entry.
- The following rating scores:
  - Clinical Global Impressions Severity of Illness (CGI-S) score (item 1) of ≥ 4 at baseline.
  - LSAS total Score ≥ 50 at screening (prestudy) and at baseline that also shows a decrease of < 30 between screening and baseline assessments.
  - Raskin Depression Scale total score ≤ 9 at screening
  - Covi Anxiety Scale total score > Raskin Depression Scale total score at screening

Ss with the following were excluded from the study (not a complete list of the exclusion criteria):

- A Hamilton Depression Depression (HAM-D) score ≥ 15 (on the first 17 items) or a score of > 2 on item 1 (Depressed Mood item) at screening.
- Raskin Depression score > 3 on any single item or a total score of > 9 at screening.
- Acutely suicidal, requiring suicidal precautions
- Any clinically important Axis I or II (DSM-IV) disorders (other than SAD) that are current or were predominant within 6 months prior to study entry

Exclusion criteria also included several conditions listed under Contraindications and Precautions sections of current approved EXR labeling (such as seizures, increased intraocular pressure or history of narrow angle glaucoma, among other conditions).

4. Design

Studies 387 and 393 employed virtually the same methods. Both studies used a randomized, double blind, placebo controlled, multi-center, flexible dose (75-225 mg/day of EXR), parallel group design. The studies had a one-week lead-in phase of single blind placebo treatment. The lead-in phase was followed by a 12 week double-blind treatment phase upon which eligible Ss were randomized (1:1) to receive either EXR or placebo. There was an optional taper phase for a period of up to 14 days.

Treatment during the lead-in phase was one capsule of single-blind placebo taken daily (orally). Treatment during the double-blind phase is shown in the following table (using 75 mg EXR capsules and matching placebo capsules).

Dosing Schedule During the Double Blind Treatment Phase (Days 1-84) of Studies 387 and 393*			
Treatment Group	**Days 1-7±3**	**Days 8-14±3**	**Days 15 (±3) - 75**
EXR**	1 EXR cap***	1 or 2 EXR cap	1,2 or 3 EXR cap
Plac**	1 Plac cap	1 or 2 Plac cap	1,2 or 3 EXR cap
*This table is similar to Table 6.4.1A of the Protocol 387 volume of the submission **EXR=Venlafaxine extended release, Plac = Placebo ** cap = capsule (using 75 mg Venlafaxine ER capsules and matching placebo capsules)			

Ss took their dose with food in the morning or evening. The dose of study drug was increased by one capsule on Days 8 and 15, not to exceed a dose of 3 capsules a day (225 mg of EXR or placebo), at the discretion of the investigator and as shown in the table above. The dosage could also be reduced to a minimum of one capsule (75 mg of EXR or placebo) daily at the discretion of the investigator to improve tolerance. No dummy dosing was employed during the treatment or taper phases of the study.

Treatment during the optional taper phase in Studies 387 and 393 lasted for up to 14 days in placebo and EXR groups. This taper phase was omitted or prolonged, as medically indicated. Ss receiving placebo or EXR for over one week at a dose of 2 or more capsules a day (75 mg EXR or placebo capsules) underwent the taper phase in which the dose was decreased at weekly intervals by decrements of one capsule per week. Consequently Ss taking 3 capsules daily during the double-blind treatment phase were decreased to 2 capsules a day for one week during the taper phase, followed by a decrease to 1 capsule a day for one week (the second week of the taper phase). Ss taking 2 capsules a day during the double-blind treatment phase took one capsule daily, for one week during the taper phase and Ss taking 1 capsule a day during the double-blind treatment phase did not undergo a taper phase.

Safety and efficacy assessments were conducted at screening and baseline visits, at study visits during the treatment and taper phases of the study, as described in the next section.

5. Assessments Employed for Studies 387 and 393

Refer to Table VI.B.3 in the appendix for the study flow chart regarding efficacy, safety and screening assessments employed in studies 387 and 393 (as provided in the submission). As shown in Table VI.B.3, various assessments were conducted at screening, baseline (following a one-week single blind placebo run-in phase), and on weeks 1, 2, 3, 4, 6, 8, 10 and 12 during the 12 week treatment phase (or upon early termination).

Primary Efficacy Assessments.

- LSAS

Secondary Efficacy Measures:

- Clinical Global Impressions Scale for Improvement (CGI-I) and CGI-Severity (CGI-S)
- Social Phobia Inventory (SPIN)
- Sheehan Disability Inventory (SDI)

  Other Depression or Anxiety Scales (conducted only at prestudy, weeks 6 and 12):
  - Covi Anxiety Scale
  - Raskin Depression Scale
  - HAM-D

Safety assessments:

- Recording of adverse events
- Vital signs (supine pulse rate, supine and standing blood pressure)
- Physical examination
- 12-lead ECG
- Laboratory parameters (fasting):
  - Hematology, blood chemistry screen (includes measures of renal function, electrolytes, glucose, liver function tests, among others)
  - Urinalysis
  - Serum beta-HCG in women of childbearing potential at screening only
  - Free thyroxine index at screening only
  - Urine drug screen at screening only

In addition to the safety assessments conducted at screening and baseline visits, as above, a psychiatric evaluation was conducted at screening, that included a Mini International Neuropsychiatric Interview (MINI).

6. Analysis Plan for Studies 387 and 393

Dataset Analyzed. The ITT Efficacy dataset was analyzed. The ITT Efficacy dataset was defined as data from Ss who had at least one dose of double blind study drug, a baseline LSAS assessment and at least one on-therapy LSAS assessment. An on-therapy assessment was defined as an assessment conducted within 3 days of the S's final full dose of study drug during the double-blind treatment phase of the study (also referred to as the 3-day rule). The last

observation carried forward (LCOF) dataset was used for the primary analysis, but the observed cases (OC) dataset was also analyzed. The sponsor notes (in the supplemental sections of the study reports of the submission) that only 3 EXR Ss in Study 387 and 6 EXR Ss in Study 393 failed to satisfy the 3-day rule on the LSAS assessment (4 to 6 EXR Ss in each study failed to satisfy the rule on the SPIN and CGI-S assessments). Consequently, data from these Ss were excluded from the primary analysis. It is also noted that all LSAS tests were complete (data was not missing from any of the test items) in Study 393, and 99.9% of the LSAS tests (a total of 2383 tests) were complete in Study 387.

The Primary Efficacy variable:

- The mean change from baseline to the last on-therapy assessment (the LOCF dataset) on the LSAS total score.

The Secondary Efficacy Variables:

a. Mean change from baseline to the last on-therapy assessment (the LOCF dataset) on the following scores:

- CGI-S
- CGI-I
- SPIN
- SDI
- LSAS fear and avoidance

b. Responders on the CGI-I was defined as having a score of 1 (very much improved) or 2 (much improved).

Statistical Tests Employed. For continuous variables, treatment and center main effects and interaction effects an analysis of covariance (ANCOVA) model was employed covarying for the baseline measure. Since the CGI-I is a score on improvement relative to baseline (a baseline measure is not applicable), this secondary efficacy variable was analyzed using a treatment by site analysis of variance (ANOVA) model. However, since only 17% of Ss scored 6 or greater on the CGI-S at baseline, the baseline CGI-S scores were categorized into two categories (a score of 4 or a score of ≥ 5) which were entered in the model.

The sponsor describes statistical methods for testing three assumptions regarding the use of ANCOVA model (in supplemental sections of the study reports). The three tested assumptions were parallelism of regression lines, homogeneity of variances and normality. A treatment group by covariate (baseline measure) interaction effect was considered significant if the p value was 0.05 or less. If a significant interaction effect was revealed, then the treatment effect results were then described at various levels of the baseline covariate. Additional statistical methods, including secondary analyses are described in detail in the submission.

7. Patient Disposition

Study 387: A total of 279 Ss were randomized (an additional S was randomized but did not return for Day –1 assessments) of which 173 (62%) were completers. Refer to Table IV.B.1 (in section IV B, above) for a breakdown of these Ss by ITT Safety and Efficacy populations and by completers and randomized Ss in each treatment group. Eight (7 EXR Ss and 1 Placebo S) of the 279 randomized Ss (3%) were not included in the primary efficacy analysis (the ITT Efficacy population, LOCF dataset). These Ss were excluded from the analysis because they failed to

have an LSAS assessment at post-baseline or within 3 days of their final full dose of study drug during the double-blind treatment phase of the study.

Table VI.B.4 in the appendix (as provided in the submission) summarizes the enumeration and disposition of Ss of the ITT Safety population for Study 387. In summary the treatment groups were similar in the incidence of withdrawals in each category of reason except for withdraw due to lack of efficacy (2% and 15% EXR and Placebo groups, respectively) or due to an adverse event (17% and 6% of Ss in each treatment group, respectively). A significant treatment group effect was observed in each of these two categories ($p \leq 0.001$ and $p < 0.01$, respectively).

Study 393: A total of 272 Ss were randomized (an additional 3 Ss were also randomized but did not return for Day –1 assessments) of which 172 (63%) were completers. Refer to Table IV.B.1 for a further breakdown of these Ss (by ITT Safety and Efficacy, by completers and randomized Ss in each treatment group). Eleven randomized Ss in the EXR group were not included in the primary efficacy analysis since they did not have an LSAS assessment at post-baseline or within 3 days of their final full-dose of study drug. Table VI.B.5 in the appendix (as provided in the submission) summarizes the enumeration and disposition of Ss of the ITT Safety population for Study 387. As shown in this table, treatment groups were similar in incidence rates of each type of reason for withdrawing from the study, except for two categories. These categories were as follows, in which the EXR group showed a significantly greater dropout rate than the placebo group (incidence rates and p values for group comparisons are shown):

- Due to any reason (44% and 30% of EXR and placebo groups, respectively, $p < 0.02$)
- Due to an adverse event (15% and 4%, respectively, $p < 0.01$).

8. Baseline Demographics/Medical/Psychiatric Comorbidity and Baseline Efficacy Measures for Studies 387 and 393

Baseline Demographics. Treatment groups (ITT Safety Population) in each study and across the two SAD trials were generally similar on various demographic parameters (mean age and weight, proportion of Ss by gender, ethnic origin, and duration of the current episode of SAD). Refer to Table VII.B.1 in Section VII.B (the Integrated Safety section of this review) for a summary of demographic features of placebo and EXR Ss in the two SAD studies, combined. This table shows that approximately 56% of the Ss in the two studies (pooled) were male, and the majority of Ss were Caucasian (approximately 78%). The mean age of the Ss was approximately 39 ±13 years in which only 5% Ss (25 Ss) were 60 years in age or older. The mean weight of the study population was approximately 79±18 kg.

Medical and Psychiatric Comorbidity. The sponsor was asked in a 10/23/01 facsimile to provide incidence rates of concomitant medical and psychiatric disorders in each treatment group (ITT Safety population) of each SAD study. However, according to that described in their 12/26/01 response submission (BZ submission), this data was not collected in a standardized manner to allow for determination of actual incidence rates of concomitant disorders. However, various exclusion criteria were employed to exclude Ss with concomitant active disorders, as previously described (including exclusion of Ss with various medical conditions and abnormal values on clinical assessments).

Using data collected from the MINI, the sponsor described the following results on concomitant psychiatric conditions (in the 12/26/01 submission). Only 14 Ss among the two SAD studies had positive responses on the MINI for current or past disorders (other than for SAD). In summary, the majority of positive responses were for a past history of depression (4 Ss, of which one S also reported a history of mania) or anxiety disorders (6 Ss who reported anxiety disorders, such as Panic disorder, agoraphobia and Post-traumatic Stress disorder).

Treatment groups (Safety Population) appeared to be numerically similar on group mean baseline efficacy scores as shown in the following table (similar to that provided by the sponsor).

Treatment Group Mean Scores (and ±SD when available) on Efficacy Measures at Baseline for Each Study (387 and 393)				
	Study 387		Study 393	
Efficacy Measure	**Placebo Group (N=138)**	**EXR group (N=133)**	**Placebo Group (N=135)**	**EXR group (N=126)**
LSAS Total	87±20	91±19	87±22	91±18
LSAS Anxiety	45	47	44	46
LSAS Avoidance	42	44	43	45
CGI-S	4.6	4.8	4.5	4.6
SPIN	42	44	43	43

Concomitant Medications.
Treatment groups within each study and across studies (during the double-blind treatment phase) appeared to be generally similar in the percentage of subjects taking concomitant medications independent of the type of medication (approximately 82% per group in each study) or for each category (by the type) of commonly used medication. Some of these more common concomitant medications were:

- Anilides (20 to 37% of Ss per treatment group)
- Propionic acid derivatives (28% to 35%/group)
- Multivitamins (15% to 28%/group)
- Salicyclic acid derivatives (10% to 18%/group)
- Progestogens and estrogens (4% to 10%/group)

9. Efficacy Results
Study 387 and 393. Results on the Primary and Secondary Efficacy Variables

Primary Efficacy Results. The efficacy results of Study 387 and 393 were generally similar. Table VI.B.6 in the appendix (as provided in the submission) shows the results on the primary efficacy and selected secondary efficacy variables. While treatment groups were similar on mean baseline efficacy scores, a significant treatment group effect was revealed in each study ($p>0.001$ and $p<0.01$, respectively) on the primary efficacy variable (the mean change from baseline to the last on-therapy LSAS total score, using the LOCF dataset and the 3-day rule). A greater improvement was observed in the EXR group than in the placebo group (the adjusted mean difference between EXR and placebo groups was –11.2 and –10.7, in Studies 387 and 393, respectively). A treatment group by study site interaction effect was not revealed in either study. Tables VI.B.7-8 in the appendix show primary efficacy results by study visit (LOCF dataset) in each of the studies.

Secondary Efficacy Results.

CGI-S, SPIN, LSAS subscale Results. Results on secondary efficacy variables (change from baseline on CGI-S, the SPIN score, the LSAS Anxiety or Avoidance subscale scores) revealed similar results to those of the primary efficacy variable (see Table VI.B.6. in the appendix). An analysis of the OC dataset on these secondary variables and on the primary variable generally revealed significantly greater improvement in the EXR group than in the Placebo group.

ANCOVA Assumption Test Results. The sponsor described results of the ANCOVA assumption tests for homogeneity, parallelism of the regression lines, and for normality of data in each of the studies (data form the LSAS total score, the SPIN and CGI-S scores were tested). These tests revealed that the assumption of normality could not be made for each of the treatment groups of each study on the primary and secondary efficacy measures (LSAS and the SPIN and CGI-S, with one exception in which the EXR group in Study 393 did show evidence for normality on the CGI). Therefore, the sponsor conducted secondary analyses on the primary and secondary variables (LSAS, SPIN and CGI-S) to determine if a significant treatment group could still be revealed, such as when nonparametric statistical methods. In summary the results of these analyses generally revealed a significant treatment effect for greater improvement in the EXR group compared to placebo in both studies (most p values ranged from 0.001 to 0.01 with each analysis on primary and secondary variables using LOCF and OC datasets). The following are the tests employed for these secondary analyses (since the hypothesis for normality of the data was rejected):

- ANCOVA based on ranks (baseline and week 12 scores were ranked for analysis of LOCF and OC datasets, without regard to any covariate)
- A one-way ANOVA on the change from baseline of the efficacy score,
- A 2-sample Wilcoxon test.

Results of Responder Analyses. A secondary efficacy variable examined by the sponsor was the percentage of responders (defined as a CGI-I score of 1 or 2 at week 12 LOCF dataset). The following table summarizes these results.

The Incidence (%) of Responders* at the Final On-Therapy CGI-I Assessment in Each Study**			
	Treatment Group		
Study	**Placebo**	**Venlafaxine ER**	**p-value versus placebo*** **
387	41/138 (30%)	58/133 (44%)	0.018
393	46/135 (34%)	63/126 (50%)	0.009
*A responder is defined as a CGI-S score of 1 or 2 on the final on-therapy visit. ** This table is similar to Table 3.3.1.2 A in the ISE volume of the submission. *** Based on a chi-square analysis with treatment group and response status as factors			

Results of Depression and Anxiety Scales. Treatment group effects on the mean change HAMD total score and the Raskin Depressions subscale score from baseline to Visit week 6 or week 12 were not revealed in either study by an ANCOVA with the baseline rating score as a covariate. However, given exclusion criteria employed for HAMD and Raskin Depression scores, it is noted that the mean scores at baseline on these scales were low (mean

HAMD of 7 units for each group and mean Raskin Depression subscale scores of 4 units per treatment group).

An ANCOVA analysis of the mean change of the Covi-Anxiety subscale score from baseline to week 6 and to week 12 showed at least a trend ($p<0.05$ in Study 393 and $p<0.01$ in Study 387) for a small treatment group effect in favor of EXR treatment on week 12, but not on week 6. The adjusted mean change in Study 387 was –2.6 and –1.9 in EXR and placebo Ss, respectively, and in Study 393 the adjusted mean change was –2.6 and –2.0 in each group, respectively.

Gender Subgroup Analysis

Due to insufficient sample sizes, results of subgroup analyses of the primary efficacy variable on the basis of age or ethnic origin are not described in this review. However, gender subgroups were of adequate sizes. This subgroup analysis revealed no significant gender main effect or treatment group by gender interaction effects for the primary efficacy variable when pooling LOCF data from both SAD studies. The following table shows the adjusted mean change from baseline to the final on-therapy on the LSAS total score in each subgroup.

The Adjusted Mean Change Mean Change on the LSAS Total Score in Each Gender Subgroup of Each Treatment Group for Studies 387 and 393 (pooled)		
Treatment Group:	**Gender Subgroup**	
EXR Group	**Male**	**Female**
	-32.8 (N=146)	-28.9 (N=113)
Placebo Group	-21.5 (N=152)	-18.3 (N=121)

10. Conclusions (Studies 387 and 393)

Both studies provide evidence for greater improvement on the primary efficacy measure (pending confirmation by the Biometric Reviewer) in outpatients with SAD treated with EXR (75-225 mg/day for 12 weeks) compared to placebo treated patients, independent of gender and study site. Secondary analyses generally results consistent with that of the primary analyses. The magnitude of the effect on the LSAS scale and in the percentage of responders appears to be consistent with that reported in other positive trials on the LSAS. Positive results in these SAD trials do not appear to be reflecting pseudospecific effects for reasons described in the next paragraph.

Psuedospecific effects are considered, particularly non-specific effects on symptoms of anxiety and depression, given that EXR is indicated for the treatment of another anxiety disorder (Generalized Anxiety disorder) and for Major depressive disorder. However, most items on the LSAS scale are cardinal symptoms of SAD, that are not observed in other anxiety disorders. Only a trend for an effect on the Covi-Anxiety subscale was observed which is an anxiety scale that is not specific to SAD. In contrast to these results, treatment group effects on the LSAS score were highly significant and appeared to be more robust. Additionally, the sponsor used inclusion/exclusion criteria to minimize potential pseudospecific effects. Consequently, Ss scored low on the HAMD and Raskin Depression scales, which in turn, failed to show significant treatment group effects. Although failure to show significant treatment group effects on these scales of depressive symptoms may be due to a floor effect, as mean scores were low at baseline. In conclusion, the positive results of the SAD trials in this submission do not appear to be reflecting pseudospecific effects, but rather an effect on SAD.

VII. Integrated Safety Information

A. Background Information

The integrated summary of safety provided in the submission were results of the two SAD trials (387 and 393). Safety information from four ongoing trials (conducted in the U.S. and Europe) is limited to information regarding 7-Day and 15-Day IND Safety reports.

The following information was provided for the two SAD trials (data was pooled): incidence rates for adverse events, descriptive statistical results of clinical parameters (laboratory, vital sign, ECG and urinalysis results). Narratives were provided for serious adverse events (SAEs) or events that were considered to be of "Clinical Interest" according to the medical monitor. Table VIIA1 in the appendix, is a listing of these SAEs (as provided by the sponsor in the 12/26/01 submission). CRFs were also provided for SAEs and deaths for the two SAD trials. This review primarily focuses on results of the two SAD trials regarding deaths, serious adverse events, adverse dropouts, incidence of adverse events, and results of laboratory, urinalysis, vital sign and ECG data.

B. Demographic Characteristics

Demographic features in the Two SAD trials combined (Studies 387 and 393). The table below summarizes the demographic features for ITT Safety population (551 total Ss), which were the randomized Ss who received at least one dose of study medication (placebo or EXR). Treatment groups were generally similar on various demographic measures (age, ethnicity, height and weight). Only 5% of Ss (25 our of 551 Ss) were 60 years in age or older.

Table VII.B.1 Summary of Demographic Features for Treatment Groups of Social Anxiety Disorder Trials, Combined (Studies 387 and 393)*

	Placebo N=274	EXR N=277
Mean±SD Age (years)	38±12	39±13
Age range (years)	18-78	18-76
Median Age	37	39
% Male	56	57
% Female	44	43
% Caucasian	77	78
% Black	9	9
% Hispanic	7	6
% Asian	3	5
% Arabic	1	<1
Afro-Caribbean	<1	0
Native American	0	<1
Other	2	1
Mean±SD Weight (kg)	78±19	79±18
Range of Weight (lbs)	47-156	45-149
Mean±SD Height (cm)	172±10	172±10
Mean±SD (Median) Duration of Social Anxiety Disorder	24±14 (24)	25±15 (25)

*This table is similar to Table 6A of the ISS in the submission.

C. Extent of Exposure

Exposure (Patient Years) of the ITT Safety Population of the Two SAD trials (Studies 387 and 393). The overall estimated exposure in patient years of the ITT Safety population is shown in the following table (the table is similar to Table 5.2A. in the ISS of the submission).

Overall Exposure in Patient Years of Subjects of the ITT Safety Population in Each Treatment Group in Studies 387 and 393		
Study	**Patient Years of Placebo Subjects**	**Patient Years of Venlafaxine ER* Subjects**
387	26.00 (N=139)	24.57 (N=140)
393	26.45 (N=135)	22.97 (N=137)
Total	52.45 (N=274)	47.54 (N=277)
*ER = extended release formulation		

Exposure (Daily Dose) of Completers in the Two SAD trials (Studies 387 and 393). The exposure of completers in EXR groups is provided in the following table. The number of completers in the placebo groups of Studies 387 and 393 were 85 Ss (61% of the ITT Safety Population) and 95 (70%) Ss, respectively.

Overall Exposure of Completers* in Venlafaxine Groups (Flexible Dose range of 75-225 mg/day) in the Social Anxiety Disorder Trials (387 and 393)					
Study (N and % of Completers in the ITT Safety Population)	**Mean±SD Daily Dose (mg)**	**Median Daily Dose (mg)**	**Range of Daily Dose (mg)**	**Distribution of Subjects by Daily Dose Range**	
				76-150 mg	**151-225 mg**
Both Studies (N=165, 59%)	184±31	198	77-211	27	138
Study 387 (N=88, 62%)	189±28	202	85-210	11	77
Study 393 (N=77, 56%)	178±33	191	77-211	16	61
*Ss who completed the study, similar to Table 1A in the 12/26/01 BZ submission in response to 10/23/01 questions					

D. Deaths

Deaths in the Two SAD Trials (Studies 387 and 393).
No deaths were reported.

Deaths in the Four Ongoing Trials (Studies 388, 389, 390, and 392)
One death was reported in the ongoing trials (Study 390). S 390005-167 is a 22 year old male who died of suicide (by gunshot). This S had a history of two suicidal attempts of overdose (with once instance also associated with wrist cutting). At the time he committed suicide, he had ongoing stressors. This death appears to be due to underlying psychiatric illness. In addition to the underlying psychopathology, the S's age, gender, and ongoing stressors were likely contributing factors (risk factors) to this S committing suicide.[1]

[1] The following provides further details of S 390005-167. The S had previously responded to Luvox and had his last dose in October of 1999. He was assigned to study drug on February 23, 2000. He had no suicidal ideations at his study visit and agreed to call if he had any suicidal ideations. Later he missed a study visit and the S's brother informed the investigator that on May 18, 2000 the S committed suicide (by gunshot). A suicide note was found, which described conflicts between the S and his boss and that the boss allegedly threatened the S of possible imprisonment.

E. Serious Adverse Events (SAEs)
SAEs in the Two SAD Trials (Studies 387 and 393).
There were only two EXR treated Ss with SAEs as follows: drug abuse (1S) and skin neoplasm (1S), each of which were likely due to underlying or pre-existing conditions. The sponsor provided a listing of Ss with SAEs, which is also shown in the appendix of this review as Table VIIA1. This Table also lists Ss with adverse events (AEs) considered "potentially serious" (such as pregnancy, seizures, suicides or attempts, symptomatic arrhythmias, and elevated liver function tests) or AEs considered as being of "clinical interest" according to the judgement of the investigator and the clinical monitor. This table lists some events that appear to be unrelated to the drug. Overall the observed SAEs, as listed, fail to reveal any new or unexpected safety results.

SAEs in the Four Ongoing Trials (Studies 388, 389, 390, and 392)
The sponsor reports that none of the AEs in ongoing trials required the submission of 7-Day or 15-Day IND Safety reports.

F. Dropouts due to Adverse Events in the Two SAD Trials (Studies 387 and 393).
The incidence of adverse dropouts (ADOs) in the two SAD trials were as follows:
- **EXR Ss:** 16.6% (46 out of 277 Ss)
- **Placebo Ss:** 5.1% (14 out 274 Ss)

In summary, the results of ADOs in the two SAD trials, as described in this section and in the submission, failed to reveal any new or unexpected events resulting in cessation of treatment or were events that appeared to be unrelated to the drug.

Incidence rates of AEs resulting in ADOs in at least 1% of EXR Ss and that were at least twice that of placebo were as follows (incidence rates of EXR and Placebo Ss are also provided):
- Asthenia (1.4%, 0.4%)
- Headache (1.8%, 0.4%)
- Nausea (3.6%, 0%)
- Anxiety (1.4%, 0.7%)
- Dizziness (1.8%, 0%)
- Insomnia (3.2%, 0.7%)
- Somnolence (2.2%, 0.4%)
- Sweating (1.1%, 0%)
- Impotence (2.5%, 0% in men)

The following are ADOs that were also listed as SAEs in Table VII.A.1:
- In EXR Ss: drug abuse (1 S).
- In Placebo Ss: hypertension (1S), cerebellar infarction (1S), pregnancy (1S), and post-study pregnancy (1S).

The following are ADOs in EXR treatment Ss that occurred because of an abnormal laboratory, vital sign or ECG parameter (as the primary or secondary reason for treatment cessation:

- 1 S: hypertension who met outlier criteria for increased blood pressure (another S 393003-088 had hypertension, but did no meet outlier criteria and is not listed in Table VII.A.1 as having discontinued study drug).
- 1 S: ventricular extrasystoles on ECG as the primary reason for treatment cessation who also met outlier criteria for abnormal ECG rhythm (S 39333010-374).
- 1 S: had a false-positive result on a home pregnancy test

G. Specific Search Strategies

Taper Phase Emergent AEs in the Two SAD Studies (387 and 393)

Studies 387 and 393 (employed a flexible dose of 75-225 mg/day of EXR) included an optional taper phase of up to 14 days in placebo and EXR groups which was omitted or prolonged, as medically indicated. Ss receiving two or more capsules of placebo or EXR a day (each EXR capsule contained 75 mg of drug) for a period of over one week, underwent the taper phase of the study. The dose was decreased by weekly intervals by one capsule per week. Consequently Ss taking 3 capsules daily during the treatment phase of the study took 2 capsules a day for one week during the taper phase, followed by 1 capsule a day for one week (the second week of the taper phase). Ss taking 2 capsules a day during the treatment phase took one capsule for one week. Ss taking 1 capsule a day during the treatment phase did not undergo a taper phase. Dummy dosing was not employed during the taper phase.

Safety assessments were conducted on the last full dosing day of the treatment phase of the study (or as soon as possible), and on taper weeks 1 (±3 days) and 2 (±3 days) and on a poststudy visit (4-10 days following completion of the taper phase or after the last dose of study drug). See the Study Flow Chart (Table VIB3 in the appendix).

The overall incidence rate for AEs (of any type) during the taper phase/post study period in both studies combined, was 19% in placebo (53/274 Ss) and 37% in EXR Ss (101/277 Ss). The following are AEs that were reported in EXR Ss at a rate of at least 1% and twice that of placebo Ss during the taper/post study periods in the two studies, combined (the incidence rates in EXR and placebo Ss, respectively, are provided in the parentheses). Common AEs (those reported in ≥ 5% of EXR Ss) are bolded.

Nausea (8.3% and 3.3%)
Dizziness (17% and 1.1%)
Nervousness (3.2% and 0.7%)
Asthenia (2.5% and 1.1%)
Vomiting (1.1% and 0%)
Insomnia (2.9% and 1.5%)
Abdominal Pain (1.1% and 0.4%)
Ataxia (1.4% and 0%)
Abnormal vision (1.1% and 0.4%)
Infection (1.8% and 0%)
Abnormal Dreams (1.8% and 0%)
Pain (1.1% and 0.4%)
Tinnitus (1.1% and 0%)
Paresthesia (1.8% and 0%)

H. Adverse Events in the Two SAD Trials (Studies 387 and 393).

The overall incidence of treatment emergent adverse events (AEs) in placebo and EXR treated Ss was 80% and 89%, respectively. See Table VII.H.1 in the appendix (as provided by the sponosor) for the incidence rate of specific AEs with an incidence of at least 2% in EXR Ss.

The following are common AEs (defined as having an incidence rate ≥5% in EXR Ss) that occurred in EXR Ss with at least twice the incidence of placebo Ss (the incidence rates in placebo and EXR Ss are shown):

- **Body As a Whole:** Asthenia (8% and 17% of placebo and EXR Ss, respectively)
- **Digestive System:** Anorexia (2%, 20%), Dry mouth (4%, 17%), nausea (9%, 29%)
- **Nervous System:** Anxiety (2.6%, 5.4%), Insomnia (7%, 23%), Libido decreased (1%, 9%), nervousness (3%, 11%), somnolence (8%, 16%)
- **Respiratory System:** Yawn (1%, 5%)
- **Skin and Appendages:** Sweating (2%, 13%)
- **Special Senses:** Abnormal vision (3%, 6%)
- **Urogenital system:** Abnormal ejaculation/orgasm (1%, 12%), anorgasmia (female: 0% and 6%, male: 1% and 5%), impotence (1%, 10% in males)

The sponsor also presented urogenital AE incidence rates when combining terms, upon the request of the Agency. These results are provided in the following table.

Incidence (%) of Treatment Emergent Urogenital Adverse Events		
	Placebo	**EXR**
Male Urogenital AEs: abnormal ejaculation (includes verbatim terms delayed ejaculation and anorgasmia	2/153 (1.3%)	26*/158 (16.5%)
Female Urogenital AEs: orgasmic dysfunction (includes verbatim terms abnormal orgasm and anorgasmia)	0/121 (0%)	10/119 (8.4%)
*One EXR Male S reported events coding to both verbatim terms and was therefore counted once, instead of twice		

Subgroup Analyses of AE's on the Basis of Gender, Age-group or Race. Due to insufficient sample size of Ss over 60 or 65 years old and Ss within each ethnic group, subgroup analyses for treatment group effects on the basis of ethnicity or age on the incidence of treatment emergent AEs are not described in this review.

The sponsor conducted a subgroup analysis on the basis of gender by calculating the placebo to venlafaxine group odds ratio for each AE of each gender using the Mantel-Haenszel method (the log odds ratio was calculated for AEs with 0 incidence rate). A comparison between male and female odds ratios was conducted by the Breslow-Day statistical test, using placebo as a control. No significant differences between the male and female odds ratios were revealed using these statistical methods.

Despite the sponsor's statistical results for no gender effect, some AEs appeared to show numerical differences between males and females upon visual inspection of the incidence rates by gender, shown in Table 14.2A in the ISS of the submission. The following table provides the incidence rates by gender and treatment groups for those AEs that appeared to show numerical differences between gender subgroups. The selection of AEs for this table, were those AEs in which the treatment group difference in incidence rates (expressed as % of Ss) in one gender was at least twice the treatment group difference in the incidence rates observed in the other gender. Note that the incidence rates across gender subgroups in placebo Ss were generally similar and therefore, do not appear to account for these AEs meeting the selection criteria.

The Incidence (%) of Selected Treatment Emergent Events* by Gender in Each Treatment Group in Studies 387 and 393, Combined						
Adverse Event	**Female**			**Male**		
	Placebo (N=121)	**Venlafaxine (N=119)**	**Group Difference****	**Placebo (N=153)**	**Venlafaxine (N=158)**	**Group Difference****
Anxiety	3 (2.5%)	11 (9.2%)	**6.7%**	4 (2.6%)	4 (2.4%)	**-0.2%**
Nervousness	3 (2.5%)	18 (15.1%)	**12.6%**	6 (3.9%)	12 (7.6%)	**3.7%**
Sweating	2 (1.7%)	9 (7.6%)	**5.9%**	3 (2.0%)	27 (17.1%)	**15.1%**
Libido Decreased	1 (0.8%)	7 (5.9%)	**5.1%**	1 (0.7%)	18 (11.4%)	**10.7%**
Impotence	0 (0%)	0 (0%)	**0%**	2 (1.3%)	16 (10.1%)	**8.8%**
*The selection of AEs were those in which the treatment group difference in incidence rates (expressed as % of Ss) in one gender was at least twice the treatment group difference in the incidence rates observed in the other gender **The difference between venlafaxine and placebo incidence rates.						

I. Laboratory Findings

The sponsor provided an integrated summary of results on laboratory parameters for the two SAD trials (387, 393). Ss were fasted (a minimum of 12 hours) prior to blood and urine sampling. Laboratory tests were conducted at the prestudy visit and on the final on-therapy visit (Day 84, on the last day of the full dose or up to three days after the last full dose).

I. 1. Analysis of Central Tendency: Hematology and Chemistry Parameters in the SAD Trials (Studies 387 and 393).

Treatment groups were generally similar on mean baseline, mean change and range of change, from baseline values to final-on-therapy values, on most parameters. However, some exceptions to this conclusion were results of some chemistry parameters (cholesterol, HDL, LDL, SGOT and alkaline phosphatase and bicarbonate levels) and some hematology parameters (hemoglobin, hematocrit and platelet count). These exceptions were of parameters that showed significant group differences in the mean change from baseline (a ANCOVA analysis with the baseline value as the covariate was employed). Refer to Table VII.I.1.1 in the appendix for a summary of results on selected parameters (as provided by the sponsor). The mean change in chloride levels only showed a trend for a treatment group difference ($p<0.02$). Other chemistry parameters (sodium and total protein) only showed significant within group mean changes in values, but did not show significant treatment group differences, as shown in Table VII.I.1.1. The magnitude of treatment group differences on each of these parameters was small, such that they generally do not appear to be clinically significant or relevant. Furthermore, the absolute values in the mean change in each of these parameters observed in the EXR Ss were also small in magnitude and in some cases were in a direction that did not appear to be clinically significant.

The mean increase in cholesterol levels observed in EXR Ss was small, yet this result appears to be reproducible, in clinical trials in other patient populations, as described in approved EXR labeling. The reproducibility of these results supports a hypothesis for a small effect of EXR treatment in cholesterol levels. A numerically greater incidence of outliers on high/increased cholesterol levels was also observed in EXR Ss compared to placebo Ss, as described in the next section. These observations provide further support for an EXR treatment induced increase in cholesterol levels.

Table VII.I.1.1 shows a mean elevation in liver enzymes in EXR Ss compared to placebo Ss. A mean elevation of liver enzymes in EXR treated patients is not described in current

approved EXR labeling. However, labeling includes increased liver enzymes being reported with an incidence of "infrequent" (between 1/100 to 1/1000 Ss) under the section of "Other Adverse Events Observed During the Premarketing Evaluation of Effexor..." Furthermore, the incidence of outliers in increased liver enzymes described in section I.2 below, fail to show evidence for a treatment group effect on this parameter.

Hematological Parameters showing significant treatment group effects on mean change from baseline to week 12 of treatment (using ANCOVA with the baseline value as a covariate, p values shown in parentheses):

- Hemoglobin (g/l): mean change of –1.53 and 0.32 in placebo and EXR Ss, respectively ($p<0.013$)
- Hematocrit (l/l): mean change of –0.00300 and –0.00100 in placebo and EXR Ss, respectively ($p<0.05$)
- Platelet count (10^9/l): mean change of –0.7 and 9.8 in placebo and EXR Ss, respectively ($p<0.01$)

I. 2. Analysis of Outliers: Hematology and Chemistry Parameters in the SAD Trials (Studies 387 and 393).

The sponsor used outlier criteria (or referred to as "Potentially Clinically Important" criteria in the submission) for various laboratory, vital sign and ECG parameters. These criteria were established by The Neuroscience Therapeutic Group at Wyeth-Ayerst (referred in this review as the Wyeth-Ayerst criteria) and are shown in Table VII.I.2.1. in the appendix (as provided by the sponsor). The Agency also provided outlier criteria for the sponsor to use on some of the parameters. The results described in this review are those using the Wyeth Ayerst criteria, unless otherwise specified (i.e. in cases when results using FDA criteria appeared to differ from those using the Wyeth-Ayerst criteria). There were no ADOs due to abnormal laboratory measures in EXR Ss. None of the SAEs in Table VII.A.1 (in the appendix) are listed as being due to abnormal laboratory parameters.

Hematology. Treatment groups demonstrated similar incidence rates of Ss meeting outlier criteria on each hematology parameter, as shown in the Table VII.I.2.2 in the appendix (parameters not shown in the table are those in which none of the Ss met outlier criteria).

Chemistry Results. Overall, treatment groups were generally similar on incidence of Ss meeting outlier criteria. Incidence rates on each parameter were 1% or less, except for those shown in the following table. In summary the table shows that total cholesterol was numerically higher in incidence rates of outliers in the EXR group compared to the placebo group. This observation is similar to that reported for other patient populations, as described in current approved EXR labeling. There were no ADOs due to abnormal chemistry test results among EXR Ss, while 2 placebo Ss had ADOs due to increased ALT levels.

Incidence (%) of Subjects in Each Treatment Group Meeting Outlier Criteria on Chemistry Parameters*			
Chemistry Parameter (units)	**Outlier Criteria**	**Placebo N=274**	**Venlafaxine ER N=277**
Bicarbonate	**Decrease ≥4 mmol/l andONR****	3/226 (1)	4/190 (2)
Total Cholesterol, fasting	**Increase ≥1.29 mmol/l and value ≥ 6.75 mmol/l**	1/177 (<1)	3/150 (2)
Total Cholesterol, nonfasting or unknown	**Increase ≥1.29 mmol/l and value ≥ 6.75 mmol/l**	0/54 (0)	2/44 (5)
*Only a selected list in which the incidence rate was ≥1% in the Venlafaxine ER group. This table is similar to Table 8.1.1B in the ISS of the submission. **ONR is outside the normal limit of the laboratory reference range.			

Similar results to those above were observed using FDA outlier criteria except for the incidence of Ss exceeding fasting or nonfasting triglyceride levels of greater than 199 mg/l, which appeared to somewhat higher incidence rates in EXR Ss compared to placebo (numerical observations with no statistical analyses conducted). The following shows these results:

- Triglycerides fasting (≥200mg/dl): 29/177 Placebo Ss (16%) and 35/150 (23%) in EXR Ss
- Triglycerides nonfasting (≥200mg/dl): 14/54 Placebo Ss (26%) and 15/44 (34%) in EXR Ss

Urinalysis.

Urinary acetone/ketones were not described in the submission since these parameters increase in fasting conditions (urine was collected under fasted conditions). Treatment groups were similar on the incidence of outliers on urinary glucose or hemoglobin/blood (any value that was not negative on either of these parameters was classified as an outlier). The following table shows a higher incidence of EXR Ss compared to placebo Ss with an incidence in EXR Ss that was at least twice that of placebo of outliers on urinary pH, protein albumin and specific gravity. These observations do not appear to be clinically significant. Upon request the sponsor provided the breakdown of the incidence of outliers on urinary pH ≥8 or ≤ 4. None of the Ss had a pH≤4, while the incidence of EXR and placebo outliers on a high pH (pH >8) were 11% (21/189) and 5% (12/226), respectively. The clinical significance of these results are not clear, but may be reflecting or be related to a slightly greater increase in bicarbonate blood levels observed in EXR Ss compared to placebo Ss (results were previously described, above).

Incidence (%) of Subjects in Each Treatment Group Meeting Outlier Criteria on Urinalysis Parameters*			
Urinalysis Parameter (units)	**Outlier Criteria**	**Placebo N=274**	**Venlafaxine ER N=277**
pH	**≤ 4 or ≥ 9**	12/226 (5)	21/189 (11)
Protein albumin	**Any value not negative**	16/227 (7)	39/189 (21)
Specific Gravity	**< 1.001 or > 1.035**	1/226 (<1)	3/189 (2)
* This table is similar to Table 8.1.1B in the ISS of the submission. **ONR is outside the normal limit of the laboratory reference range.			

J. Vital Signs and Body Weight

J.1 Analysis of Central Tendency: Vital Signs and Body Weight in SAD Trials (Studies 387 and 393).

Table VII.J.1.1 in the appendix (as provided by the sponsor) shows the mean baseline and mean change from baseline to each study visit on various vital sign and body weight parameters. In summary, the results are similar to those previously observed in other patient populations and as described in current EXR labeling. Significant treatment group effects on group mean blood pressure and pulse rate (small increases in EXR Ss compared to placebo Ss) and on body weight (a small decrease in EXR compared to placebo Ss). These results are described in more detail in below.

As show in Table VII.J.1.1 (in the appendix), the EXR group showed significant mean increases in the following parameters on most study visits:

- Supine systolic blood pressure (mean increases of up to 3.39 mmHg)
- Supine diastolic blood pressure (mean increases of up to 2.51 mmHg)
- Supine pulse rate (mean increases of up to 4.91 bpm)

Placebo Ss showed either no change, significantly smaller changes or changes in the opposite direction to those of the EXR Ss.

Similar results were observed with standing blood pressure measures, but the observed mean increases in the EXR group appeared to be less robust and occurred on fewer visits than that observed for the supine measures. The incidence of Ss with sustained increases in blood pressure (using prespecified outlier criteria) were also examined by the sponsor, as described in the next section.

A significant mean decrease (from baseline to the Final On-Therapy Visit) in weight was also observed in EXR Ss (-0.75 kg) that was not observed in the placebo Ss (+0.01 kg). These results (as shown in Table VII.J.1.1 in the appendix).

J.2 Analysis of Outliers: Vital Signs and Weight in SAD Trials (Studies 387 and 393).

The incidence of outliers on each of the vital sign parameters and on body weight parameters was less than one percent in EXR Ss except for the following:

- Decrease postural blood pressure of ≥25 mm HG systolic (supine to standing) in
  4/272 (1%) of Placebo Ss and 9/259 (3%) EXR Ss
- Decrease ≥10 mmHg diastolic (supine to standing) in
  25/272 (9%) Placebo Ss and 28/259 (11%) EXR Ss

The sponsor describes four EXR treated patients identified by the medical monitor as having "clinically important changes" in their vital sign measures. One S had a decrease in pulse rate (decreased from 76 bpm at baseline to 50 bpm during treatment with an "abnormal rhythm" on ECG) and 3 Ss had postural hypotension (maximum decreases of systolic pressure of –42, -42 and –39 in each S, respectively). 2 of these Ss met outlier criteria for decreased orthostatic systolic or diastolic blood pressure changes on at least one baseline visit. Two Ss were symptomatic (light headedness or dizziness). It is not clear if these events were drug-related or if EXR played a contributory role in at least the Ss with abnormal baseline values. One S also had diarrhea that may have resulted in dehydration and in turn orthostatic hypotension. The diarrhea may be drug related event. None of the Ss were reported as discontinuing treatment due to their

abnormal vital sign measures or classified as having an SAE, except for one S (S393002-048) who withdrew from the study due to anxiety and tremor.

These Ss are listed in Table VII.J.2.1 in the appendix (as provided by the sponsor) and are also described below:

S387013-504 met outlier criteria for **orthostatic hypotension** on the diastolic blood pressure at baseline (-11 mm Hg). The following are supine to standing changes on systolic blood pressure (in units of mmHg): 10 and -6 on two consecutive prestudy visits, a range of –20 to –42 on each study visit during treatment (weeks 1, 2, 3, 4, 6, 8, 10 and 12) and an increase of 2 on the poststudy visit. Poststudy visits occurred approximately two weeks after week 12 of treatment.

S393009-330: This S had the following changes from supine to standing values on systolic blood pressure (in units of mmHg): 2 and –3 at two baseline visits, a range of –3 to –21 on most visits on treatment, except for weeks 3, 4, and 6, which showed decreases of –39. –36 and –31, respectively, and on the poststudy visit a change of –30. This S also reported diarrhea. Perhaps the orthostatic hypotension in this S was due to dehydration secondary to diarrhea.

S393005-173: This S had a **decreased supine pulse rate** from 76 bpm at baseline to a minimum pulse rate of 50 bpm during treatment and an **"abnormal rhythm"** on ECG.

393002-048 who had orthostatic blood pressure changes had a maximum decrease of –52 mmHg (systolic) on a prestudy (pretreatment) visit and met outlier criteria. This S also had decreases in both systolic and diastolic blood pressures on subsequent visits during treatment and on the final visit.

Due to some of the above reports and the possibility of autonomic system effects of EXR treatment over time, the sponsor was asked to provide descriptive statistical results on orthostatic vital sign measures. These results were provided in their 2/28/02 BM submission. The sponsor conducted a one-way ANCOVA on adjusted mean change from baseline to study visit on orthostatic measures. Significant treatment group differences were observed on some of the study visits (p values <0.001 on some visits) that were in the direction of greater mean change in orthostatic drop in systolic or diastolic pressure from baseline to study visit in EXR compared to placebo Ss. However, these differences were not typically significant at the final-on-therapy visit or on week 12 and group differences on the adjusted mean change from baseline to each study visit were small (only 1-2 mmHg adjusted mean group difference on most visits).

Sustained Increase in Blood Pressure. The incidence of Ss who met outlier criteria for sustained increases in supine diastolic blood pressure (as defined as an increase in blood pressure of ≥10 mmHg to an on-therapy value of ≥90 mmHg for at least 3 consecutive visits) was as follows: Four EXR Ss (1.4%) and two (0.7%) placebo Ss. The maximum diastolic blood pressure observed among these four EXR Ss was 98 mmHg, which is compared to a maximum diastolic blood pressure of 106 mm Hg among the two placebo Ss. Sustained increase blood pressure is described in current EXR labeling.

The listing of SAEs (Table VII.A.1 in the appendix) lists three Ss with SAEs of hypertension as follows: two EXR Ss (one discontinued study drug) and 1 Placebo S (also discontinued study drug). No other ADOs were reported to be due to abnormal vital sign measures or because of changes in weight.

K. Electrocardiographic Results

K.1 Analysis of Central Tendency: Electrocardiographic Parameters in SAD Trials (Studies 387 and 393).

Similar to that revealed for pulse rate on vital sign data, a significantly mean increase from baseline to final-on-therapy in heart rate was revealed by ECG in the EXR Ss (mean increase of 5.43 bpm, $p<0.001$) that was not observed in placebo Ss (-0.36). The following table summarizes the ECG results on mean change from baseline to the final-on therapy visit values. Note that a small yet significant increase in mean QTc (Bazett's correction) was observed in the EXR Ss, but not in placebo Ss. A small increase in QTc was previously observed in other patient populations, as described in current, approved EXR labeling. Mean PR and QRS intervals showed significant decreases in the EXR group that was not observed in the placebo Ss may be reflecting the increased ventricular rate.

Mean Change from Baseline to Final On-Therapy Visit on ECG Parameters in Each Treatment Group for Studies 387 and 393, Combined[a]

ECG Parameter:	n	Placebo	n	Venlafaxine ER	Treatment Group Comparison (p value)[b]
Ventricular Heart Rate (bpm)	228	-0.36	193	5.43**	<0.001
QTc Interval (msec)	227	-2.02	195	2.76*	<0.001
PR Interval (msec)	228	0.99	194	-4.47**	<0.001
QRS Interval (msec)	228	0.86	194	-0.99*	0.0003

[a]This table is similar to Table 10.2A in the ISS of the submission

[b] Based on an ANCOVA for a treatment group effect on mean change from baseline with the baseline value as the covariate

* $p<0.01$, ** $P< 0.001$ based on a paired t-test a comparison between baseline and the Final-on-Therapy Visit values within each treatment group

K.2 Analysis of Outliers: Electrocardiographic Parameters in SAD Trials (Studies 387 and 393).

The incidence rates of outliers for each ECG parameter are shown in the following table. However, since no Ss exceeded the cut-off criteria for QTc prolongation (either as defined as >500 msec, as defined as an increase of ≥10% and >440 msec). Upon request the sponsor provided (in a 12/26/01 BZ submission) incidence rates of ECG parameter outliers using the Agency criteria (e.g. using a QT interval cut-off of ≥480 msec, PR interval ≥ 200 msec). These results failed to reveal any new observations (incidence rates were numerically lower in the EXR Ss compared to placebo Ss on each parameter).

Incidence (%) of Outliers on ECG Parameters in Each Treatment Group for Studies 387 and 393, Combined[a]

ECG Parameter:	Placebo (N=274)	Venlafaxine ER (N=277)
PR Interval Increase ≥10% and > 200 msec	5/228(2%)	1/195 (<1%)
QRS Interval ≥120 msec	2/228 (<1%)	1/195 (<1%)
Heart Rate Decrease ≥15 bpm and rate ≤ 50 bpm	1/228 (<1%)	0/195 (0%)
Rhythm change from normal to abnormal	12/227 (5%)	6/195 (3%)

[a]This table is similar to Table 101.1B in the ISS of the submission.

There were no SAEs listed in Table VII.A.1 as being due to an abnormal ECG. However, there was one ADO (S 393010-374) who discontinued EXR treatment due to ventricular extrasystoles, as previously described in the section on ADOs.

L. Overdose Experience
There were no reports of acute overdose in the two SAD trials (Studies 387 and 393).

M. Safety Results from Other Sources

Literature:
The sponsor conducted the literature search for published papers and abstracts on SAD and Social Phobia using the terms and databases itemized below with the search periods provided (present time corresponds to January 11, 2001).
Databases:
- MEDLINE (1966- present)
- EMBASE (1988- present)
- BIOSIS (1992 – present)
- Current Contents (Week 1, 1999- present)
- Wyeth-Ayerst Product Literature Database for EXR (1984-present)

Terms:
- Ef(f)exor/Ef(f)exor XR
- Venlafaxine
- Venlafaxine ER
- Venlafaxine XR

Approximately 55 publications were listed. Upon conducting a thorough review of the world literature update by the sponsor's medical monitor, no issues were revealed that would adversely impact on conclusions made about the safety of EXR.

Post Marketing Reports: As previously described EXR "has not been withdrawn from any country for any reason." Upon request the sponsor provided a listing of post marketing deaths and SAEs for EXR (capsule) and Effexor® IR (tablet) when used in association with SAD. The search terms employed for the SAD indication were as follows: anxiety, social (neurosis) phobia, anxiety, social phobia, social anxiety, social anxiety, fearfulness and poor self-esteem, social phobia, agoraphobia, and panic attacks. The following were revealed from this search and were generally events that are not unexpected and/or are events that are already described in labeling:
- **Hepatic failure and Headache NOS** (dates of onset 9/12/97 for each) with a **fatal outcome** in a 45 year old female treated with venlafaxine (tablet) as early as 9/1996 to 4/1997 at doses of up to 150 mg a day. This S was also on the following concomitant medications: naproxen, paracetamol, buspiroine, orhenadrine, fluphenthixol, propiomazine and alpraxolam. Given these concomitant medications, liver toxicity associated with other drugs may be considered. It is not clear if non-drug related factors were involved (i.e. infectious hepatitis, among others). Hepatic failure and other related events are currently listed in the postmarketing section of approved labeling.
- **Intestinal obstruction/abdominal distension** (dates not given) in a 15 year old female who took venlafaxine (tablet) from January through April of 2000. This patient is indicated as "not recovered." This SAE is listed as a rare event in current labeling under the "Other Adverse Events Observed During the Premarketing Evaluation of ..."

- **Swelling NOS, oliguria, nausea, irritability, headache NOS** (onset of each was 9/30/01) in a 38 year old female who took 75 mg of venlafaxine (capsule) daily, from 9/27-9/30/2001. She was also taking diazepam (9/26-9/28), oxazepam (started on 9/28/01), risperidone (started on 8/28/01) and zopiclone (start date not given). The oliguria resolved, while the outcome of other AEs is listed as "unknown." One possible consideration with that the S was having a syndrome of inappropriate anti-diuretic hormone secondary to EXR treatment. However, classic symptoms of this syndrome were not described in this S. Given that this S had nausea, another possibility is that she may have been dehydrated resulting in oliguria. The etiology of her symptoms is unclear some of which may or may not be drug-related. Oliguria-like conditions are currently listed under the "Other Adverse Events Observed During the Premarketing Evaluation of ..." The other SAEs in this patient are not atypical AEs reported by Ss in clinical trials and several are listed in the incidence table for AEs in approved labeling.
- **Hyperlipidemia and condition aggravated** in a 42 year old male after approximately one month of venlafaxine (capsule) treatment at doses of up to 150 mg daily (also taking alprazolam and vitamins). His condition resolved. Hypercholesterolemia is already described in labeling.

N. Conclusions on Safety Results.

Safety results failed to show any remarkable, new or unexpected findings. The safety profiles of EXR treatment emergent AEs and Taper Phase Emergent AEs, at doses employed in the two 12 week trials in SAD patients, were generally similar to that shown in other patient populations and as described in current labeling. Safety results on clinical safety parameters were also generally similar to that already described in EXR labeling. In conclusion EXR treatment at the doses and duration employed in the two clinical trials, is adequately safe for the SAD population.

Three additional safety observations are noted but are considered to be preliminary. One safety observation is regarding results of orthostatic vital sign measures. A second observation pertains to results of incidence rates on high urinary pH outliers together with small treatment group differences on bicarbonate and chloride chemistry parameters. A third observation is a possible gender group difference on potential treatment group effects on the incidence rates of some AEs. While, these three safety observations are noted and described further below, these results are considered preliminary for several reasons. The magnitude of each of the observed treatment group differences on laboratory and orthostatic vital sign measures was small and not clinically significant. Furthermore, the possibility for a Type I error exists, as multiple comparisons were conducted on multiple parameters. Finally, these results are based on a *post hoc* examination of the sponsor's results.

A small signal for orthostatic hypotension in EXR treated Ss may be suggested by the safety results on orthostatic vital sign measures. A few Ss in the SAD trials were identified as having "clinically important changes" on these parameters. However, some of these Ss were found to have other potential underlying etiologies (i.e. pre-existing orthostatic hypotension). Results on treatment group mean orthostatic measures failed to show consistent results that would support a clinical significant orthostatic hypotensive effect of EXR treatment. These results showed a treatment group adjusted mean difference of only 1 to 2 mmHg, that was significant on some of the study visits (not correcting for multiple comparisons). Treatment group differences were not significant on the final-on-therapy visit. The incidence rates of

outliers on decreased orthostatic blood pressure values show a small numerical trend for greater rates in EXR Ss compared to placebo Ss. But none of the SAEs or ADOs were identified as being due to orthostatic hypotension and none of the EXR Ss had the AE of syncope (as shown in Table ST-3 in the ISS of the submission). One possibly related observation is regarding the results on AEs in Table VII.H.I. This table shows that the incidence rates of "vasodilatation" and "dizziness" in EXR Ss were at least twice that of the incidence rates in placebo Ss. However, vasodilatation typically refers to "hot flashes," as noted in earlier depression trials (refer to the 2/26/97 review of the original NDA by Dr Gregory Dubitsky). Dizziness can also be due to a myriad of symptoms not related not to orthostatic hypotension.

The following was revealed upon an examination of previous clinical reviews of results on orthostatic measures in earlier EXR trials in other patient populations. A significant treatment group effect on the incidence of Ss meeting outlier criteria for decreased postural diastolic blood pressure was observed in earlier depression trials. 32% of EXR Ss (112 out of 354 Ss) compared to 25% of placebo Ss (69 out of 282 Ss) met outlier criteria for decreased diastolic blood pressure with postural change (defined as ≤10 mmHg decrease from supine to standing in diastolic blood pressure; see Table 8.1.7.3.2.2 in the appendix of the original 2/26/07 NDA review). In the Phase 3 trials of 719 Ss, 36 % of Effexor® Ss met this outlier criterion. However, none of the EXR treated ADOs were listed as dropouts due to abnormal vital signs involving orthostatic hypotension (see Table 8.1.7.3.3.1 of the original review of EXR). Short-term trials conducted by the sponsor to support the Generalized Anxiety Disorder indication failed to reveal any clinically significant or remarkable evidence for a treatment group effect of EXR compared to placebo on orthostatic blood pressure measures. In conclusion, the results of the SAD trials and some of the earlier trials in other patient populations, may suggest a small signal for orthostatic hypotension, but a clear, remarkable or clinically robust effect is not apparent from these results. Postural hypotension is currently listed as a frequent event under the "Other Adverse Events Observed During the Premarketing Evaluation of Effexor..." section of approved EXR labeling.

Another safety observation, that is not described in current EXR labeling for other patient populations are results on incidence rates of AEs in male Ss compared to female Ss of each treatment group in the SAD trials, combined. As shown in the table in Section VII H of this review, the following AEs appear to show gender differences in treatment group effects on these AEs: anxiety, nervousness, sweating, decreased libido, and impotence. These AEs showed a treatment group difference in an incidence rate in one gender that was at least twice that of the treatment group difference in incidence rate in the other gender. The results suggest that while female Ss tended to show a greater EXR related effect on incidence rate of anxiety and nervousness, male Ss tended to show a greater EXR related effect on decreased libido, impotence and sweating. It is difficult to interpret these results. One possible consideration are potential confounding variables, such as possible gender differences in reporting patterns or expectations. However, men and female Ss on placebo treatment had similar incidence rates on these AEs. It is also not known if these results are reproducible. Furthermore, the possibility for a Type I error must be considered (due multiple comparisons).

Finally, results on outliers on urinary pH revealed that while no Ss had a pH≤4, the incidence of EXR and placebo outliers on a high pH (pH >8) was 11% (21/189) and 5% (12/226), respectively. These results may be reflecting or may be related to a slightly greater increase in bicarbonate blood levels and lower chloride blood levels observed in EXR Ss compared to placebo Ss. While the magnitude of these laboratory blood parameters and results

of urinary pH do not appear to be remarkable regarding their clinical relevance or significance, one consideration is that the results may be reflecting a possible direct or indirect metabolic effect of EXR treatment. One metabolic condition to consider is the syndrome of inappropriate antidiuretic hormone secretion (SIADH) that is described under "Precautions" in current EXR labeling. A metabolic alkalosis and alkalinization of the urine might be consistent with SIADH if these metabolic parameters were due to hyponatremia. However, results on the incidence of outliers and mean change on sodium levels in EXR compared to placebo Ss were not consistent with a treatment group effect on sodium levels. Nevertheless, current labeling already has precautionary statements about SIADH and provides a warning about the use of EXR in volume-depleted or elderly patients and the concomitant use of EXR with diuretic agents.

Several safety observations in the SAD trials were clinically relevant, but are not new or unexpected and are already described in current EXR labeling. One observation revealed in the SAD trials was a mean increase (from the baseline to final-on-therapy visit) in cholesterol levels in EXR Ss that was not found in placebo Ss. There were also numerically higher incidence rates of outliers for high triglyceride (fasting levels showed less of a numerical difference between groups) and high cholesterol levels in EXR Ss compared to placebo Ss. The magnitude of mean values and incidence rates on these parameters were similar to that observed in other patient populations. The reproducibility of these results strongly suggests, if not establishes, a small effect of EXR treatment on cholesterol and triglyceride levels.

The known hypertensive effect of EXR was observed in the SAD trials, in which the magnitude of the effect appeared to be similar to that observed in other patient populations. A small prolongation of QTc, as previously observed in other patient populations was also observed. Mean ventricular rate was also increased in EXR Ss compared to placebo. One S out of a total of 277 EXR Ss discontinued EXR treatment due to ventricular extrasystoles and an abnormal ECG. These observations are not unexpected. Results on QTc and mean heart rate are described under the "Precautions" section of current labeling.

Results of some of the chemistry or hematological parameters showed small numerical differences between treatment groups on mean levels or incidence rates. A small mean elevation in some of the liver function tests appeared to exist in EXR Ss compared to the controls, similar to that already described in labeling. Possible group differences on other parameters were typically inconsistent (e.g. a numerical difference in mean values but not in outlier incidence rates, or the direction of a possible effect was clinically inconsistent). Furthermore, the group differences or within group mean values were generally small or appeared to be clinical insignificant. Therefore, these results do not appear to be of clinical relevance of significance.

VIII. Dosing, Regimen and Administration Issues

Refer to Section IA of this review. The recommended dose and titration schedule is the same as that recommended for other approved indications and is also is similar to that employed in the SAD trials. A section on symptoms associated with the discontinuation of EXR treatment and recommendations for tapering the dose are provided. The sponsor's proposed treatment recommendations for the SAD population is adequately safe and is reasonable, based on their safety results. Nausea and dizziness were common AEs that had an incidence in EXR Ss of at least twice that of placebo Ss during the taper phase of Studies 387 and 393. Tapering of the dose was optional, such that these results reflect AEs in Ss who did not undergo the taper phase, as well as Ss who's dose was tapered and labeling specifies that "individualization of tapering may be necessary."

IX. Use in Special Populations

The sponsor does not provide any new information regarding special populations in this submission.

X. Conclusions and Recommendations

A. Conclusions

Two adequately controlled 12-week multicenter trials (Study 387 and 393) revealed positive results that support the sponsor's efficacy claim for the new indication of EXR, SAD. The results of the studies also support the sponsor's proposed treatment regimen for EXR (a starting daily dose of 75 mg/day that is titrated up to a maximum dose of 225 mg/day). EXR treatment, as employed in the SAD trials, is also adequately safe for this patient population based on the safety results of these two trials, together with that already known about EXR in other patient populations. Furthermore, the safety profile of EXR in the SAD population is generally similar to that observed in previous clinical trials and to that described in current labeling. However, possible gender differences on treatment group effects on incidence rates of some AEs are noted in this review.

B Recommendations

From a Clinical perspective (pending confirmation of efficacy results by Biometrics) it is recommended that this NDA be given an approvable status.

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APPENDIX AND ATTACHMENTS 1 AND 2

Table VI.B.1. List of Investigators for Study 387 (number of randomized subjects for each site is also shown).

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Table VI.B.2 LIST OF INVESTIGATORS OF STUDY 393
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Table VI.B.3. Flow Chart for Studies 387 and 393

Visit number:			3	4	5	6	7	8	9	10	13
Study day:	1	2	7	14	21	28	42	56	70	84	
Weeks on study medication:	Prestudy[a]	Baseline (- 1)	1	2	3	4	6	8	10	12[b]	Post-study
Procedure:											
Medical and psychiatric history and patient orientation	X										
Mini- International Neuropsychiatric Interview (MINI)	X										
Diagnostic criteria for social anxiety disorder; major depression; Generalized Anxiety Disorder	X										
Hamilton Psychiatric Rating Scale for Depression	X						X			X	
Covi Raskin Scale	X						X			X	
Dispense study medication, complete dose record [d]	X	X	X	X	X	X	X	X	X		X
Recording adverse events [e] , prior/ concomitant		X	X	X	X	X	X	X	X	X	X
Dispense taper study medication/ complete dose record										X	X
Efficacy determinations [f]											
LSAS; CGI- S	X	X	X	X	X	X	X	X	X	X	
Clinical Global Impression (CGI- I)			X	X	X	X	X	X	X	X	
Social Phobia Inventory (SPIN)		X	X	X	X	X	X	X	X	X	
Sheehan Disability Inventory (SDI)		X				X				X	

Footnotes are included on the last page of the table.

Table VI.B.3. Flow Chart for Studies 387 and 393, continued

Visit number:			3	4	5	6	7	8	9	10	13
Study day:	1	2	7	14	21	28	42	56	70	84	
Weeks on study medication:	**Prestudy [a]**	**Baseline (- 1)**	**1**	**2**	**3**	**4**	**6**	**8**	**10**	**12[b]**	**Poststudy**
Procedure:											
Safety determinations											
Physical examination	X									X	
Height	X										
Weight		X								X	
Vital signs [g]	X	X	X	X	X	X	X	X	X	X	X
Laboratory determinations [h]	X									X	
Electrocardiogram (ECG)	X									X	

a: Seven (7) ± 3 days before study day 1. The single- blind placebo lead- in period may have been extended an additional 7 days (± 3 days) in order to complete evaluations.

b: Final efficacy determinations were obtained on the last day the patient took a full dose of study medication (ie, before taper) or as soon as possible thereafter, but within 3 days of the last full dose in any case. Final safety evaluations for the double- blind period were obtained on the last day the patient took a full dose of study medication (ie, before taper) or as soon as possible thereafter.

c: Four (4) to 10 days poststudy. Patients returned to the study site after completing taper week 1 (± 3 days), and taper week 2 (± 3 days), and at visit 13. The dosage regimen for taper weeks 1 and 2 was recorded on the study medication record. Poststudy determinations were obtained 4 to 10 days after the study medication had been discontinued or after the completion of the taper period for all patients who received the study medication, regardless of
duration of treatment.

d: The first dose of double- blind study medication was taken on day 1.

e: Must have been recorded from the time of informed consent signing.

f: LSAS (Liebowitz Social Anxiety Scale); CGI- S (Clinical Global Impressions- Severity).

g: Supine pulse rate and supine and standing blood pressure.

h: Hematology, blood chemistry, and urinalysis. Free thyroxine index, urine drug screen, and serum beta- HCG pregnancy test were tested prestudy only. Fasting (minimum 12 hour) laboratory determinations were done at the prestudy visit, and day 84 (± 3 days) or whenever a patient withdrew from the study.

Table VI.B.4. Study 387: Enumeration of Subjects Who Withdrew By Primary Reason[a]

Primary Reason	Placebo (n = 139)	Venlafaxine ER (n = 140)	p- Value[b]
Any reason	54 (39)	52 (37)	0.805
Adverse event	8 (6)	24 (17)	0.004
Failed to return	10 (7)	11 (8)	1. 000
Patient request unrelated to study	7 (5)	5 (4)	0. 571
Unsatisfactory response - efficacy	21 (15)	3 (2)	<0.001
Protocol violation	4 (3)	2 (1)	0. 447
Other event	4 (3)	7 (5)	0. 540

a: This table is Table 8.1.1 A in the submission. Data from CDR 3- 5 (12 Jun 01).
b: P- value based on Fisher's exact test.

Table VI.B.5. Study 393: Enumeration of Subjects Who Withdrew By Primary Reason[a]

Primary Reason	Placebo (n = 135)	Venlafaxine ER (n = 137)	P- Value[b]
Any reason	40 (30)	60 (44)	0.017
Adverse event	6 (4)	21 (15)	0.003
Failed to return	15 (11)	20 (15)	0.469
Patient request unrelated to study	1 (1)	5 (4)	0. 213
Unsatisfactory response - efficacy	14 (10)	10 (7)	0. 400
Protocol violation	2 (1)	2 (1)	1. 000
Other event	2 (1)	2 (1)	1. 000

a: This table is Table 8.1.1 A in the submission. Data from CDR 3- 5 (16 May 01).
b: P- value based on Fisher's exact test.

Table VI.B.6. ADJUSTED MEAN CHANGES FROM BASELINE FOR PRIMARY AND SELECTED SECONDARY EFFICACY VARIABLES AT FINAL ON- THERAPY VISIT: ITT PATIENTS FROM STUDIES 0600B4- 387- US/ CA AND –393- US (Table 3.3.1.1.A. of the ISE of the submission)

Variable Study Number Treatment Group	Number of Patients	Adjusted Mean Change From Baseline	p- Value vs Placebo
Primary Variable			
LSAS			
0600B4- 387- US/ CA			
Venlafaxine ER [a]	133	-31.0	<0.001
Placebo	138	-19.9	
0600B4- 393- US			
Venlafaxine ER	126	-32.8	0. 003
Placebo	135	-22.1	
Selected Secondary Variables			
CGI- S			
0600B4- 387- US/ CA			
Venlafaxine ER	133	-1. 1	<0.001
Placebo	138	-0. 6	
0600B4- 393- US			
Venlafaxine ER	126	-1. 2	0.005
Placebo	135	-0. 8	
SPIN			
0600B4- 387- US/ CA			
Venlafaxine ER	133	-13.3	0. 002
Placebo	138	-8. 5	
0600B4- 393- US			
Venlafaxine ER	126	-13.6	0. 024
Placebo	134	-9. 4	

a: Flexible dose range for venlafaxine ER in both studies was 75- 225 mg/ day.
Abbreviations: ITT = intent- to- treat; LSAS = Liebowitz Social Anxiety Scale; CGI- S = Clinical Global Impressions— severity; SPIN = Social Phobia Inventory.

Table VI.B.7. TREATMENT COMPARISON FOR LSAS TOTAL: LOCF ANALYSIS IN ITT PATIENTS (STUDY 0600B4- 387- US/ CA, Table 3.3.2.1.1.A in the ISE of the submission).

Week	Treatment	n	Raw Mean Score	Raw Mean Change From Baseline	Adjusted Mean Change From Baseline	Difference in Adj. Means Standard Error	Ven ER Minus Placebo (95% CI)	p- Value vs Placebo
Baseline	Placebo	138	86.7	--	--	--	--	--
	Venlafaxine ER	133	91.1	--	--	--	--	--
1	Placebo	136	83.1	-3.9	-4.3	0. 98		
	Venlafaxine ER	132	84.2	-6.9	-6.8	0. 98	-2.5 (0.1, -5. 1)	0. 055
2	Placebo	138	78.2	-8.5	-9.0	1. 31		
	Venlafaxine ER	133	80.0	-11.0	-11.0	1. 31	-2.0 (1.5, -5. 4)	0. 270
3	Placebo	138	76.3	-10.4	-11.7	1. 60		
	Venlafaxine ER	133	75.5	-15.5	-15.9	1. 60	-4.2 (0.0, -8. 4)	0. 052
4	Placebo	138	72.8	-13.9	-15.7	1. 82		
	Venlafaxine ER	133	72.0	-19.1	-19.7	1. 82	-4.0 (0.8, -8. 8)	0. 102
6	Placebo	138	70.5	-16.2	-18.2	2. 12		
	Venlafaxine ER	133	67.1	-24.0	-24.8	2. 12	-6.6 (- 1.0, -12.2)	0.022
8	Placebo	138	68.6	-18.2	-20.4	2. 17		
	Venlafaxine ER	133	64.9	-26.2	-27.1	2. 17	-6.7 (- 1.0, -12.5)	0.022
10	Placebo	138	69.1	-17.6	-19.6	2. 21		
	Venlafaxine ER	133	63.2	-27.9	-28.6	2. 21	-9.0 (- 3.1, -14.9)	0.003
12	Placebo	138	68.9	-17.9	-19.9	2. 22		
	Venlafaxine ER	133	60.9	-30.2	-31.0	2. 22	-11.2 (- 5.3, -17.1)	<0.001

CI = confidence interval, ITT = intent- to- treat, LOCF = last- observation- carried- forward, LSAS = Liebowitz Social Anxiety Scale, Ven ER = venlafaxine ER.

Table VI.B.8. TREATMENT COMPARISON FOR LSAS TOTAL: LOCF ANALYSIS IN ITT PATIENTS (STUDY 0600B4- 393- US, Table 3.3.2.2.1A in the ISE of the submission)

Week	Treatment	n	Raw Mean Score	Raw Mean Change From Baseline	Adjusted Mean Change From Baseline	Standard Error	Difference in Adj. Means Ven ER Minus Placebo (95% CI)	p- Value vs Placebo
Baseline	Placebo	135	87.4	--	--	--	--	--
	Venlafaxine ER	126	90.8	--	--	--	--	--
1	Placebo	129	82.2	-4.8	-4.0	1. 22		
	Venlafaxine ER	121	85.6	-5.1	-4.4	1. 20	-0.4 (2.7, -3. 5)	0. 817
2	Placebo	135	77.9	-9.4	-8.9	1. 47		
	Venlafaxine ER	126	79.4	-11.3	-10.8	1. 49	-1.8 (2.0, -5. 7)	0. 346
3	Placebo	135	75.0	-12.4	-12.8	1. 67		
	Venlafaxine ER	126	74.0	-16.8	-16.8	1. 69	-4.0 (0.4, -8. 4)	0. 072
4	Placebo	135	73.6	-13.8	-14.8	1. 88		
	Venlafaxine ER	126	69.0	-21.8	-22.1	1. 90	-7.4 (- 2.4, -12.3)	0.004
6	Placebo	135	69.6	-17.7	-18.3	2. 18		
	Venlafaxine ER	126	64.1	-26.7	-26.6	2. 21	-8.3 (- 2.6, -14.0)	0.004
8	Placebo	135	67.7	-19.7	-20.6	2. 42		
	Venlafaxine ER	126	62.0	-28.8	-28.7	2. 44	-8.1 (- 1.8, -14.5)	0.012
10	Placebo	135	66.6	-20.7	-21.5	2. 59		
	Venlafaxine ER	126	59.5	-31.3	-31.2	2. 62	-9.7 (- 2.9, -16.4)	0.005
12	Placebo	135	66.0	-21.3	-22.1	2. 66		
	Venlafaxine ER	126	57.7	-33.1	-32.8	2. 69	-10.7 (- 3.7, -17.6)	0.003

CI = confidence interval, ITT = intent- to- treat, LOCF = last- observation- carried- forward, LSAS = Liebowitz Social Anxiety Scale, Ven ER = venlafaxine ER.

Table VII.A.1 (Table 13.2 A in the 12/26/02 submission). LISTING OF PATIENTS WITH SERIOUS ADVERSE EVENTS AND OTHER EVENTS OF CLINICAL INTEREST, STUDIES 387 AND 393

Treatment *Body System* Patient Number	Age [a] (y)	Sex	Mean Daily Dose (mg)	Days on Therapy at Onset	Adverse Event Preferred Term (Verbatim)	Discontinuation Because of Identified Adverse Event
Venlafaxine ER						
Body as a whole						
387003- 094 [b,]	24	M	158	27	Drug abuse (substance abuse)	Yes
Cardiovascular						
387019- 752	43	F	75	18	Hypertension (hypertension)	Yes
393003- 088	41	M	132.5	14	Hypertension (increased blood pressure)	No
Hemic and lymphatic						
387014- 536 [b]	19	M	206	Poststudy	Skin neoplasm (cutaneous lymphoma vs pseudolymphoma)	No
Adverse event associated with miscellaneous factors						
393004- 131 [b, c]	29	F	166.5	Not applicable	(Accidental ingestion by 20-month- old child)	No
Placebo						
Cardiovascular						
387008- 295 [b]	60	F	--	25	Hypertension (elevated blood pressure)	Yes
393005- 174 [b,]	36	M	--	44	(Cerebellar infarction)	Yes
Urogenital						
387019- 754 [b,]	36	F	--	Poststudy	Pregnancy (pregnancy)	Yes
393018- 693 [b]	24	F	--	41	(Pregnancy)	Yes
Adverse event associated with miscellaneous factors						
387013- 502 [b]	52	F	--	21	(Intraoperative bladder perforation)	No

a: Age at study entry.
b: Patients who were classified as having a serious adverse event.
c: An IND safety report was filed for this patient.

Table VII.H.1. Incidence rates (%) of Treatment Emergent Adverse Events that Occurred in ≥2% of Venlafaxine ER Subjects in Studies 387 and 393, combined (this is Table 7.2.1A in the ISS of the submission)

Body System Adverse Event a	Placebo (n = 274)	Venlafaxine ER (n = 277)
Any adverse event	218 (79.6)	247 (89.2)
Body as a whole		
Abdominal pain	9 (3.3)	10 (3. 6)
Accidental injury	8 (2.9)	14 (5. 1)
Asthenia	21 (7. 7)	46 (16.6)
Back pain	13 (4. 7)	12 (4. 3)
Flu syndrome	13 (4. 7)	16 (5. 8)
Headache	90 (32.8)	94 (33.9)
Infection	24 (8. 8)	21 (7. 6)
Pain	18 (6. 6)	18 (6. 5)
Cardiovascular system		
Hypertension	10 (3. 6)	15 (5. 4)
Palpitation	3 (1.1)	8 (2.9)
Vasodilatation	4 (1.5)	9 (3.2)
Digestive system		
Anorexia	4 (1.5)	55 (19.9)
Constipation	11 (4. 0)	22 (7. 9)
Diarrhea	14 (5. 1)	16 (5. 8)
Dry mouth	11 (4. 0)	47 (17.0)
Dyspepsia	19 (6. 9)	18 (6. 5)
Eructation	0	6 (2.2)
Nausea	25 (9. 1)	81 (29.2)
Vomiting	5 (1.8)	8 (2.9)
Metabolic and nutritional		
Weight loss	0	10 (3. 6)
Nervous system		
Abnormal dreams	1 (0.4)	12 (4. 3)
Agitation	4 (1.5)	12 (4. 3)
Anxiety	7 (2.6)	15 (5. 4)
Dizziness	22 (8. 0)	43 (15.5)
Insomnia	20 (7. 3)	64 (23.1)
Libido decreased	2 (0.7)	25 (9. 0)
Nervousness	9 (3.3)	30 (10.8)
Paresthesia	2 (0.7)	7 (2.5)
Somnolence	21 (7. 7)	44 (15.9)
Tremor	2 (0.7)	11 (4. 0)
Twitching	0	6 (2.2)
Respiratory system		
Pharyngitis	16 (5. 8)	12 (4. 3)
Rhinitis	16 (5. 8)	11 (4. 0)
Sinusitis	3 (1.1)	6 (2.2)
Upper respiratory infection	23 (8. 4)	13 (4. 7)
Yawn	2 (0.7)	14 (5. 1)

Continued on the next page.

Table VII.H.1, continued. Incidence rates (%) of Treatment Emergent Adverse Events that Occurred in ≥2% of Venlafaxine ER Subjects in Studies 387 and 393, combined

Body System Adverse Event [a]	Placebo (n = 274)	Venlafaxine ER (n = 277)
Skin and appendages		
Herpes simplex [b]	1 (0.4)	6 (2.2)
Sweating	5 (1.8)	36 (13.0)
Special senses		
Abnormal vision	8 (2.9)	17 (6. 1)
Urogenital system [c]		
Abnormal ejaculation/ orgasm [d]		
Female	0	3 (2.5)
Male	1 (0.7)	19 (12.0)
Anorgasmia [d]		
Female	0	7 (5.9)
Male	1 (0.7)	8 (5.1)
Dysmenorrhea (female)	12 (9. 9)	6 (5.0)
Impotence (male)	2 (1.3)	16 (10.1)
Menstrual disorder [e] *(female)*	2 (1.7)	3 (2.5)
Sexual function abnormal [e] *(male)*	0	6 (3.8)
Adverse event assoc. w. misc. factors		
Allergic reaction other than drug	5 (1.8)	6 (2.2)

a: TEAEs shown in italics occurred more often in patients treated with venlafaxine ER than in those treated with placebo and are proposed for inclusion in Table 5 of the Effexor XR package insert (Item 2).
b: Will not be listed in labeling per Food and Drug Administration request.
c: Denominators for calculation of incidence based on whether events can occur in both men and women (total placebo n = 274, total venlafaxine ER n = 277), women only (placebo n = 121, venlafaxine ER n = 119), or men only (placebo n = 153, venlafaxine ER n = 158).
d: At the request of the Food and Drug Administration, verbatim terms that coded to these COSTART terms have been regrouped in the Effexor XR package insert into those reported by men and those reported by women as shown in Table 7.2. 1B.
e: Terms not included in Effexor XR package insert because the verbatim and COSTART terms were too vague or general to be informative.
Abbreviation: TEAE = treatment- emergent adverse event.

Table VII.I.1.1 Descriptive Statistical Results of Selected Laboratory Parameters in Studies 387 and 393, combined[†]

	---------- Placebo ----------			------- Venlafaxine ER -------			Venlafaxine ER
Parameter, Units		Baseline	Mean		Baseline	Mean	vs Placebo
Time Periods	n	Mean	Change	n	Mean	Change	p- Value [a]
Sodium, mmol/ L							
Week 12	146	143.2	-0.8**	129	143.0	-0.9**	
Poststudy [b]	13	143.3	-0.1	28	143.2	-0.9	
Final on- therapy	183	143.2	-0.9***	152	143.1	-0.7**	
Chloride, mmol/ L							
Week 12	146	104.0	-0.2	129	103.6	-0.7**	0. 018
Poststudy	13	103.5	0. 0	28	104.7	-0.8	
Final on- therapy	183	104.0	-0.4	152	103.7	-0.6**	
Bicarbonate, mmol/ L							
Week 12	146	24.5	1.3***	129	24.3	2.3***	0.013
Poststudy	13	26.1	0.3	27	23.2	3.0***	
Final on- therapy	183	24.5	1.3***	152	24.3	2.3***	0.010
BUN, mmol/ L							
Week 12	146	5.020	-0. 002	129	5.361	-0. 094	
Poststudy	13	5. 218	-0. 220	27	5.051	-0. 278	
Final on- therapy	183	5.072	-0. 036	152	5.294	-0. 057	
Creatinine, μ mol/ L							
Week 12	146	76.3	0. 3	129	77.9	-0.9	
Poststudy	13	73.4	7. 1	27	69.1	1. 5	
Final on- therapy	183	76.0	0. 1	152	76.7	-0.3	
Total cholesterol, mmol/ L[c]							
Week 12	140	4.924	-0. 049	119	4.992	0.340***	<0.001
Poststudy	11	5. 193	-0. 026	26	5.318	0.016	
Final on- therapy	170	5.009	-0. 058	139	5.010	0.295***	<0.001
HDL cholesterol, mmol/ L[c]							
Week 12	140	1.285	-0. 012	118	1.235	0.073***	<0.001
Poststudy	11	1. 166	-0. 038	26	1.185	0.014	
Final on- therapy	170	1.288	-0. 007	138	1.232	0.069***	0. 001
LDL cholesterol, mmol/ L[c]							
Week 12	135	2.952	-0. 056	111	2.973	0.244***	<0.001
Poststudy	11	3. 169	0.087	25	3.327	-0. 001	
Final on- therapy	164	3.005	-0. 059	131	3.002	0.212***	<0.001
Triglycerides, mmol/ L[c]							
Week 12	140	1.463	0.061	119	1.629	0.052	
Poststudy	11	1. 868	-0. 159	26	1.817	-0. 078	
Final on- therapy	170	1.513	0.048	139	1.629	0.029	

[†]This is taken from Table 8.2.A. in the submission. Selected parameters are considered by the sponsor to 'be most apt to elicit unusual trends of clinical relevance." However, additional parameters have been added to this table based on Supportive Table 17 (ST-17).

Table key is on the next page.

Continued on the next page.

Table VII.I.1.1, continued. Descriptive Statistical Results of Selected Laboratory Parameters

	---------- Placebo ----------			------- Venlafaxine ER -------			Venlafaxine ER
Parameter, Units		Baseline	Mean		Baseline	Mean	vs Placebo
Time Periods	n	Mean	Change	n	Mean	Change	p- Value[a]
AST/ SGOT, U/ L							
Week 12	145	22.7	1. 0	129	23.4	3. 2***	0. 013
Poststudy	13	26.9	-2.4	28	22.2	6. 0	
Final on- therapy	182	22.4	1. 6**	152	23.3	2. 6***	
Alkaline phosphatase, U/ L							
Week 12	146	76.3	-1.6	127	74.8	4. 4***	<0.001
Poststudy	13	85.1	0. 1	28	74.8	2. 0	
Final on- therapy	183	76.7	-1.7*	150	75.1	4. 1***	<0.001
AST/ SGOT, U/ L							
Week 12	145	22.7	1. 0	129	23.4	3. 2***	0. 013
Poststudy	13	26.9	-2.4	28	22.2	6. 0	
Final on- therapy	182	22.4	1. 6**	152	23.3	2. 6***	
Alkaline phosphatase, U/ L							
Week 12	146	76.3	-1.6	127	74.8	4. 4***	<0.001
Poststudy	13	85.1	0. 1	28	74.8	2. 0	
Final on- therapy	183	76.7	-1.7*	150	75.1	4. 1***	<0.001
Total protein, g/ L							
Week 12	146	74.93	-0. 97**	129	74.83	-0. 34	
Poststudy	13	75.00	0.92	28	74.50	-0. 21	
Final on- therapy	183	74.99	-0. 92***	152	74.68	-0. 32	
Glucose, mmol/ L[c]							
Week 12	133	4.91	-0. 03	118	4.91	-0. 08	
Poststudy	10	4. 75	0. 42*	24	5.19	0.17	
Final on- therapy	163	4.91	-0. 03	138	4.93	-0. 09	

a: Comparison between groups based on adjusted means using ANCOVA with baseline as covariate; shown only if $p < 0.05$.
b: The poststudy period was defined as the period beginning the day after the last dose of study medication, regardless of the duration of treatment.
c: Fasting.
*,**, *** Significantly different from the baseline mean at the 0.05, 0.01, and 0.001 levels, respectively. To determine level of significance in the mean change from baseline values within a treatment group paired t-test comparisons were conducted.

Table VII.I.2.1. Criteria for Determining Potentially Clinically Important Changes (Outlier Criteria) in Laboratory Test Results, Studies 387 and 393*

Test [a]	Criteria
Hemoglobin	Decrease of ≥ 20 g/ L
Hematocrit	Decrease of ≥ 0.05
WBC count	Increase or decrease of ≥ 2.0 x 10 /L and ONR
Platelet count	Increase ≥20% above baseline value and abnormally high, or decrease of ≥20% below baseline value and abnormally low
Sodium	Increase or decrease of ≥ 5.0 mmol/ L and ONR
Potassium	Increase or decrease of ≥ 0.5 mmol/ L and ONR
Calcium	Increase or decrease of ≥ 0.5 mmol/ L and ONR
Chloride	Increase or decrease of ≥ 5.0 mmol/ L and ONR
Bicarbonate	Increase or decrease from baseline of ≥ 4 mmol/ L and ONR
BUN	≥ 1.5 x ULN
Creatinine	≥1.5 x ULN
Total bilirubin	≥1.5 x ULN
ALT/ SGPT	≥3 x ULN
AST/ SGOT	≥3 x ULN
Alkaline phosphatase	≥3 x ULN
Total cholesterol	Increase of ≥1.29 mmol/ L and value ≥ 6.75 mmol/ L
HDL cholesterol	Decrease of > 0.21 mmol/ L and value < 0.91 mmol/ L
LDL cholesterol[b]	Increase of ≥1.29 mmol/ L and value ≥ 4.91 mmol/ L
Triglycerides [b]	Increase of ≥2.26 mmol/ L and value ≥ 5.65 mmol/ L
Glucose	≥9.99 mmol/ L or < 2.78 mmol/ L
Uric acid	Increase of ≥ 178.44 µmol/ L and ONR
Total protein	Increase or decrease of 10 g/ L and ONR
Albumin	Decrease of 10 g/ L and ONR
Urinalysis	
Specific gravity	< 1.001 or > 1.035
pH	≤4 or ≥9
Protein albumin	Any value not negative
Glucose/ sugar	Any value not negative
Hemoglobin/ blood	Any value not negative

* This is Table 8.1.1.A. in the ISS of the submission.
a: All changes were measured from pretherapy/ baseline unless otherwise noted.
b: Criteria applied only if patient had fasted.
Abbreviations: ALT = alanine aminotransferase (SGPT = serum glutamic pyruvic transaminase), AST = aspartate aminotransferase (SGOT = serum glutamic oxaloacetic transaminase), BUN = blood urea nitrogen, HDL = high- density lipoprotein, LDL = low-density lipoprotein, ONR = outside of normal range, pH = hydrogen ion concentration, ULN = upper limit of normal range, WBC = white blood cell.

Table VII.I.2.2. Incidence of Outliers on Hematology Parameters

Incidence (%) of Subjects Meeting Outlier Criteria on Hematology Parameters*			
Hematology Parameter (units)	**Outlier Criteria**	**Placebo N=274**	**Venlafaxine ER N=277**
Hematocrit (l)	Decrease ≥ 20 g/l	3/222 (1)	0/187 (0)
Hemoglobin (mmol/l)	Decrease ≥ 0.05	2/221 (<1)	4/186 (2)
White Cell count (g/l)	Increase ≥ $2.0x10^9$/l and ONR**	1/222 (<1)	0/187 (0)
	Decrease ≥ $2x10^9$/l and ONR**	1/222 (<1)	1/187 (<1)
* This table is similar to Table 8.1.1B in the ISS of the submission. This table only lists those hematological parameters in which at least one S met outlier criteria. **ONR is outside the normal limit of the laboratory reference range			

Table VII.J.1.1 Descriptive Statistical Results of Vital Signs and Weight Results (pooled data from Studies 387 and 393)

	---------- Placebo ----------			--------- Venlafaxine ER ---------			Venlafaxine ER vs Placebo
Parameter, Units		Baseline	Mean		Baseline	Mean	
Time Periods	n	Mean	Change	n	Mean	Change	p- Value[a]
Supine systolic BP, mm Hg							
Week 1	263	119.29	-0. 87	252	120.25	1.82***	<0.001
Week 2	255	119.30	-0. 77	226	120.57	2.67***	<0.001
Week 3	248	119.15	-1. 32*	219	120.35	1.80*	<0.001
Week 4	249	119.20	-1. 13*	211	120.23	2.40***	<0.001
Week 6	224	119.04	-0. 66	196	120.51	3.39***	<0.001
Week 8	211	119.12	-0. 86	194	120.67	1.70*	0. 001
Week 10	192	119.68	-1. 35*	173	120.69	2.75***	<0.001
Week 12	179	119.49	-1. 75*	166	120.46	2.20**	<0.001
Poststudy b	185	118.81	-0. 38	191	120.38	1.98**	0.006
Final on- therapy	270	119.31	-2. 61***	257	119.98	1.87**	<0.001
Supine diastolic BP, mm Hg							
Week 1	263	75.72	-0. 99*	252	76.54	0.67	0.002
Week 2	255	75.61	-1. 39***	226	76.49	1.78***	<0.001
Week 3	248	75.73	-1. 30**	219	76.44	2.24***	<0.001
Week 4	249	75.68	-1. 25**	211	76.31	1.79***	<0.001
Week 6	224	75.66	-0. 88	196	76.55	2.51***	<0.001
Week 8	211	75.92	-1. 23*	194	76.47	1.90***	<0.001
Week 10	192	76.14	-1. 69***	173	76.70	1.94***	<0.001
Week 12	179	76.07	-0. 78	166	76.61	2.01***	<0.001
Poststudy	185	75.46	-0. 95	191	76.63	0.32	0.029
Final on- therapy	270	75.74	-1. 10*	257	76.40	1.61***	<0.001
Supine pulse rate, beats/ min							
Week 1	264	68.49	0.99*	251	68.42	1.97***	
Week 2	255	68.38	1.28*	226	68.66	2.40***	
Week 3	249	68.38	0.87	218	68.91	4.45***	<0.001
Week 4	249	68.35	0.96*	211	68.95	4.41***	<0.001
Week 6	224	68.33	1.24*	195	69.02	4.91***	<0.001
Week 8	211	68.25	1.62*	194	68.90	4.77***	<0.001
Week 10	192	68.49	1.25*	173	68.82	4.66***	<0.001
Week 12	179	68.53	-0. 30	166	68.88	3.78***	<0.001
Poststudy	185	68.41	1.10	189	68.81	2.99***	0. 006
Final on- therapy	271	68.38	-0. 34	257	68.42	3.72***	<0.001

See table key on the next page

Continued on the next page

Table VII.J.1.1, continued. Descriptive Statistical Results of Vital Signs and Weight Results (pooled data from Studies 387 and 393)

	---------- Placebo ----------			--------- Venlafaxine ER ---------			Venlafaxine ER
Parameter, Units		Baseline	Mean		Baseline	Mean	vs Placebo
Time Periods	n	Mean	Change	n	Mean	Change	p- Value [a]
Standing systolic							
BP, mm Hg							
Week 1	263	119.31	-0. 67	252	119.99	1.43*	0. 003
Week 2	254	119.25	-1. 77**	226	120.39	0.23	0.009
Week 3	249	118.99	-1. 25*	219	120.35	-0. 43	
Week 4	250	119.13	-1. 63**	211	120.23	-0. 50	
Week 6	223	119.00	-1. 29	197	120.64	0.05	
Week 8	211	119.05	-1. 25	195	120.73	-0. 09	
Week 10	192	119.76	-2. 07**	173	120.69	1.02	0.001
Week 12	179	119.58	-1. 62*	166	120.68	1.02	0.005
Poststudy	184	118.73	-0. 40	190	120.19	1.00	
Final on- therapy	269	119.29	-1. 99***	256	119.82	1.29*	<0.001
Standing diastolic							
BP, mm Hg							
Week 1	263	78.64	-0. 30	252	79.47	1.31**	<0.001
Week 2	254	78.58	-1. 09**	226	79.77	0.78	<0.001
Week 3	249	78.55	-0. 28	219	79.76	0.70	0.036
Week 4	250	78.64	-0. 87*	211	79.57	0.89	0.001
Week 6	223	78.62	-0. 74	197	79.96	1.39**	<0.001
Week 8	211	78.84	-1. 10*	195	79.91	1.64**	<0.001
Week 10	192	79.05	-0. 40	173	79.99	1.18*	0. 010
Week 12	179	78.98	-0. 89	166	79.81	1.13*	0. 002
Poststudy	184	78.62	-0. 88	190	79.67	0.02	
Final on- therapy	269	78.64	-0. 79	256	79.33	1.23**	<0.001
Weight, kg							
Week 12	173	78.58	-0. 01	157	79.01	-0. 56**	0. 034
Poststudy	15	70.81	-0. 34	31	77.31	-1. 65	
Final on- therapy	220	77.57	0.01	188	78.62	-0. 75***	0.001

a: Comparison of adjusted mean changes from baseline for the venlafaxine ER and placebo treatment groups in the 2 pooled studies are provided if significant ($p < 0.05$).
b: The poststudy period was defined as the period beginning the day after the last dose of study medication, regardless of the duration of treatment.
*, **, *** Significantly different from baseline at the 0.05, 0.01, and 0.001 levels, respectively.
Abbreviation: BP = blood pressure.
This table is Table 9.2.A. in the ISS of the submission.

Table VII.J.2.1. Venlafaxine Treated Subjects with Clinically Important Changes in Vital Signs*

STUDIES 387 AND 395

Patient No.	Age/ Sex	Mean Daily Dose (mg)	Total Days on Therapy	Event	Change in Value	Related Laboratory Value	Other Laboratory Value	Symptoms Possibly Related[a]	Drug Related[a]	Outcome	Other Events
387013-504	47/F	200.0	84	Orthostatic BP decreased	-42/-21[b] mm Hg	None	None	Light-headed	Possibly	Persisted	None
393002-048[c]	44/F	90.0	30	Orthostatic BP change	Systolic: -2/-52/-34 mm Hg; Diastolic: +3/-18/-19 mm Hg[d]	None	None	None	No	Persisted	None
393005-173[e]	34/M	150.0	33	Decrease in supine pulse rate	76/50[f] beats/min	None	ALT 83/71[g] U/L	None	Unlikely	Resolved	Abnormal rhythm
393009-330[h]	74/F	137.5	84	Decreased orthostatic BP	Systolic: +2/-39/-30 mm Hg; Diastolic: +2/-17/+2 mm Hg[d]	None	None	Postural dizziness	Possibly	Persisted	Diarrhea

a: Assessment of relationship to study drug judged by the Wyeth-Ayerst medical monitor.
b: Maximal change in systolic BP/maximal change in diastolic BP.
c: Patient 393002-048 had a history of thrombophlebitis, migraine, anemia, and urinary tract infection.
d: Baseline value/maximum value/final value.
e: Patient 393005-173 had clinically important changes in both vital signs and ECG.
f: Actual baseline/minimum values.
g: Baseline/final value.
h: Patient 393009-330 had a history of hypertension and palpitations.
Abbreviations: ALT = alanine aminotransferase, BP = blood pressure.

*This is Table 9.1.2 A. in the ISS of the submission.

ATTACHMENT 1.
A Summary of Pharmacokinetic Properties of EXR, as described in current labeling (See Section III of the Review).

The table below shows PK results of the IR and XR formulations of Effexor.® This table shows that the XR formulation has a longer Tmax and lower Cmax of the parent compound and the active major metabolite, O-desmethylvenlafaxine (ODV).

PK Data of IR and XR Formulations of Effexor®

Treatment	Tmax (hours) of Venlafaxine	Tmax (hrs) of ODV*	Cmax (ng/ml) of Venlafaxine	Cmax (ng/ml) of ODV
150 mg Q24 hrs of Effexor® XR	5.5	9	150	260
75 mg Q12hrs of Effexor® IR	2	3	225	290

*ODV is O-desmethylvenlafaxine, an active metabolite of venlafaxine

Steady state venlafaxine and ODV plasma levels are achieved within 3 days of oral multiple dosing. The apparent elimination half-life of the parent compound and ODV is 52 and 11±2 hours, respectively and both show 27 and 30% protein binding, respectively, at therapeutic levels. The parent compound and its metabolite show linear kinetics There is no food effect on bioavailability for either venlafaxine or ODV and PK parameters are not affected by morning versus evening dosing regimens of the 75 mg EXR capsule.

Venlafaxine is extensively metabolized by the liver, primarily to ODV. Renal elimination is the primary route of elimination of venlafaxine and ODV. Minor metabolites of venlafaxine include N-desmethylvenlafaxine, N,O-didesmethylvenlafaxine and others. Poor CYP2D6 metabolizers show higher plasma levels of venlafaxine and lower plasma levels of ODV than extensive CYP2D6 metabolizers. However the sum of venlafaxine and ODV is similar between the poor and extensive CYP2D6 metabolizers and the parent compound and the major metabolite are approximately equiactive and equipotent. Based on these results no dosage adjustment is recommended in poor metabolizers or with concomitant use of a CYP2D6 inhibitor. *In vitro* studies show that venlafaxine is a weak inhibitor of CYP2D6. Venlafaxine coadministered with imipramine results in no effect on PK parameters of imipramine and 2-OH imipramine, but increased plasma levels of desipramine, while the PK parameters of venlafaxine or ODV PK were unaffected. Coadministration of venlafaxine with respiridone resulted in a decrease in CYP2D6 mediated metabolism of risperidone to its active metabolite, 9-OH risperidone, while the PK profile of the sum of risperidone and its metabolite was not significantly altered. Idonavir levels are reduced when administered concomitantly with venlafaxine, while the PK parameters of venlafaxine remain unaltered. Refer to current labeling for additional information on drug-drug interactions involving venlafaxine.

Age and gender do not alter trough plasma levels of venlafaxine or ODV when the parent compound is administered in b.i.d and t.i.d. regimens. The PK of the drug and its metabolite is altered in patients with hepatic cirrhosis, renal impairment, or who are on dialysis, such that dosage adjustment in these patients is indicated.

ATTACHMENT 2.
Detailed Description of Comparisons Made Within the Submission for Assessing Data Quality and Completeness (See Section V.B. of the Review).

Each item below describes various comparisons made of listings, CRFs and narratives in the submission.

- The listing of CRFs matched the listing of adverse dropouts and serious adverse events in the Cross-Reference Master List of Safety Information (Table 19A) in the submission, except for three subjects with SAEs (Ss: 387014536, 387013502, 393004131, and 393003088). The CRFs of these 3 Ss, which were listed in Table 19A and described in the Integrated Summary of Safety of the submission were not provided. However the sponsor provided the narratives on these Ss and upon request CRFs (in a 10/23/01 as an amendment submission) on these Ss were also provided. These 3 Ss are described in the following and appeared to have SAEs that were not drug-related except for an accidental ingestion of 4 EXR pills by a 20 month old child of one S.

  One S was reported as having an SAE because her 20 month old child accidentally ingested her study drug which was reported to be only a total of 4 pills and to be nontoxic. Another S was a 52 year old female assigned to placebo who had surgery ("tension free vaginal tape") related to a pre-existing urinary incontinence who developed a post operative complication of "perforation of the urinary bladder and bacterial infection" that required hospitalization. The third S was diagnosed with skin neoplasm which was reported in February 2001 (last dose of EXR was July 5, 2000).
- Narratives were provided for all SAEs (N=8) described in the ISS and listed in Table 19A of the submission.
- The following narratives and CRFs were compared for consistency and accuracy (comparisons were arbitrarily selected), as follows:
  - S295 in Study 387: compared reason (terms) for SAE, dates of the SAE, start and stop dates of study drug, selected demographic information and past medical history and May 27th date vital sign measures (date arbitrarily selected). These areas matched between the CRF and narrative, except the narrative described the diagnostic work-up of this patient while hospitalized which could not be found in the CRF.
  - S131 in Study 393: compared SAE term, date and description in the narrative to the CRF and were generally matched.

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/s/

Karen Brugge
4/25/02 04:14:38 PM
MEDICAL OFFICER

Thomas Laughren
5/16/02 10:11:21 AM
MEDICAL OFFICER
I agree that this supplement is approvable; see memo to file for more detailed comments.--TPL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-699/S-022

ENVIRONMENTAL ASSESSMENT

REVIEW

OF

ENVIRONMENTAL ASSESSMENT

FOR

EFFEXOR XR (venlafaxine hydrochloride) Extended Release Capsules

NDA 20-699 / S-022
Treatment of Social Anxiety Disorder (SAD)

Food and Drug Administration
Center for Drug Evaluation and Research

Division of Neuropharmacological Drug Products
(HFD-120)

December 13, 2002

Environmental Assessment Review #1, NDA 20-699 / S-022

EFFEXOR XR (venlafaxine hydrochloride), Extended Release Capsules

SUMMARY

A FONSI is recommended

FONSIs were signed for this Active Pharmaceutical Ingredient in the past.

NDA / Supplement	EA Dated	FONSI Signed	Indication
NDA 20151	July 15, 1993	Dec 17, 1993	Depression
NDA 20151 / S-017	Nov 29, 1999	Nov 29, 1999	Prevention of recurrence of depression
NDA 20699	Mar 25, 1996	Jan 17, 1997	Depression
NDA 20699 / S-001	Jan 14, 1999	Mar 2, 1999	Generalized Anxiety Disorder (GAD)
NDA 20669 / S-007	Apr 21, 1999	Jan 4, 2000	Longer duration of use for GAD

This supplement (NDA 20699 / S-022) provides for a new indication, namely the treatment of Social Anxiety Disorder (SAD). The EA is dated April 24, 2001. It contains new information about the quantity of venlafaxine hydrochloride required for use in all products manufactured by Wyeth-Ayerst. All other information is identical to that submitted previously.

The confidential EA that was submitted with NDA 20-699 / S-022 states that the total amount of venlafaxine hydrochloride manufactured for all products and all indications is expected to increase to [redacted] kg/year in 2005. This corresponds to [redacted] ppb EIC.

Subsequently, additional supplements pertaining to venlafaxine hydrochloride were submitted by Wyeth-Ayerst. Assuming that all the additional supplements are approved, the production estimate for the year 2006 is expected to be [redacted] kg/year. This corresponds to [redacted] ppb EIC.

Previously submitted environmental effects test data for *Daphnia Magna* revealed EC_{50} = [redacted] ppm and NOEC = [redacted] ppm for venlafaxine (free base).

On the basis of [redacted] ppb EIC, a FONSI is recommended for NDA 20699 / S-022 because EC_{50} is more than 1000 greater than EIC and the NOEC is greater than the EIC.

REVIEW OF EA FOR NDA 20699/S-022
Treatment of Social Anxiety Disorder (SAD)

I. DATE: April 24, 2001

II APPLICANT: Wyeth-Ayerst Pharmaceuticals, Inc

III ADDRESS: PO Box 8299
Philadelphia, PA 19101-1245

IV PROPOSED ACTION:

This supplemental application request approval of a new indication for Effexor XR (venlafaxine HCl), namely the treatment of Social Anxiety Disorder (SAD).

The total amount of drug substance (venlafaxine HCl) manufactured for all indications in 2005 is estimated to be ——— kg. (Ref: Current EA, Confidential Appendix I dated April 24, 2001).

The firm submitted several additional supplements that contain a production estimate for 2006, namely NMT ——— kg. (Ref: EA submitted to NDA 20-699, S-030 and S-031, Confidential Appendix I dated Nov 5, 2001). The EIC corresponding to the higher production estimate is — ppb. This EIC is used for evaluating environmental effects.

ADEQUATE

V IDENTIFICATION OF CHEMICALS

NDA 20699 / S-022 refers to

(a) EA information submitted April 25, 1991 to NDA 20-151
(b) EA information submitted May 16, 1996 to NDA 20-699
(c) EA information submitted January 30, 1998 to NDA 20-699 / S-001
(d) EA information submitted Sept 15, 1999 to NDA 20-699 / S-007

ADEQUATE

VI ENVIRONMENTAL ISSUES

Information about environmental fate and effects is provided by reference to the previously submitted EAs (Please see the previous section)

Assuming that all the supplements submitted by Wyeth-Ayerst will be approved, the amount of venlafaxine hydrochloride used for all products and all indications is expected to increase to [redacted] kg/year in 2006. This corresponds to [redacted] ppb EIC.

The applicant predicts that virtually all the venlafaxine hydrochloride remains in the aquatic environment. The sorption / desorption data indicate that some venlafaxine hydrochloride may enter the terrestrial environment bound to solid organic materials such as sludge. However, if this happens, it appears that venlafaxine hydrochloride will remain tightly bound thereby limiting its bioavailability to terrestrial environmental organisms. The most likely environmental exposure route is expected to be aquatic.

Previously submitted environmental effects test data for *Daphnia Magna* revealed EC_{50} = [redacted] ppm and NOEC = [redacted] ppm for venlafaxine (free base).

A FONSI is recommended for NDA 20699 / S-022 because EC_{50} is more than 1000 greater than EIC and the NOEC is greater than the EIC.

ADEQUATE

VII MITIGATION MEASURES

Information not required because no potential adverse environmental effects have been identified.

ADEQUATE

VIII ALTERNATIVES

Information not required because no potential adverse environmental effects have been identified.

ADEQUATE

IX PREPARER

Name, job title and qualifications provided.

ADEQUATE

X CERTIFICATION

Provided.

ADEQUATE

XI APPENDICES

The production estimate is provided in Confidential Appendix I, calculation of EIC is provided in Confidential Appendix II.

ADEQUATE

Review by: Florian Zielinski on December 13, 2002
Chemist, Center for Drug Evaluation and Research

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/s/

Florian Zielinski
12/6/02 03:15:41 PM
ENV ASSESSMENT

Nancy Sager
12/17/02 09:19:26 AM
ENV ASSESSMENT

Yuan-Yuan Chiu
12/17/02 05:08:40 PM
CHEMIST
Concurred

FINDING OF NO SIGNIFICANT IMPACT

AND

ENVIRONMENTAL ASSESSMENT

FOR

EFFEXOR XR (venlafaxine hydrochloride)
Extended Release Capsules

NDA 20-699 / S-022
Treatment of Social Anxiety Disorder (SAD)

Food and Drug Administration
Center for Drug Evaluation and Research

Division of Neuropharmacological Drug Products
(HFD-120)

December 13, 2002

FINDING OF NO SIGNIFICANT IMPACT
NDA 20-699 / S-022

The National Environmental Policy Act of 1969 (NEPA) requires all Federal agencies to assess the environmental impact of their actions. FDA is required under NEPA to consider the environmental impact of approving certain drug product applications as an integral part of its regulatory process.

The Food and Drug Administration, Center for Drug Evaluation and Research, has carefully considered the potential environmental impact of this action and has concluded that this action will not have a significant effect on the quality of the human environment and that an environmental impact statement, therefore, will not be prepared.

In support of its supplemental new drug application for Effexor XR (venlafaxine HCl) Extended Release Capsules, Wyeth-Ayerst Pharmaceuticals, Inc. has prepared an environmental assessment (attached) in accordance with 21 CFR Part 25 which evaluates the potential environmental impacts of the use and disposal of the product.

Venlafaxine HCl is a chemically synthesized drug that is currently approved for use in

(a) treating depression
(b) treating generalized anxiety disorder (GAD)
(c) prevention of recurrence of depression

The supplemental application provides for a new indication, namely the treatment of Social Anxiety Disorder, SAD.

Venlafaxine may enter the environment from patient use and disposal. It is expected to enter into the aquatic environment. As the drug is expected to persist in the environment for some time, the toxicity of venlafaxine to aquatic organisms was characterized. The results indicate that the compound is not expected to be toxic to aquatic organisms at expected environmental concentrations.

In U.S. hospitals and clinics, empty or partially empty packages will be disposed of according to hospital/clinic procedures. From home use, empty or partially empty containers will typically be disposed of by a community's solid waste management system which may include landfills, incineration and recycling, while minimal quantities of the unused drug may be disposed of in the sewer system.

The Center for Drug Evaluation and Research has concluded that the product can be used and disposed of without any expected adverse environmental effects. Adverse effects are not anticipated upon endangered or threatened species or upon property listed in or eligible for listing in the National Register of Historic Places.

PREPARED BY
Florian Zielinski
Chemist, Center for Drug Evaluation and Research

CONCURRED BY
Nancy B. Sager
Environmental Officer, Center for Drug Evaluation and Research

CONCURRED BY
Yuan-yuan Chiu, Ph.D.
Director, Office of New Drug Chemistry, Center for Drug Evaluation and Research

Attachment: Environmental Assessment
Appended Electronic Signature Page

Non-Confidential

Environmental Assessment Information

for

EFFEXOR® XR (Venlafaxine HCl) Extended-Release

Capsules (37.5, 75, 100 and 150 mg)

Supplement to NDA 20-699 S-022

Wyeth-Ayerst Pharmaceuticals

April 24, 2001

[redacted]

SUMMARY

Wyeth-Ayerst Pharmaceuticals is seeking approval of Effexor® XR (venlafaxine HCl) Extended-Release Capsules (37.5, 75, 100 and 150 mg) for a new indication, the treatment of social anxiety disorder. This environmental assessment, arranged as specified in the Center for Drug Evaluation and Research's (CDER) *Guidance for Industry Environmental Assessment of Human Drug and Biologics Applications* (July, 1998), is part of the New Drug Application Supplement for Effexor® XR. The New Drug Application for Effexor® XR (NDA 20-699) was approved October 29, 1997 by the FDA. Under the proposed action, the drug products will contain the same active moiety and will not be administered at higher dosage levels or for longer durations than the products previously approved by the FDA. The proposed action is expected to increase the use of the drug products. Approval of the proposed action is not reasonably expected to result in any adverse impact to the environment.

[redacted]

ENVIRONMENTAL ASSESSMENT

Effexor® XR

Supplement to NDA No. 20-699

DATE

April 24, 2001

NAME OF APPLICANT

Wyeth-Ayerst Pharmaceuticals

ADDRESS

P.O. Box 8299
Philadelphia, PA 19101-1245

REQUEST FOR APPROVAL

Pursuant to Title 21CFR25, this environmental assessment is prepared for a supplement to NDA No. 20-699. Wyeth-Ayerst Pharmaceuticals (Wyeth) is seeking approval of Effexor® XR (venlafaxine HCl) for a new indication, the treatment of social anxiety disorder (SAD). Effexor® XR is supplied as capsules in 37.5, 75, 100 and 150 mg strengths (approved under NDA No. 20-699).

NEED FOR ACTION

The proposed action is to seek a new indication, i.e. for the treatment of SAD. Under the proposed action, the drug product, Effexor® XR capsules will not be administered at higher dosage levels and/or for longer duration than the drug products previously submitted to the FDA. The proposed action will increase the use of the drug products.

This environmental assessment will update the information provided in the previously submitted environmental assessments. For information concerning Locations of Use, Disposal Sites, and Identification of Chemical Substances that are Subject to the Proposed Action, which has not changed, please refer to the following environmental assessment reports which have been previously submitted to the FDA:

- Environmental Assessment Information for Effexor® Tablets, NDA 20-151 (April 25, 1991)
  Environmental Assessment Information for Effexor® XR Extended -Release Capsules, NDA 20-699 (May 16, 1996)

[redacted]

Environmental Assessment Information for Effexor® XR Supplement (Acute GAD, S-001) to NDA 20-699 (January 30, 1998)
Environmental Assessment Information for Effexor® XR Supplement (Long-term GAD, S-007) to NDA 20-699 (September 15, 1999)

ENVIRONMENTAL ISSUES

Expected Introduction Concentration (EIC) From Use

As a result of the approval of the proposed action for a new treatment, an increase in the production of the drug products is expected. Confidential Appendix I contains a five-year forecast of the bulk requirement for venlafaxine HCl.

The EIC for the aquatic compartment, assuming all venlafaxine HCl will be used and evenly distributed throughout the United States, is listed below.

EIC = ppb

Calculation of the EIC is found in Confidential Appendix II.

The EIC for terrestrial compartment is estimated to be zero because virtually all venlafaxine HCl remains in the aqueous compartment. The EIC for the atmospheric compartment is estimated to be zero since venlafaxine HCl is a solid at room temperature and is expected to have a negligible vapor pressure.

Expected Introduction Concentration From Disposal

The EIC from disposal is zero since all rejected batches, damaged products and pharmaceutical waste containing venlafaxine HCl are disposed of via incineration. The amount of venlafaxine HCl expected to be disposed of in the sewer system, due to manufacturing equipment washdown and cleaning, will not be significant.

Expected Environmental Concentration (EEC)

The expected environmental concentration (EEC) of venlafaxine HCl has been calculated to be mg/l. This concentration was calculated by taking the EIC (mg/l), a worst case discharge scenario, and assuming a conservative dilution factor of one order of magnitude. The result, mg/l, is a conservative estimate of the concentration of venlafaxine HCl in the surface waters of the United States. No further depletion mechanisms have been taken into account in this calculation.

Maximum Expected Emitted Concentration (MEEC)

The maximum expected emitted concentration (MEEC) is equal to the expected environmental concentration (EEC) or the expected introduction concentration (EIC), whichever is greater. In the case of venlafaxine HCl, the MEEC is mg/l or ppb.

[redacted]

Fate Of Emitted Substances In The Environment

Several studies were conducted in order to assess the environmental fate of venlafaxine HCl. These studies include Acute Microbial Inhibition Testing, Aerobic Biodegradation Study, Anaerobic Biodegradation Study and Sorption/Desorption Studies. These results, previously reported in the January 30, 1998 Effexor ® XR supplement, are briefly summarized below.

Acute Microbial Inhibition: This test was conducted using various concentrations of pure venlafaxine, acid hydrolyzed, alkali hydrolyzed and ozonated venlafaxine and is based on ASTM publication (ASTM STP 528, Pgs. 221-226-1973). The test involves the measurement of oxygen uptake (unacclimated seed organisms) with comparison among blank controls, known substrate (glucose) controls, the test compound and theory. Venlafaxine was tested at concentrations ranging between 0.001 and 100 percent by volume using a 500 mg/l solution.

Venlafaxine shows acute microbial inhibition (using an aerobic mixed culture - unacclimated seed) at concentrations above 10% (50 mg/l). Acid and alkaline hydrolysis, as a pretreatment step, removes inhibition, however, the treated compound remains relatively resistant to dissimilative metabolism, based on the fact that respiration data shows no net oxygen uptake.

Aerobic Biodegradation: This test was conducted using C^{14} - venlafaxine and followed the CO_2 evolution test method for biodegradation as presented in the FDA's Environmental Assessment Technical Assistance Handbook. The test concentration was 100 ug/l C^{14} venlafaxine HCl.

The actual amount of carbon dioxide produced during the test period, for the test compound (venlafaxine HCl) was less than 60% theoretical carbon dioxide evolution. Although the test data indicates that venlafaxine does not meet the FDA definition of "readily biodegradable", the continued evolution of CO_2 throughout the study suggests that the compound is not toxic to microlife.

Anaerobic Biodegradation: The anaerobic biodegradation test was also conducted using venlafaxine HCl and followed the gas production/pressure measurement method described in 40 CFR 796.3140 "Anaerobic Biodegradability of Organic Chemicals". The test concentration was 77 mg/l venlafaxine.

The actual amount of gas produced during the test period, for the test compound (venlafaxine HCl) was less than control and approximately equal to the blank. Therefore, we have concluded that under the conditions of our test that venlafaxine HCl is not readily biodegradable by anaerobic organisms.

Sorption/Desorption: This test was conducted using C^{14} - venlafaxine to determine the partitioning of the compound between soil/activated carbon and water.

Test data indicates that venlafaxine is adsorbed to a high degree (99.6%) on Powdered Activated Carbon (PAC). The test data for soil (types 1, 4 and 3) indicates that venlafaxine is also adsorbed to a high degree (79.1%, 85.2% and 95.3% respectively). Desorption data indicates that the compound is not readily desorbed.

[redacted]

Based on the test data, it has been concluded that venlafaxine should not be mobile in the environment. The PAC data indicate that carbon adsorption is a potentially viable treatment process for removing venlafaxine from wastewater.

Potential Toxicity Effects

A substance is considered toxic in the environment if the maximum concentration of the substance at any point in the environment, i.e., either at any point of entry or any point where higher concentrations are expected as a result of bioaccumulation or other types of concentration processes, exceeds the concentration of the substance that causes any adverse effect in a test organism species (minimum effect level-MEL) or exceeds 1/100 of the concentration that causes 50% mortality in a test organism species (LD_{50} or LC_{50}), whichever concentration is less. This concentration is defined as the "Criterion Concentration" (CC). The Criterion Concentration for venlafaxine HCl was determined to be 0.38 mg/L by an aquatic toxicity testing of *Daphnia magna*. Test data was provided in the environmental assessment for Effexor® tablets on April 25, 1991.

The EIC for venlafaxine HCl in the aquatic compartment is estimated to be mg/L which is significantly lower than the CC of 0.38 mg/L. Therefore, the proposed action is not expected to cause any toxic effect to aquatic species or result in any adverse impact on the environment.

MITIGATION MEASURES

Means of controlling environmental releases during the production process of Effexor® XR has been described in previously submitted environmental assessments. Emergency plans consist of the established emergency procedures by WAL and AWPI. Waste minimization is achieved primarily through strict manufacturing control which ensures that no significant quantities of the drug substances will be released into the environment.

Other mitigation measures include the use of hoods and HEPA filters, containment of wastes (bagging, drumming, etc.), and the utilization of incineration, municipal water treatment and sanitary landfill technologies. There are no foreseen consequential effects on the environment.

ALTERNATIVES TO THE PROPOSED ACTION

Since the approval of Effexor® XR, there has been no reported adverse effects or any identified potential impacts. Therefore, no alternatives are needed for the proposed action.

[redacted]

LIST OF PREPARERS

Harry Yekel
Senior Project Engineer
Wyeth-Ayerst Pharmaceuticals

Over 15 years' experience in environmental, health and safety related fields. At Wyeth, Mr. Yekel is responsible for preparing and reviewing all environmental assessment documents for FDA New Drug Applications and European Dossiers, and coordinating environmental fate testing for new drug substances. Mr. Yekel has BS and MS degrees in Environmental Engineering from Pennsylvania State University and Drexel University respectively.

Craig Seyfried
Senior Director, Global Environmental, Health and Safety
Wyeth-Ayerst Pharmaceuticals

Over 25 years' experience in environmental, health and safety related fields. Mr. Seyfried is responsible for Wyeth's global EH&S program. Mr. Seyfried has a BS degree in Environmental Science, MS degree in Pharmaceutical Chemistry and an MBA.

CERTIFICATION

The undersigned certifies that the information presented is true, accurate, and complete to the best of the knowledge of Wyeth-Ayerst Pharmaceuticals.

Date May 4, 2001

Signature Craig F. Seyfried

Craig Seyfried
Senior Director, Global Environmental, Health and Safety
Wyeth-Ayerst Pharmaceuticals

REFERENCE

Center for Drug Evaluation and Research, *Guidance for Industry Environmental Assessment of Human Drug and Biologics Applications*, July, 1998.

APPENDICES

Appendix I Five-Year Forecast of Venlafaxine HCl Production (Confidential)

Appendix II Environmental Introduction Concentration Calculation (Confidential)

[redacted]

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

/s/

Florian Zielinski
12/16/02 02:27:48 PM

Nancy Sager
12/17/02 09:17:06 AM

Yuan-Yuan Chiu
12/17/02 05:02:49 PM
Concurred

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-699/S-022

STATISTICAL REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

STATISTICAL REVIEW AND EVALUATION

NDA:	20,699 (S-002)
DRUG NAME:	Effexor XR ® (venlafaxine)
INDICATION:	Social Anxiety Disorder
SPONSOR:	Wyeth-Ayerst
STATISTICAL REVIEWER:	Kun He
DATE OF DOCUMENT:	September 10, 2001

DISTRIBUTION:

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HFD-700 Charles Anello, Sc. D., Deputy Director

TABLE OF CONTENTS

Statistical Review and Evaluation

1. Summary

The current submission NDA 20-699 for Effexor XR ® (venlafaxine) includes two studies to compare the safety and efficacy of venlafaxine with placebo in outpatients with generalized social anxiety disorder.

Study 387 was a 12-week, randomized, double-blind, placebo-controlled, multi-center, flexible dose, and parallel study conducted in USA and Canada. A total of 280 outpatients were randomized, and 271 were in the intent-to-treat population.

Study 393 was a 12-week, randomized, double blind, placebo-controlled, multi-center, flexible dose, and parallel study conducted in USA. A total of 276 outpatients were randomized, and 261 were in the intent-to-treat population.

P-values of the primary analyses performed on the mean change from baseline to week 12 on the Liebowitz Social Anxiety Scale (LSAS) total score are .001 for study 387, and .003 for study 393, which provide statistically significant evidence that venlafaxine-treated patients had a greater mean change of the LSAS total score from baseline to week 12 than that placebo-treated patients did.

2. Introduction

The current submission NDA 20-699 for Effexor XR ® (venlafaxine) includes two studies to compare the safety and efficacy of venlafaxine with placebo in outpatients with generalized social anxiety disorder.

Study 387 was a 12-week, randomized, double-blind, placebo-controlled, multi-center, flexible dose, and parallel study conducted in USA and Canada. A total of 280 outpatients were randomized, and 271 were in the intent-to-treat population.

Study 393 was a 12-week, randomized, double blind, placebo-controlled, multi-center, flexible dose, and parallel study conducted in USA. A total of 276 outpatients were randomized, and 261 were in the intent-to-treat population.

3. Study 387

3.1. Objective

The objective was to determine the anxiolytic efficacy, safety, and tolerability of a flexible dose (75 to 225 mg/day) of venlafaxine extended release (ER) administered for 12 weeks in the treatment of

outpatients with generalized social anxiety disorder in a placebo-controlled study.

3.2. Study Design

This was a multicenter, double blind, placebo-controlled, randomized, parallel-group, flexible-dose study in outpatients who met DSM-IV criteria for social anxiety disorder. Following a 7 ± 3 day single-blind placebo lead-in period, eligible patients received venlafaxine ER or placebo for up to 12 weeks, followed by a taper period of up to 14 days (± 3 days) in duration. The taper period may have been omitted or prolonged if medically indicated. Upon sponsor approval, the single-blind placebo lead-in period may have been extended an additional 7 days (± 3 days) to complete evaluations. Patients returned for a poststudy evaluation 4 to 10 days after taking the last dose of study medication (taper).

Study medication was taken once daily with food in the morning or in the evening, if necessary, to improve tolerability. The dose regimen included a possible 3-step dose escalation. From study day 1 through study day 7 (± 3 days), patients were given a starting dose of 75 mg of venlafaxine ER or placebo. Beginning on study day 8 (± 3 days) through study day 14, patients had their dose increased to 2 capsules daily (150 mg/day venlafaxine ER, or placebo), if clinically indicated to improve response at the discretion of the investigator. On study day 15 (± 3 days), the dose was increased to 3 capsules daily (225 mg/day of venlafaxine, or placebo), if clinically indicated to improve response, at the discretion of the investigator. The dosage was not increased to more than 3 capsules daily, although the dosage could be reduced at the discretion of the investigator to improve tolerance to a minimum of 1 capsule (75 mg) daily. On study completion or early termination, patients who had taken venlafaxine ER or placebo for more than 1 week and who were taking more than 1 capsule per day had their dosage tapered. Patients receiving 3 capsules daily took 2 capsules daily the first week of taper and 1 capsule daily during the second week of taper. Patients receiving 2 capsules daily took 1 capsule the first week of taper. Patients receiving 1 capsule daily did not need to have their dose tapered. (The taper period may have been omitted or prolonged if medically indicated.)

In Amendment II dated August 22, 2000 the following changes were made: Upon sponsor approval, the single-blind placebo lead-in period was permitted to be extended an additional 7 days (± 3 days) in order to complete evaluations. Administration of study medication to patients was permitted in the evening to improve tolerability. In Amendment III dated November 08, 2000 the following changes were made: A period of ±3 days was permitted in addition to the protocol-defined dose titration schedule. This allowed study sites flexibility in scheduling patient visits (e.g., to avoid weekend or holiday periods)

3.3. Efficacy Measures

The primary endpoint is the change from baseline to week 12 on the Liebowitz Social Anxiety Scale (LSAS) total score. LSAS includes 24 items with each item, fear and avoidance, ranges from 0 (none), 1 (mild), 2 (moderate), and 3 (severe), respectively. Rating scales were administered at

baseline (study day –1) and at the end of weeks 1, 2, 3, 4, 6, 8, 10, and 12. The primary time point is the final score while the patient is on-therapy. An observation is considered to be on-therapy if it occurs within 3 days of the patient's final full dose of the test article. Doses taken during the taper period are not considered in determining whether an observation is on-therapy.

Secondary efficacy variables include the CGI-I, the CGI-S, the Social Phobia Inventory (SPIN), the Sheehan Disability Inventory (SDI), the Work Productivity and Activity Impairment Questionnaire (WPAI), the fear and the avoidance subscales of the LSAS, and whether a patient is a responder. A responder is defined as scoring much improved or very much improved on the CGI-I. Rating scales were administered at baseline (study day –1) and at the end of weeks 1, 2, 3, 4, 6, 8, 10, and 12.

3.4. Statistical Analysis Plan

The primary analysis for the change from baseline to week 12 on the LSAS total is analysis of covariance with treatment and investigator as main effects and baseline score as the covariate, using LOCF in the "intent-to-treat" population.

Secondary analyses for the changes from baseline on the LSAS subscales, the SPIN, the SDI, and the WPAI will be analyzed using an analysis of covariance with treatment and investigator as main effects and baseline score as the covariate. Changes from baseline on the CGI-S will be analyzed using an analysis of variance with treatment, investigator and baseline CGI-S as main effects. The CGI-I will be analyzed using the same model as the CGI-S except that there is no baseline CGI-I to enter the model. A secondary analysis will be done that uses the repeated measures of the primary efficacy variable over time in a single model.

Three assumptions of the analysis of covariance model will be tested: parallelism of regression lines, homogeneity of variances and normality. These tests will be applied to the primary variable at the primary time print. Alpha for all tests will be set at 0.05. To assess whether the regression lines for the treatment groups are parallel, the interaction between the (baseline) covariate and the treatment groups will be tested. This will be done by entering a covariate-by-treatment-group interaction term into the model and testing its significance. If the assumption of parallelism is rejected the treatment effect at various levels of the baseline covariate will be described. However, an overall test of treatment effect, across all levels of the baseline covariate, will be done using the primary ANCOVA model. To assess the homogeneity of variances assumption the Levene's test will be used. If the homogeneity assumption is rejected, additional non-parametric analyses will be performed. To assess whether the data are approximately normally distributed, a test using a function of the Kolomogorov D statistic will be used. This test for normality is the one implemented in SAS for sample sizes that are greater than 50. If the normality assumption is rejected, additional non-parametric analyses will be performed.

The date were August 30, 1999 for the original protocol, November 2, 1999 for the Amendment I, August 22, 2000 for the Amendment II, and November 8, 2000 for the Amendment III, and January

15, 2002 for the Amendment IV, respectively.

3.5. Study Population

A total of 280 patients are included on the database. One (1) of these 280 patients (387010-377) was considered to be a "no-data" patient. Patient 387010-377 was randomized to treatment and was dispensed venlafaxine ER, but failed to return after the day -1 visit and did not provide any data after baseline. This patient is not included in the safety population or in the primary efficacy analysis of this study report, but is included in the "all-randomized" efficacy population. The remaining 279 patients who completed the prestudy period and received randomly assigned study medication under double-blind conditions are included in all safety analyses. Eight (8; 3%) of these 279 patients had no post-baseline LSAS evaluation or had no LSAS evaluation within 3 days of the final full dose of study drug. (Doses taken during the taper period were not considered a "full dose.") These patients did not meet the intent-to-treat criteria so their data were not included in the primary efficacy evaluation.

Table 3.5.1. Study Population

Population	PBO	VENL
Randomized	139	141
Safety	139	140
Intent-to-Treat	138	133

Table 3.5.2 shows the demographic and baseline characteristics for the safety population. There were no statistically significant differences between the treatment groups for any of the demographic or baseline characteristics.

Table 3.5.2. Demographic and Baseline Characteristics (Safety Population)

Characteristic		PBO (n=139)	VENL (n=140)
Age (years)	Mean ± SD	35.8 ± 11.5	35.1 ± 11.6
	Range	18-70	18-65
Sex	Female	64 (46%)	61 (44%)
	Male	75 (54%)	79 (56%)
Ethnic origin	White	113 (81%)	113 (81%)
	Black	7 (5%)	9 (6%)
	Hispanic	8 (6%)	7 (5%)
	Afro-Caribbean	1 (<1%)	0
	Arabic	1 (<1%)	0
	Asian	5 (4%)	8 (6%)
	Native American	0	1 (<1%)
	Other	4 (3%)	2 (1%)
Weight (kg)	Mean ± SD	79.0 ± 20.1	77.7 ± 17.2
	Range	47-156	45-136
Duration of Current Episode (years)	Mean ± SD	22.2 ± 13.5	21.0 ± 14.0
	Range	0-61.4	0-59.8
Duration of Current Episode (years)	< 10	28 (20%)	34 (24%)
	10 - <20	40 (29%)	37 (26%)
	20 - <30	33 (24%)	27 (19%)
	30 - <40	21 (15%)	27 (19%)
	≥ 40	17 (12%)	15 (11%)
Baseline LSAS Total	Mean ± SD	86.50 ± 19.89	90.79 ± 19.07
	Range	140-150	133-150
Baseline CGI Severity	4	70 (50.4%)	56 (40.0%)
	5	49 (35.2%)	48 (41.4%)
	6	20 (14.4%)	24 (17.1%)
	7	0	2 (1.4%)

None of the patients were known to have any illnesses at baseline that might have interfered with the activity of the study medication or the interpretation of the results. The demographic and baseline characteristics of the patients in the safety population did not differ appreciably from those of the intent-to-treat population.

Table 3.5.3 shows the demographic and baseline characteristics for the intent-to-treat population. There were no statistically significant differences between the treatment groups for any of the demographic or baseline characteristics.

Table 3.5.3. Demographic and Baseline Characteristics (Intent-to-Treat Population)

Characteristic		PBO (n=138)	VENL (n=133)
Age (years)	Mean ± SD	36.9 ± 11.4	34.9 ± 11.7
	Range	18-70	18-65
Sex	Female	64 (46%)	59 (44%)
	Male	74 (54%)	74 (56%)
Ethnic origin	White	112 (81%)	106 (80%)
	Black	7 (5%)	9 (7%)
	Hispanic	8 (6%)	7 (5%)
	Afro-Caribbean	1 (<1%)	0
	Arabic	1 (<1%)	0
	Asian	5 (4%)	8 (6%)
	Native American	0	1 (<1%)
	Other	4 (3%)	2 (2%)
Weight (kg)	N	136	128
	Mean ± SD	78.7 ± 20.0	77.7 ± 17.2
	Range	47-156	45-136
Duration of Current Episode (years)	Mean ± SD	22.4 ± 13.5	21.0 ± 14.1
	Range	0-61	0-60
Duration of Current Episode (years)	< 10	27 (20%)	32 (24%)
	10 - <20	40 (29%)	36 (27%)
	20 - <30	33 (24%)	26 (20%)
	30 - <40	21 (15%)	25 (19%)
	≥ 40	17 (12%)	14 (11%)
Baseline LSAS Total	Mean ± SD	86.75 ± 19.74	91.07 ± 19.01
	Range	140-150	133-150
Baseline CGI Severity	4	69 (50.0%)	52 (39.1%)
	5	49 (35.5%)	56 (42.1%)
	6	20 (14.5%)	23 (17.3%)
	7	0	2 (1.5%)

None of the patients were known to have any illnesses at baseline that might have interfered with the activity of the study medication or the interpretation of the results. The demographic and baseline characteristics of the patients in the intent-to-treat-analysis population did not differ appreciably from those of the safety population.

A total of 106 (38%) patients discontinued from the study. Table 3.5.4 summarizes the number of patients who discontinued by primary reasons for each treatment group.

Table 3.5.4. Number (%) of Patients Who Withdrew by Primary Reason

Primary Reason	PBO (n=139)	VENL (n=140)
Any reason	54 (39%)	52 (37%)
Adverse event	8 (6%)	24 (17%)
Failed to return	10 (7%)	11 (8%)
Patient request unrelated to study	7 (5%)	5 (4%)
Unsatisfactory response – efficacy	21 (15%)	3 (2%)
Protocol violation	4 (3%)	2 (1%)
Other event	4 (3%)	7 (5%)

Adverse events were the most common reason (24/140; 17%) for discontinuation among venlafaxine ER-treated patients. Significantly more (p = 0.004 based on Fisher's exact test) patients in the venlafaxine ER group (17%) than in the placebo group (6%) discontinued because of adverse events. Unsatisfactory response (lack of efficacy) was the most common reason (21/139; 15%) for discontinuation among placebo-treated patients. Significantly more (p =0.001 based on Fisher's exact test) patients in the placebo group (15%) than in the venlafaxine ER group (2%) discontinued because of lack of efficacy.

3.6. Sponsor's Efficacy Results

The primary analysis is ANCOVA based on the change from baseline to week 12 on the LSAS Total score using LOCF for ITT population, which gives p-value .001.

Table 3.6.1 ANCOVA for the LSAS Total using LOCF for ITT

Therapy	n	Baseline Mean	Mean change from Baseline at Week 12	p-value
PBO	138	86.7	-17.8	.001
VENL	133	91.1	-30.2	

Table 3.6.2 gives ANCOVA results based on the change from baseline on the LSAS Total score using OC for ITT population. P-values are smaller than .05 for Week 3, 6, 8, 10 and 12.

Table 3.6.2 ANCOVA for the LSAS Total using OC for ITT

Week	Therapy	n	Change from Baseline	p-value
Baseline	PBO VENL	138 133		
1	PBO VENL	136 132	-3.860 -6.894	.0548
2	PBO VENL	129 117	-8.899 -11.79	.2854
3	PBO VENL	127 114	-10.62 -16.81	.0427
4	PBO VENL	124 105	-14.77 -21.70	.0590
6	PBO VENL	114 105	-18.38 -27.42	.0262
8	PBO VENL	106 102	-21.75 -30.93	.0358
10	PBO VENL	96 91	-21.46 -35.67	.0010
12	PBO VENL	87 88	-21.34 -39.07	.0001

Secondary analyses for ITT population using LOCF give p-values .001 for CGI-S; .002 for SPIN; .0009 for CGI-I; .0002 for LSAS Fear/Anxiety; .0005 for LSAS Avoidance; .0004 for SDI (Sheehan Disability Work); and .0096 for SDI (Sheehan Disability Social/Leisure Activities).

3.7. Reviewer's Analysis

The reviewer duplicated the sponsor's analyses according to the protocol.

The sponsor checked the assumptions of the parallelism of regression lines, homogeneity of variances and normality. The normality assumption failed. This reviewer performed the Wilcoxon nonparametric test on the percentage change from baseline, i.e., LSAS at week 12 minus baseline divided by baseline, which gives p-value .0001. The Shapiro-Wilk test on ratio failed but the result of the Wilcoxon test indicates the robustness.

Because the normality failed, medians of the change from baseline at week 12 are calculated, which are -26 for VENL, and -12 for PBO, respectively.

The information of each investigator is presented in the following table to check whether the significance result is mainly contributed by one investigator. In the following table, NVENL and NPBO are the number of patients in VENL and PBO groups, respectively. T is TTEST statistic

performed on the difference of the mean changes from baseline for unequal variances between two treatment groups.

Table 3.7.1 T Statistic by Investigator

OBS	INVEST	NVENL	NPBO	T
1	1370	5	7	0.8563
2	1676	7	6	1.0414
3	1730	9	7	1.3136
4	2071	6	9	1.7889
5	4298	5	5	1.6714
6	4378	12	12	1.8289
7	4382	8	8	1.2000
8	7125	6	5	2.0951
9	7911	10	10	-0.0647
10	7913	6	6	0.5182
11	7924	6	6	0.4393
12	7925	11	12	0.7342
13	7926	11	12	1.6340
14	7936	2	1	.
15	7991	6	8	0.5575
16	8055	7	7	1.2726
17	8064	7	6	-0.0292
18	865	5	5	1.5199
19	872	4	6	0.5001

There is no outlier found from the above table.

The following table gives the treatment difference by sex. DIFF is the mean change from baseline to week 12 on the LSAS Total. VPDIFF is the difference between DIFF of VENL and PBO.

Table 3.7.2 VPDIFF by Sex

Sex	Therapy	Patient	DIFF	VPDIFF
Male	VENL	74	-30.46	-10.34
	PBO	74	-20.12	
Female	VENL	59	-29.87	-14.65
	PBO	64	-15.22	

The above table shows that VENL has treatment effect in both male and female groups.

4. Study 393

4.1. Objective

The objective was to determine the anxiolytic efficacy, safety, and tolerability of a flexible dose (75 to 225 mg/day) of venlafaxine extended release (ER) administered for 12 weeks in the treatment of outpatients with generalized social anxiety disorder in a placebo-controlled study.

4.2. Study Design

This was a multicenter, double blind, placebo-controlled, randomized, parallel-group, flexible-dose study in outpatients who met DSM-IV criteria for social anxiety disorder. Following a 7 ± 3 days single-blind placebo lead-in period, eligible patients received Venlafaxine ER or placebo for up to 12 weeks, followed by a taper period of up to 14 days (± 3 days) in duration. The taper period may have been omitted or prolonged if medically indicated. Upon sponsor approval, the single-blind placebo lead-in period may have been extended an additional 7 days (± 3 days) to complete evaluations. Patients returned for a poststudy evaluation 4 to 10 days after taking the last dose of study medication (taper).

Study medication was taken once daily with food in the morning or in the evening, if necessary, to improve tolerability. The dose regimen included a possible 3-step dose escalation. From study day 1 through study day 7 (± 3 days), patients were given a starting dose of 75 mg of Venlafaxine ER or placebo. Beginning on study day 8 (± 3 days) through study day 14, patients had their dose increased to 2 capsules daily (150 mg/day venlafaxine ER, or placebo), if clinically indicated to improve response at the discretion of the investigator. On study day 15 (± 3 days), the dose was increased to 3 capsules daily (225 mg/day of venlafaxine, or placebo), if clinically indicated to improve response, at the discretion of the investigator. The dosage was not increased to more than 3 capsules daily, although the dosage could be reduced at the discretion of the investigator to improve tolerance to a minimum of 1 capsule (75 mg) daily. On study completion or early termination, patients who had taken venlafaxine ER or placebo for more than 1 week and who were taking more than 1 capsule per day had their dosage tapered. Patients receiving 3 capsules daily took 2 capsules daily the first week of taper and 1 capsule daily during the second week of taper. Patients receiving 2 capsules daily took 1 capsule the first week of taper. Patients receiving 1 capsule daily did not need to have their dose tapered. (The taper period may have been omitted or prolonged if medically indicated.)

In Amendment I dated August 22, 2000 the following changes were made: Upon sponsor approval, the single-blind placebo lead-in period was permitted to be extended an additional 7 days (± 3 days) in order to complete evaluations. Administration of study medication to patients was permitted in the evening to improve tolerability. In Amendment II dated November 06, 2000 the following changes

were made: A period of ±3 days was permitted in addition to the protocol-defined dose titration schedule. This allowed study sites flexibility in scheduling patient visits (e.g., to avoid weekend or holiday periods)

4.3. Efficacy Measures

The primary endpoint is the change from baseline to week 12 on the Liebowitz Social Anxiety Scale (LSAS) total score. LSAS includes 24 items with each item, fear and avoidance, ranges from 0 (none), 1 (mild), 2 (moderate), and 3 (severe), respectively. Rating scales were administered at baseline (study day –1) and at the end of weeks 1, 2, 3, 4, 6, 8, 10, and 12. The primary time point is the final score while the patient is on-therapy. An observation is considered to be on-therapy if it occurs within 3 days of the patient's final full dose of the test article. Doses taken during the taper period are not considered in determining whether an observation is on-therapy.

Secondary efficacy variables include the CGI-I, the CGI-S, the Social Phobia Inventory (SPIN), the Sheehan Disability Inventory (SDI), the Work Productivity and Activity Impairment Questionnaire (WPAI), the fear and the avoidance subscales of the LSAS, and whether a patient is a responder. A responder is defined as scoring much improved or very much improved on the CGI-I. Rating scales were administered at baseline (study day –1) and at the end of weeks 1, 2, 3, 4, 6, 8, 10, and 12.

4.4. Statistical Analysis Plan

The primary analysis for the change from baseline to week 12 on the LSAS total is analysis of covariance with treatment and investigator as main effects and baseline score as the covariate, using LOCF in the "intent-to-treat" population.

Secondary analyses for the changes from baseline on the LSAS subscales, the SPIN, the SDI, and the WPAI will be analyzed using an analysis of covariance with treatment and investigator as main effects and baseline score as the covariate. Changes from baseline on the CGI-S will be analyzed using an analysis of variance with treatment, investigator and baseline CGI-S as main effects. The CGI-I will be analyzed using the same model as the CGI-S except that there is no baseline CGI-I to enter the model. A secondary analysis will be done that uses the repeated measures of the primary efficacy variable over time in a single model.

Three assumptions of the analysis of covariance model will be tested: parallelism of regression lines, homogeneity of variances and normality. These tests will be applied to the primary variable at the primary time print. Alpha for all tests will be set at 0.05. To assess whether the regression lines for the treatment groups are parallel, the interaction between the (baseline) covariate and the treatment groups will be tested. This will be done by entering a covariate-by-treatment-group interaction term into the model and testing its significance. If the assumption of parallelism is rejected the treatment effect at various levels of the baseline covariate will be described. However, an overall test of treatment effect, across all levels of the baseline covariate, will be done using the primary ANCOVA

model. To assess the homogeneity of variances assumption the Levene's test will be used. If the homogeneity assumption is rejected, additional non-parametric analyses will be performed. To assess whether the data are approximately normally distributed, a test using a function of the Kolomogorov D statistic will be used. This test for normality is the one implemented in SAS for sample sizes that are greater than 50. If the normality assumption is rejected, additional non-parametric analyses will be performed.

The Amendment date were October 18, 1999 for the original protocol, August 22, 2000 for the Amendment I, November 6, 2000 for the Amendment II, and January 15, 2001 for the Amendment III, respectively.

4.5. Study Population

A total of 276 patients are included on the database. Four (4) of these 276 patients were considered to be "no-data" patients. One (1) patient (393016-613) was dispensed placebo medication but returned the medication unused. Three (3) patients were randomized to treatment and were dispensed venlafaxine ER (393004-123) or placebo (393011-402 and 393018-699) but failed to return after the day -1 visit and did not provide any data after baseline. These 3 patients are not included in the safety population or in the primary efficacy analysis of this study report, but are included in the "all-randomized" efficacy population. The remaining 272 patients who completed the prestudy washout period and received randomly assigned study medication under double-blind conditions are included in all safety analyses. Eleven (11, 4%) of these 272 patients had no post-baseline LSAS evaluation or had no LSAS evaluation within 3 days of the final full dose of study drug. (Doses taken during the taper period were not considered a "full dose.") These patients did not meet the intent-to-treat criteria so their data were not included in the primary efficacy evaluation.

Table 4.5.1. Study Population

Population	PBO	VENL
Randomized	138	138
Safety	135	137
Intent-to-Treat	135	126

Table 4.5.2 shows the demographic and baseline characteristics for the safety population. There were 2 statistically significant differences between the treatment groups: the duration of current episode ($p = 0.005$) and the CGI-S score ($p = 0.0374$).

Table 4.5.2. Demographic and Baseline Characteristics (Safety Population)

Characteristic		PBO (n=135)	VENL (n=137)
Age (years)	Mean ± SD	40.3 ± 11.9	43.0 ± 12.3
	Range	20-78	19-76
Sex	Female	57 (42%)	58 (42%)
	Male	78 (58%)	79 (58%)
Ethnic origin	White	97 (72%)	102 (74%)
	Black	18 (13%)	15 (11%)
	Hispanic	12 (9%)	11 (8%)
	Afro-Caribbean	1 (<1%)	0
	Arabic	2 (<1%)	2 (1%)
	Asian	3 (2%)	5 (4%)
	Other	2 (1%)	2 (1%)
Weight (kg)	N	134	136
	Mean ± SD	77.0 ± 17.7	80.1 ± 18.8
	Range	47.3-130.9	44.5-148.6
Duration of Current Episode (years)	Mean ± SD	25.9 ± 14.5	28.9 ± 15.2
	Range	0.7-61.1	0.8-67.4
Duration of Current Episode (years)	< 10	24 (18%)	20 (15%)
	10 - <20	23 (17%)	18 (13%)
	20 - <30	29 (21%)	30 (22%)
	30 - <40	35 (26%)	33 (24%)
	≥ 40	24 (18%)	36 (26%)
Baseline LSAS Total	Mean ± SD	87.36 ± 21.91	90.84 ± 18.27
	Range	50-139	52-130
Baseline CGI Severity	4	77 (57.0%)	64 (46.7%)
	5	49 (36.3%)	55 (40.2%)
	6	9 (6.7%)	18 (13.1%)

None of the patients were known to have any illnesses at baseline that might have interfered with the activity of the study medication or the interpretation of the results. The demographic and baseline characteristics of the patients in the safety population did not differ appreciably from those of the intent-to-treat population.

Table 4.5.3 shows the demographic and baseline characteristics for the intent-to-treat population. There were no statistically significant differences between the treatment groups for any of the demographic or baseline characteristics.

Table 4.5.3. Demographic and Baseline Characteristics (Intent-to-Treat Population)

Characteristic		PBO (n=135)	VENL (n=126)
Age (years)	Mean ± SD	40.3 ± 11.9	42.7 ± 12.6
	Range	20-78	19-76
Sex	Female	57 (42%)	54 (43%)
	Male	78 (58%)	72 (57%)
Ethnic origin	White	97 (72%)	97 (77%)
	Black	18 (13%)	12 (10%)
	Hispanic	12 (9%)	10 (8%)
	Afro-Caribbean	1 (<1%)	0
	Arabic	2 (<1%)	1 (1%)
	Asian	3 (2%)	5 (4%)
	Other	2 (1%)	1 (1%)
Weight (kg)	N	134	125
	Mean ± SD	77.0 ± 17.7	79.9 ± 19.0
	Range	47.3-130.9	44.5-148.6
Duration of Current Episode (years)	Mean ± SD	25.9 ± 14.5	28.6 ± 15.6
	Range	0.7-61.1	0.8-67.4
Duration of Current Episode (years)	< 10	24 (18%)	20 (16%)
	10 - <20	23 (17%)	18 (14%)
	20 - <30	29 (21%)	25 (20%)
	30 - <40	35 (26%)	31 (25%)
	≥ 40	24 (18%)	32 (25%)
Baseline LSAS Total	Mean ± SD	87.36 ± 21.91	90.77 ± 18.19
	Range	50-139	52-130
Baseline CGI Severity	4	77 (57.0%)	61 (48.4%)
	5	49 (36.3%)	51 (40.5%)
	6	9 (6.7%)	14 (11.1%)

None of the patients were known to have any illnesses at baseline that might have interfered with the activity of the study medication or the interpretation of the results. The demographic and baseline characteristics of the patients in the intent-to-treat population did not differ appreciably from those of the safety population.

A total of 100 (37%) patients discontinued from the study. Table 4.5.4 summarizes the number of patients who discontinued by primary reasons for each treatment group.

Table 4.5.4. Number (%) of Patients Who Withdrew by Primary Reason

Primary Reason	PBO (n=135)	VENL (n=137)
Any reason	40 (30%)	60 (44%)
Adverse event	6 (4%)	21 (15%)
Failed to return	15 (11%)	20 (15%)
Patient request unrelated to study	1 (<1%)	5 (4%)
Unsatisfactory response – efficacy	14 (10%)	10 (7%)
Protocol violation	2 (1%)	2 (1%)
Other event	2 (1%)	2 (1%)

Adverse events were the most common reason (21/137; 15%) for discontinuation among venlafaxine ER-treated patients. Significantly more (p = 0.003 based on Fisher's exact test) patients in the venlafaxine ER group (15%) than in the placebo group (4%) discontinued because of adverse events. Failure to return was the most common reason (15/135; 11%) for discontinuation among placebo-treated patients.

4.6. Sponsor's Efficacy Results

The primary analysis is ANCOVA based on the change from baseline to week 12 on the LSAS Total score using LOCF for ITT population, which gives p-value .003.

Table 4.6.1 ANCOVA for the LSAS Total using LOCF for ITT

Therapy	n	Baseline Mean	Mean change from Baseline at Week 12	p-value
PBO	135	87.4	-21.3	.003
VENL	126	90.8	-33.1	

Table 4.6.2 gives ANCOVA results based on the change from baseline on the LSAS Total score using OC for ITT population. P-values are smaller than .05 for Week 3, 4, 6, 8, 10 and 12.

Table 4.6.2 ANCOVA for the LSAS Total using OC for ITT

Week	Therapy	n	Change from Baseline	p-value
Baseline	PBO VENL	135 126		
1	PBO VENL	129 121	-4.791 -5.066	.8174
2	PBO VENL	127 109	-9.945 -12.04	.3204
3	PBO VENL	123 106	-13.24 -18.04	.0466
4	PBO VENL	126 107	-15.02 -24.14	.0009
6	PBO VENL	111 93	-19.92 -30.10	.0026
8	PBO VENL	107 93	-23.23 -33.42	.0078
10	PBO VENL	99 84	-25.05 -37.36	.0070
12	PBO VENL	95 77	-26.54 -41.47	.0020

Secondary analyses for ITT population using LOCF give p-values .005 for CGI-S; .024 for SPIN; .0053 for CGI-I; .0054 for LSAS Fear/Anxiety; .0019 for LSAS Avoidance; .0062 for SDI (Sheehan Disability Work); and .0003 for SDI (Sheehan Disability Social/Leisure Activities).

4.7. Reviewer's Analysis

The reviewer duplicated the sponsor's analyses according to the protocol.

The sponsor checked the assumptions of the parallelism of regression lines, homogeneity of variances and normality. The normality assumption failed. This reviewer performed the Wilcoxon nonparametric test is performed on the percentage change from baseline, i.e., LSAS at week 12 minus baseline divided by baseline, which gives p-value .0021. The Shapiro-Wilk test on ratio failed but the result of the Wilcoxon test indicates the robustness.

Because the normality failed, medians of the change from baseline at week 12 are calculated, which are -28 for VENL, and -14 for PBO, respectively.

The information of each investigator is presented in the following table to check whether the significance result is mainly contributed by one investigator. In the following table, NVENL and NPBO are the number of patients in VENL and PBO groups, respectively. T is TTEST statistic

performed on the difference of the mean changes from baseline for unequal variances between two treatment groups.

Table 4.7.1 T Statistic by Investigator

OBS	INVEST	NVENL	NPBO	T
1	1033	6	7	-0.8718
2	10976	8	7	0.2931
3	10978	8	12	-0.0399
4	10996	6	6	1.6218
5	11021	3	1	.
6	1271	6	5	1.4237
7	1958	6	8	-0.2051
8	4398	9	11	1.8716
9	4545	13	14	0.3474
10	5092	7	6	2.0213
11	5460	12	11	2.5261
12	8064	13	14	2.1087
13	8065	9	9	2.9799
14	8071	12	12	-0.6555
15	853	6	9	-1.5152
16	9999	2	3	1.0071

From the above table, it is seen that T of the investigators 8065 is very large. After removing investigators 8065, ANCOVA gives p-value .0184.

The following table gives the treatment difference by sex. DIFF is the mean change from baseline to week 12 on the LSAS Total. VPDIFF is the difference between DIFF of VENL and PBO.

Table 4.7.2 VPDIFF by Sex

Sex	Therapy	Patient	DIFF	VPDIFF
Male	VENL	72	-35.38	-14.29
	PBO	78	-21.09	
Female	VENL	54	-29.98	-8.32
	PBO	57	-21.67	

The above table shows that VENL has treatment effect in both male and female groups.

5. Conclusion

The primary analyses of the change from baseline to week 12 on the LSAS total are statistically nominally significant for both Studies 387 and 393. Based on the analyses, the studies provide statistically significant evidence that venlafaxine-treated patients had a greater mean change on the LSAS total score from baseline to week 12 than that placebo-treated patients did.

Because the normality assumption failed, median might be more appropriate to describe the treatment effect in the labeling.

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/s/

Kun He
5/7/02 02:11:31 PM
BIOMETRICS

Kun Jin
5/7/02 02:27:41 PM
BIOMETRICS

George Chi
5/8/02 02:34:37 PM
BIOMETRICS

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-699/S-022

ADMINISTRATIVE DOCUMENTS

EXCLUSIVITY SUMMARY for NDA # 20-699/S-022

Trade Name Effexor® XR Extended-release Capsules Generic Name venlafaxine HCl

Applicant Name Wyeth-Ayerst HFD- 120
Approval Date 2/11/03

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "YES" to one or more of the following questions about the submission.

   a) Is it an original NDA? YES/__/ NO /_X__/

   b) Is it an effectiveness supplement? YES /_X__/ NO /__/

      If yes, what type(SE1, SE2, etc.)? SE-1

   c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "NO.")

      YES /_X_/ NO /___/

      If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

      _____

      _____

      If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

      _____

      _____

d) Did the applicant request exclusivity?

YES /_X__/ NO /__/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

3 years

e) Has pediatric exclusivity been granted for this Active Moiety?

(was granted 12/02)

YES /_X__/ NO /_@_/

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use? (Rx to OTC Switches should be answered No - Please indicate as such).

YES /___/ NO /_X_/

If yes, NDA # _____ Drug Name _____

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /_X_/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (even if a study was required for the upgrade).

PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /_X__/ NO /__/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # 20-699 _____ _____

NDA # _____ _____

NDA # _____ _____

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # _____ _____

NDA # _____ _____

NDA # _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9. IF "YES," GO TO PART III.

PART III: THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /_X__/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis

for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /_X__/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON Page 9:**

_____

_____

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /_X__/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /___/

If yes, explain: _____

_____

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /_X__/

If yes, explain: _____

_____

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study # 387

Investigation #2, Study # 393

Investigation #3, Study # _____

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

(a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /___/ NO /_X__/

Investigation #2 YES /___/ NO /_X__/

Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # _____ Study # _____
NDA # _____ Study # _____
NDA # _____ Study # _____

(b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /_X__/

Investigation #2 YES /___/ NO /_X__/

Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _____ Study # _____

NDA # _____ Study # _____

NDA # _____ Study # _____

(c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #_1_, Study # __387_____

Investigation #_2_, Study # __393_____
Investigation #__, Study # _____

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

(a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # 41,412 YES /_X__/ NO /___/ Explain: _____

Investigation #2

IND # 41,412 YES /_X__/ NO /___/ Explain: _____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES /___/ Explain _____ NO /___/ Explain _____

Investigation #2

YES /___/ Explain _____ NO /___/ Explain _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /_X__/

If yes, explain: _____

_____

_____

_____ Date_____

Signature of Preparer

Title:Regulatory Health Project Manager

_____ _____

Signature of Office of Division Director Date

cc:
Archival NDA
HFD-120/Division File
HFD-120/Homonnay
HFD-093/Mary Ann Holovac
HFD-104/PEDS/T.Crescenzi

Form OGD-011347
Revised 8/7/95; edited 8/8/95; revised 8/25/98, edited 3/6/00

NDA No. 20-699
Efficacy Supplement -
Treatment of Social Anxiety Disorder

PATENT INFORMATION UNDER SECTION 505 (b)

EFFEXOR® XR (venlafaxine hydrochloride) Extended-Release Capsules, Oral, is covered by U.S. Patent 4,535,186 which claims the compound venlafaxine and its salts. Pursuant to a Certificate Extending Patent Term Under 35 USC 156, issued April 26, 1996, the expiration date of the patent is now December 13, 2007. The parent company of applicant is the owner of this patent. In the opinion of the applicant and to the best of applicant's knowledge, there is no other U.S. patent which claims the drug for which applicant has sought approval or which claims the use of the drug for the treatment of social anxiety disorder for which applicant is seeking approval.

WYETH-AYERST LABORATORIES

By: _____
George Tarnowski
Patent Attorney

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: December 6, 2002

FROM: Thomas P. Laughren, M.D.
Team Leader, Psychiatric Drug Products
Division of Neuropharmacological Drug Products
HFD-120

SUBJECT: Recommendation for Approval Action for
Effexor XR (venlafaxine) for the treatment of social anxiety disorder

TO: File NDA 20-699/S-022
[**Note:** This overview should be filed with the 8-29-02 response to our 7-9-02 approvable letter.]

We issued an approvable letter for this supplement on 7-9-02, requesting the following prior to final approval: (1) safety update; (2) regulatory status update; and (3) world literature update. We also included draft labeling.

The 8-29-02 submission was a complete response to our letter. This response was reviewed by Karen Brugge, M.D., from the clinical group.

Safety Update
-Safety data were provided from 3 additional studies in social anxiety disorder. Dr. Brugge concluded that no important new safety findings were revealed by these data.

Regulatory Status Update
-The social anxiety disorder claim has been approved in Mexico and the Philippines, and applications are pending in [redacted]

World Literature Update
-Dr. Brugge concluded that no important new safety findings were revealed by the literature update.

Final Labeling
-The sponsor provided satisfactory responses in several sections where we had requested additional data and clarification, and they agreed with the remainder of our proposed labeling, with the exception of minor editorial changes which we find to be acceptable.

Conclusions and Recommendations

I believe that Wyeth-Ayerst has submitted sufficient data to support the conclusion that Effexor XR is effective and acceptably safe in the treatment of social anxiety disorder. I recommend that we issue the attached approval letter with the mutually agreed upon final labeling.

cc:
Orig NDA 21-346
HFD-120
HFD-120/TLaughren/RKatz/KBrugge/AHomonnay

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/s/

Thomas Laughren
12/6/02 02:37:15 PM
MEDICAL OFFICER

REGULATORY PROJECT MANAGER
LABELING REVIEW

Drug: Effexor XR (venlafaxine hydrochloride) Extended Release 37.5 mg, 75 mg, and 150 mg Capsules
NDA: 20-699
Sponsor: Wyeth
Indication: Major Depressive Disorder (MDD)/Generalized Anxiety Disorder (GAD)/Social Anxiety Disorder (SAD)
Supplements:

NDA	Supplement	Dated	Action
Effexor XR (venlafaxine hydrochloride) Extended Release 37.5 mg, 75 mg, and 150 mg Capsules			
20-699	SE1-022	10-10-01	AP letter dated 2-11-03

Review

1. The Agency approved the new indication of SAD (SE1-022) in an action letter dated 2-11-03. The sponsor, as requested in the referenced action letter, submitted FPL for this supplement in a submission dated 2-21-03.

2. I compared the labeling submitted on 2-21-03, with the labeling attached to the 2-11-03 AP letter, and they were identical except for some stylistic changes noted in the 2-21-03 cover letter.

3. The labeling only provides for the agreed upon changes except for some minor stylistic revisions. Therefore, I recommend that we issue an acknowledge and retain letter.

{See appended electronic signature page}

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

{See appended electronic signature page}

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

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/s/

Paul David
8/26/03 09:37:42 AM
CSO

Robbin Nighswander
8/26/03 01:22:15 PM
CSO

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: May 16, 2002

FROM: Thomas P. Laughren, M.D.
Team Leader, Psychiatric Drug Products
Division of Neuropharmacological Drug Products
HFD-120

SUBJECT: Recommendation for Approvable Action for
Effexor XR (venlafaxine) for the treatment of social anxiety disorder

TO: File NDA 20-699/S-022
[**Note:** This overview should be filed with the 9-10-01
original submission.]

1.0 BACKGROUND

Venlafaxine is a potent inhibitor of neuronal serotonin and norepinephrine reuptake and a weak inhibitor of neuronal dopamine reuptake. Effexor, an immediate release formulation of venlafaxine, was approved for the treatment of depression 12-28-93 (NDA 20-151) at divided doses (2 to 3) up to 375 mg/day. Effexor XR, an extended release formulation of venlafaxine, was approved for the short-term treatment of depression 10-20-97 (NDA 20-699) at single daily doses of up to 225 mg/day. Effexor XR was approved for the short-term treatment of generalized anxiety disorder (GAD) 3-11-99 (NDA 20-699/S-001), in a dose range of 75-225 mg/day as a single dose. Supplement 022 includes data in support of a claim for Effexor XR in the treatment of social anxiety disorder. At the present time, there is only one other drug approved for the treatment of social anxiety disorder, i.e., Paxil.

We held an EOP2 meeting with the sponsor on 8-19-99. We generally endorsed their planned studies and the overall plan to come in initially with studies to support an acute claim in adults, followed later by longer-term efficacy data and adolescent data. We advised them that the studies would need to be significant at $p<0.05$ on all specified primary endpoints, and we asked them to provide more detailed statistical plans. Over the next 12 to 18 months there was an exchange of correspondence to solidify statistical plans and other study details. There was no preNDA meeting. Studies in support of this claim were conducted under IND 41,412.

Since the proposal is to use the currently approved Effexor XR formulations for this additional claim, there was no need for chemistry, pharmacology, or biopharmaceutics reviews of this supplement. Consequently, the focus was on clinical data. The primary review of the efficacy and safety data was done by Karen Brugge, M.D., from the clinical group. Kun He, Ph.D., from the Division of Biometrics, also reviewed the efficacy data.

The original supplement for this additional claim (S-022) was submitted 9-10-01. A filing meeting was held on 11-09-01, and the application was considered fileable.

We decided not to take this supplement to the Psychopharmacological Drugs Advisory Committee.

2.0 CHEMISTRY

As Effexor XR is a marketed product, there were no CMC issues requiring review for this supplement.

3.0 PHARMACOLOGY

As Effexor XR is a marketed product, there were no pharmacology/toxicology issues requiring review for this supplement.

4.0 BIOPHARMACEUTICS

As Effexor XR is a marketed product, there were no biopharmaceutics issues requiring review for this supplement.

5.0 CLINICAL DATA

5.1 Efficacy Data

5.1.1 Overview of Studies Pertinent to Efficacy

Our review of efficacy was focused on the results of studies 387 and 393, both 12-week, acute studies of Effexor XR in adult outpatients with social anxiety disorder.

5.1.2 Summary of Study 387

This was a randomized, double-blind, parallel group, 12-week, flexible-dose, multicenter (19 US and Canadian sites) study comparing Effexor XR, in a dose range of 75 to 225 mg/day, and placebo in adult

outpatients meeting DSM-IV criteria for generalized social anxiety disorder. Randomization was preceded by a 7-day single-blind placebo run-in. Treatment was initiated at 75 mg for 1 week, then increased to 150 mg for the second week, and finally increased to 225 mg at the beginning of week 3. Dose could be subsequently reduced to as low as 75 mg if not well-tolerated. Patients taking more than 1 capsule per day at study end were tapered, at a rate of 1 capsule per week.

The primary endpoint was change from baseline to endpoint (12 weeks) in the Liebowitz Social Anxiety Scale (LSAS), an assessment that was administered at the ends of weeks 1,2,3,4,6,8,10, and 12. Secondary endpoints included the CGI, the Social Phobia Inventory (SPIN), the Sheehan Disability Inventory (SDI), the Work Productivity and Activity Impairment Questionnaire (WPAI), the fear and avoidance subscales of the LSAS, and responder status (much improved or very much improved on the CGI). The primary analysis model was ANCOVA with treatment and investigator as main effects and baseline score as covariate, using LOCF in our usual intent-to-treat population (all randomized patients who received at least one dose of assigned treatment, and had baseline and at least one followup LSAS assessment).

There were n=271 patients in the ITT sample (n=138 for pbo and n=133 for Efffexor XR). There were substantial dropouts before reaching the 12 week endpoint, with the % completing to 12 weeks ranging from 62% for placebo to 66% for Effexor XR. The patients were about 55% male, about 80% Caucasian, and the mean age was about 35 years. The median daily Effexor XR dose for completers to 12 weeks in this trial was 202 mg.

Effexor XR was superior to placebo on change from baseline to endpoint in LSAS:

Efficacy Results on LSAS Total Score for Study 387 (LOCF)

	Baseline LSAS	**• baseline LSAS**	**[P-value(vs pbo)]**
Effexor XR (n=133)	**91.1**	**-30.2**	**p=0.001**
Placebo (n=138)	**86.7**	**-17.8**	

The OC analyses for LSAS also statistically significantly favored Effexor XR for weeks 3,6,8,10, and 12. Analyses of secondary outcomes also generally favored Efffexor XR over placebo. Dr. He performed a Wilcoxon nonparametric test for LSAS, since the data failed on a normality test, and the result again was highly favorable for Effexor XR (p=0.0001). An evaluation by investigator revealed consistent findings favoring Effexor XR across centers, and an analysis by gender also showed positive results for Effexor XR in both strata.

Analyses of HAMD and Raskin Depression scores revealed to drug effect; this was not a surprising result, given that mean baseline HAMD and Raskin Depression scores were 7 and 4, respectively.

Comment: Both Drs. Brugge and He considered this a positive study, and I agree.

5.1.3 Summary of Study 393

This study was identical in design to study 387. There were 17 US sites.

There were n=261 patients in the ITT sample (n=135 for pbo and n=126 for Efffexor XR). There were substantial dropouts before reaching the 12 week endpoint, with the % completing to 12 weeks ranging from 70% for placebo to 61% for Effexor XR. The patients were about 58% male, about 75% caucasian, and the mean age was about 41 years. The median daily Effexor XR dose for completers to 12 weeks in this trial was 191 mg.

Effexor XR was superior to placebo on change from baseline to endpoint in LSAS:

Efficacy Results on LSAS Total Score for Study 393 (LOCF)

	Baseline LSAS	**• baseline LSAS**	**[P-value(vs pbo)]**
Effexor XR (n=126)	**90.8**	**-33.1**	**p=0.003**
Placebo (n=135)	**87.4**	**-21.3**	

The OC analyses for LSAS also statistically significantly favored Effexor XR for weeks 3,4,6,8,10, and 12. Analyses of secondary outcomes also generally favored Efffexor Xrover placebo. Dr. He performed a Wilcoxon nonparametric test for LSAS, since the data failed on a normality test, and the result again was favorable for Effexor XR (p=0.002). An evaluation by investigator revealed consistent findings favoring Effexor XR across centers, except for 1 investigator with a somewhat larger treatment effect. A re-analysis without this center still significantly favored Effexor XR. An analysis by gender also showed positive results for Effexor XR in both strata.

Analyses of HAMD and Raskin Depression scores revealed to drug effect; this was not a surprising result, given that mean baseline HAMD and Raskin Depression scores were 7 and 4, respectively.

Comment: Both Drs. Brugge and He considered this a positive study, and I agree.

5.1.4 Comment on Other Important Clinical Issues Regarding Effexor XR in Social Anxiety Disorder

Evidence Bearing on the Question of Dose/Response for Efficacy

Neither of the 2 studies provided any information pertinent to the question of dose response for efficacy. Labeling will simply describe how patients were dosed in these 2 trials.

Clinical Predictors of Response

Exploratory analyses were done to detect subgroup interactions on the basis of gender, and these analyses suggested treatment effects in both strata.

Size of Treatment Effect

The effect size as measured by difference between drug and placebo in change from baseline in the LSAS observed in these 2 studies was similar to that seen in the positive trials for Paxil, the only other drug approved for social anxiety disorder. I consider this a sufficient effect to support a claim for this product in social anxiety disorder.

Duration of Treatment

There were no data presented in this supplement pertinent to the question of the longer-term efficacy of Effexor XR in social anxiety disorder.

5.1.4 Conclusions Regarding Efficacy Data

The sponsor has, in my view, provided sufficient evidence to support the claim of short-term efficacy for Effexor XR in social anxiety disorder.

5.2 Safety Data

Dr. Brugge's safety review of this NDA was based predominantly on the safety data from the two pivotal studies, i.e., 387 and 393. Other safety data included expedited IND safety reports from 4 ongoing studies in social anxiety disorder. There were n=277 patients exposed to Effexor XR across the 2 completed studies, representing about 48 patient years of exposure.

Given our prior knowledge of the risks associated with Effexor XR in the other populations for which this drug is approved, the focus in the safety review was on any differences between the recognized safety profile in these other populations with that observed in the social anxiety disorder population.

5.2.1 Overview of Adverse Event Profile for Effexor XR in Social Anxiety Disorder

Overall, the adverse events profile for Effexor XR in the social anxiety disorder population was similar to that observed for this drug in MDD and GAD. Of note, the same modest effects on increasing cholesterol, triglycerides, and blood pressure were observed in this population. In addition, a modest withdrawal syndrome was observed, despite the tapering that was included in these trials.

5.2.2 Conclusions Regarding Safety of Effexor XR in Social Anxiety Disorder

There were no new safety findings to suggest a substantially different safety profile for Efffexor XR in social anxiety disorder compared to that seen in the other populations in which it is approved.

5.3 Clinical Sections of Labeling

We have modified the clinical sections of the draft labeling that is included with the approvable letter. The explanations for the changes are provided in bracketed comments in the draft labeling.

6.0 WORLD LITERATURE

The sponsor provided a literature review focused on Effexor XR and social anxiety disorder, including 55 references. Dr. Brugge examined a review of this literature provided by the sponsor and indicated that it revealed no new safety findings that would impact on the labeling of Effexor XR.

7.0 FOREIGN REGULATORY ACTIONS

To my knowledge, Effexor XR is not approved for the treatment of social anxiety disorder anywhere at this time. We will ask for an update on the regulatory status of Effexor XR for the treatment of social anxiety disorder in the approvable letter.

8.0 PSYCHOPHARMACOLOGICAL DRUGS ADVISORY COMMITTEE (PDAC) MEETING

We decided not to take this NDA to the PDAC.

9.0 DSI INSPECTIONS

To my knowledge, no inspections were requested for this supplement.

10.0 LABELING AND APPROVABLE LETTER

10.1 Final Draft of Labeling Attached to Approvable Package

Our proposed draft of labeling is attached to the approvable letter. As noted, we have made changes to the sponsor's draft dated 9-10-01.

10.2 Foreign Labeling

Effexor XR is not approved for the treatment of social anxiety disorder anywhere at this time.

10.3 Approvable Letter

The approvable letter includes draft labeling and requests for a literature update and a regulatory status update.

11.0 CONCLUSIONS AND RECOMMENDATIONS

I believe that Wyeth-Ayerst has submitted sufficient data to support the conclusion that Effexor XR is effective and acceptably safe in the treatment of social anxiety disorder. I recommend that we issue the attached approvable letter with our labeling proposal and the above noted requests for updates, in anticipation of final approval.

cc:
Orig NDA 21-346
HFD-120
HFD-120/TLaughren/RKatz/KBrugge/AHomonnay

DOC: MEMEFXSA.AE1

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/s/

Thomas Laughren
5/16/02 10:14:52 AM
MEDICAL OFFICER

MEETING MINUTES

Date: August 19, 1999
IND: 41,412
Location: Woodmont II, Conference Room E
Firm: Wyeth-Ayerst
Drug: Effexor XR (venlafaxine hydrochloride) Extended-release Capsules
Indication: sNDA for Social Anxiety Disorder
Meeting Type: pre-phase 3 meeting for sNDA
Participants:

FDA Attendees:
Russell Katz, MD
Tom Laughren, MD
Greg Dubitsky, MD
Susan Molchan, MD
Kun Jin, PhD
O Siddiqui, PhD

Wyeth-Ayerst Attendees:
Dr. Loren Aguiar
Mr. Roy Baranello, Jr.
Mr. Ken Bonk
Dr. Richard Entsuah
Dr. Charles Gombar
Dr. Tom Haskins
Mr. Allan Pallay
Dr. Eliseo Salinas

BACKGROUND:
Wyeth-Ayerst requested this meeting to obtain FDA feedback for the proposed Phase III clinical development program for an efficacy supplement for Effexor XR in the treatment of social anxiety disorder. They plan to submit an initial supplement with two short-term adult studies [redacted]

DISCUSSION:
Studies in Adults:

- The Division agreed that the inclusion/exclusion criteria proposed are adequate, including the additional exclusion criteria specified at the meeting for the Ham-D scale,)2 on HAM-D item 1, or)15 score on 17-item HAM-D total.

- The proposed primary endpoints for the adult studies are acceptable; however, the sponsor was reminded of the general divisional policy for multiplicity for two endpoints, hence, both the LSAS and the CGI would need to be positive at the 0.05 level for the study to be considered positive, unless only one was specified as primary. Further, only results on primary endpoints may be cited in the labeling, even if other secondary measures were tested. FDA prefers the LSAS over the CGI since it seems to map closely to the diagnostic criteria, in fact, FDA would not accept the CGI as the sole primary outcome. FDA may also request exploratory analysis on the data to try to determine if the social anxiety response is independent of any antidepressant response.

- FDA advised that statistical protocols and plans should be pre-specified in detail. Pooling of dose comparisons to determine best dose is not favored. We usually test the treatment by center interaction at the 0.1 level. The issue of handling missing data was also discussed. A prospective plan should be specified for handling missing scale items. It was agreed that Wyeth-Ayerst should make a proposal.

- FDA agreed that the overall registration strategy, submission of an initial supplement with two flexible dose adult studies [redacted], was acceptable; The initial supplement should have a request for a pediatric waiver for the under 12 age group, and a request for a deferral for adolescent studies. FDA also cautioned that while use of an active control for assay sensitivity may be appropriate, the proposed study design may not lead to a comparative claim in the labeling.

- FDA agreed to the proposed study durations [redacted]

ACTION ITEMS:

- Sponsor will submit full protocols for these studies, to include statistical plans for handling missing data.

Signature, minutes preparer:
Anna M. Homonnay-Weikel, R.Ph.
Regulatory Project Manager

Concurrence Chair: 9-22-97
Thomas Laughren, MD
Teamleader, Psychiatric Drug Products

attachment

ACTION ITEMS:

- Sponsor will submit full protocols for these studies, to include statistical plans for handling missing data.

Signature, minutes preparer: _____
Anna M. Homonnay-Weikel, R.Ph.
Regulatory Project Manager

Concurrence Chair:_____
Thomas Laughren, MD
Teamleader, Psychiatric Drug Products

attachment

cc:
Orig IND 41,412 NDA 9-22-99
HFD-120/Laughren/9.21.99
HFD-120/Dubitsky/9.20.99/Molchan/9.20.99
HFD-710/Siddiqui
HFD-120/Homonnay

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MEETING MINUTES

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-699/S-022

CORRESPONDENCE

********** -COMM. JOURNAL- ********** DATE JAN-29-2002 ***** TIME 10:18 *** P.01

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Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation I

FACSIMILE TRANSMITTAL SHEET

DATE: Janaury 29, 2002

To: Mr. Ken Bonk

Company: Wyeth-Ayerst

Fax number: (484) 865-9224

Phone number: (484) 865-3103

Subject:

From: Anna Marie Homonnay, R.Ph.
Regulatory Health Project Manager
Division of Neuropharmacological Drug Products

Fax number: (301) 594-2859

Phone number: (301) 594-5535

Total no. of pages including cover: 3

Re: NDA 20-699/S-022

Additional questions regarding the submission.

Document to be mailed: ☐YES ☑NO

January 29, 2002
FDA Request for Information #2
Re: sNDA 22-699/S-022 Effexor XR/Social Anxiety Disorder

The review of your submission is underway. To assist us in this process, we request the information listed below. If any of the information already exists in the submission please provide the volume, section and page numbers where it can be found. Otherwise please provide us with a response to our questions, as soon as possible. Please notify us if a response cannot be provided by the end of February. We appreciate your prompt response and please do not hesitate to contact the Project Manager, Anna Marie Homonnay, as needed for clarification.

Please provide the following:

1. **Descriptive statistical results on the HAM-D, Covi-Anxiety and Rankin Depression scores for baseline measures and mean change from baseline scores on each visit (weeks 6 and 12) for each treatment group of each study (Studies 367 and 393). Please conduct the following analysis for each of the two studies: 1) an ANCOVA for treatment and study site main and interaction effects on mean change from baseline to week 6 and 12 assessments (for the HAM-D, Covi-Anxiety, and Rankin Depression scores) 2) using the baseline score as the covariate (using LOCF dataset and the 3-day rule; the final on-therapy observation is defined as an assessment conducted within 3 days of the last final dose of study drug).**

2. **Please provide a listing of all postmarketing deaths and serious adverse events (events that meet the criteria for classification as a serious adverse event) for venlafaxine (for any marketed formulation) when used in association with social anxiety disorder.**

3. **As described in the submission Effexor subjects met outlier criteria on the urinalysis pH (≤ 4 or ≥ 9). Please specify the number of subjects (and %) per treatment group who were at the lower limit (pH ≤ 4) and how many (and the %) per treatment group that were at the upper limit (pH ≥ 9).**

4. **Please define QTc (one of the ECG safety parameters in Studies 378 and 393).**

5. **Please provide statistical descriptive results on orthostatic measure changes (the difference between supine and standing blood pressure measures) for each treatment group by visit for each study (387 and 393). Also provide the mean change (±SD, median and range) from baseline of the supine to standing (orthostatic) blood pressure differences by each visit for each treatment group in each study. Please conduct pairwise comparisons between the treatment groups for each visit.**

6. **What statistical test was used to determine treatment group effects on incidence of responders (defined as a CGI-I score of 1 or 2) in each study (397 and 393) as shown in Table 9.3.3 A of each study report?**

7. **The test for the normality assumption for each treatment group on the LSAS total score of the "on-final therapy" assessment revealed negative results, in that the distribution of individual scores within each treatment group was skewed in each of the two studies (Studies 387 and 393), as described in section 2 of supplemental volume 2 of each study report. Please provide a scatterplot of individual subject "on-final therapy" scores for each treatment group for each study. Please provide a similar scatterplot for individual scores at baseline and a scatterplot of the individual change in scores from baseline to final-on-therapy for each treatment group of each study.**

********** -COMM. JOURNAL- ********** DATE OCT-23-2001 ***** TIME 13:05 *** P.01

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********** - ***** - 3015942859- *********

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation I

FACSIMILE TRANSMITTAL SHEET

DATE: September 13, 2001

To: Mr. Ken Bonk

Company: Wyeth-Ayerst

Fax number: (484) 865-9224

Phone number: (484) 865-3103

From: Anna Marie Homonnay, R.Ph.
Regulatory Health Project Manager
Division of Neuropharmacological Drug Products

Fax number: (301) 594-2859

Phone number: (301) 594-5535

Subject:

Total no. of pages including cover: 3

Re: NDA 20-699/S-022

Additional questions regarding the submission. Please provide in written format as a desk copy and one for the archival file. A duplicate electronic submission may also be submitted for archiving purposes.

Document to be mailed: ☐ YES ☑ NO

Questions to the sponsor
Re: sNDA 22-699 S-022 Effexor XR/Social Anxiety Disorder

Please provide the following information, which will assist us in the processing of your application (S-022). If any of the information already exists in the submission please provide the volume, section and page numbers where it can be found. Otherwise please provide us with a response to our questions, if possible by November 2nd.

Please provide the following:

1. The exposure (mean±SD, median, range of the daily dose in mg units) of completers and the number of completers in each treatment group of each study (for Studies 287 and 393).
2. The ISS provides incidence tables of Ss (outliers) meeting "potentially clinically important"(PCI) criteria for each of the following safety parameters: laboratory, vital sign, weight and ECG parameters, using criteria as specified by the Neuroscience Therapeutic Group at Wyeth. The following pertains to safety information of outliers using FDA specified criteria (10/14/97 correspondence):
   - Please provide incidence tables (like those in the ISS) for each of the safety parameters (laboratory, vital sign/weight and ECG parameters), using the FDA specified criteria (10/14/97 correspondence).
   - Also provide subject line listings of outliers, using FDA specified criteria for laboratory, vital sign/weight and ECG parameter and for parameters that were solely specified by the Wyeth Group criteria (those that were not specified by the FDA), organized as follows. Please provide this information using columns and a layout similar to that provided in the Tables on pages 43, 50, 58 (these tables were listings of subjects with parameters judged to be "clinically important") for each study (one table for study 387 and a separate table for 393). For each study, please categorize the subject listings by each laboratory parameter (BUN, glucose, etc), vital sign/weight parameter (sysBP, diastolic BP, HR, etc) and ECG parameter. Within each parameter, please categorize the subject line listings by treatment group. Also, if a given patient under a given parameter was an outlier on any other parameters, please indicate this in the line listing (i.e. with an asterisk or by using the "other events column" or creating a separate column, indicating which additional parameters also met PCI to allow for cross-referencing).
3. Does the description of adverse dropouts due to abnormal laboratory, vital sign/weight or ECG parameters on page 63 (sections 12.2.1-3) of the ISS include subjects meeting PCI criteria (using each type of criteria: FDA and Wyeth Group criteria)? If not, please provide a cross-reference table like that in Table 19 A (page 76 of the ISS), that includes a column for subjects that met any outlier criteria (either FDA or Wyeth PCI criteria indicating which of these two criteria applied). Please provide a hyperlink e-version of the table that hyperlinks these subjects to the above line listings of these subjects. If the November 2nd date does not allow sufficient time for providing an e-version, then please provide the section and page number where the line listing of the given subject can be found.

4. Please provide narratives for each adverse dropout.

5. Mean results are provided in various tables in the ISS of various laboratory, vital sign/weight and ECG parameters, however these tables do not include other descriptive statistical results (median and range values at baseline, week 12 and poststudy and the median and range change from baseline). Please provide this information such that it is included with the mean values provided in the ISS tables (such as, to allow for visual comparisons of means with median values, etc.).
6. Please provide the following information regarding the ITT Efficacy populations for each of the two studies (387 and 393): incidence tables of current medical conditions/disorders and incidence tables of ongoing or current psychiatric disorders (DSM-IV).
7. Please provide the CRFs of the following subjects who were reported as having serious adverse events: 387014536, 387013502, 393004131, 393003088.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-699/S-022

PRIOR APPROVAL SUPPLEMENT

Wyeth-Ayerst Laboratories
Attention: Kenneth Bonk
Associate Director II, Worldwide Regulatory Affairs
P.O. Box 8299
Philadelphia, PA 19101

Dear Mr. Bonk :

We have received your supplemental drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Effexor XR (venlafaxine HCl) Extended-release Capsules

NDA Number: 20-699

Supplement Number: S-022

Review Priority Classification: Standard (S)

Date of Supplement: September 10, 2001

Date of Receipt: September 13, 2001

This supplement provides for the treatment of Social Anxiety Disorder as a new indication.

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on November 13, 2001 in accordance with 21 CFR 314.101(a). If the application is filed, the primary user fee goal date will be July 12, 2002 and the secondary user fee goal date will be September 12, 2002.

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 *FR* 66632). If you have not already fulfilled the requirements of 21 CFR 314.55 (or 601.27), please submit your plans for pediatric drug development within 120 days from the date of this letter unless you believe a waiver is appropriate. Within approximately 120 days of receipt of your pediatric drug development plan, we will review your plan and notify you of its adequacy.

If you believe that this drug qualifies for a waiver of the pediatric study requirement, you should submit a request for a waiver with supporting information and documentation in accordance with the provisions of 21 CFR 314.55 within 60 days from the date of this letter. We will make a determination whether to grant or deny a request for a waiver of pediatric studies during the review of the application. In no case, however, will the determination be made later than the date action is taken on the application. If a waiver is not granted, we will ask you to submit your pediatric drug development plans within 120 days from the date of denial of the waiver.

Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products (pediatric exclusivity). You should refer to the *Guidance for Industry on Qualifying for Pediatric Exclusivity* (available on our web site at www.fda.gov/cder/pediatric) for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request" (PPSR) in addition to your plans for pediatric drug development described above. We recommend that you submit a Proposed Pediatric Study Request within 120 days from the date of this letter. If you are unable to meet this time frame but are interested in pediatric exclusivity, please notify the division in writing. FDA generally will not accept studies submitted to an NDA before issuance of a Written Request as responsive to a Written Request. Sponsors should obtain a Written Request before submitting pediatric studies to an NDA. If you do not submit a PPSR or indicate that you are interested in pediatric exclusivity, we will review your pediatric drug development plan and notify you of its adequacy. Please note that satisfaction of the requirements in 21 CFR 314.55 alone may not qualify you for pediatric exclusivity. FDA does not necessarily ask a sponsor to complete the same scope of studies to qualify for pediatric exclusivity as it does to fulfill the requirements of the pediatric rule.

Please cite the application number listed above at the top of the first page of any communications concerning this application. All communications concerning this supplemental application should be addressed as follows:

U.S. Postal Service:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Neuropharmacological Drug Products, HFD-120
Attention: Division Document Room 4008
5600 Fishers Lane
Rockville, Maryland 20857

Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Neuropharmacological Drug Products, HFD-120
Attention: Division Document Room 4008
1451 Rockville Pike
Rockville, Maryland 20852-1420

If you have any questions, please call Anna Marie Homonnay, R.Ph., Regulatory Project Manager, at (301) 594-5535.

Sincerely,

{See appended electronic signature page}

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

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

/s/

Anna-Marie Homonnay
9/24/01 10:26:16 AM

Document Information Page

This page is for FDA internal use only. **Do NOT send this page with the letter.**

Application #(s):	20-699/SE1-022
Document Type:	Supplement Letter
Document Group:	Acknowledge and Retain
Document Name:	To Acknowledge And Retain (Accept) FPL For A Supplemental Application Approved With Labeling Text
Letter Code:	SNDA-C1
COMIS Decision:	AR: ACKNOWLEDGE AND RETAIN ()
Drafted by:	David 8-22-03
Revised by:	Katz 9-2-03
Initialed by:	Nighswander 8-26-03; Dubitsky 8-26-03; Laughren 8-27-03
Finalized:	David 9-3-03
Filename:	EFFEXOR XR 20-699 SE1-022 ACK-RT FPL LETTER
DFS Key Words:	
Notes:	
Linking Instructions:	

END OF DOCUMENT INFORMATION PAGE

The letter begins on the next page.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville MD 20857

NDA 20-699/S-022

Wyeth Pharmaceuticals
Attention: Tracy D. Rockney, JD
Director, Global Brand Management
Worldwide Regulatory Affairs
P.O. Box 8299
Philadelphia, PA 19101-1245

Dear Ms. Rockney:

Please refer to your supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Effexor XR (venlafaxine hydrochloride) Extended Release 37.5 mg, 75 mg, and 150 mg Capsules.

Reference is also made to the Agency approval letter dated February 11, 2003, providing for revisions to the product labeling, and requesting 20 copies of final printed labeling (FPL) identical to the labeling attached in the above mentioned approval letter.

We acknowledge receipt of your submission dated February 21, 2003, providing for 20 copies of FPL as requested in our approval letter.

We have completed our review of the labeling submitted on February 21, 2003, and it is acceptable. Therefore, this labeling will be retained in our files.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call Paul David, R.Ph., Senior Regulatory Project Manager, at (301) 594-5530.

Sincerely,

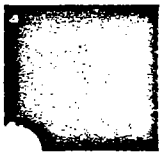
{See appended electronic signature page}

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

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

/s/

Russell Katz
9/3/03 04:37:29 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 41,412

Wyeth-Ayerst Research
Attention: Kenneth Bonk
Associate Director, Worldwide Regulatory Affairs
P.O. Box 8299
Philadelphia, PA 19101-8299

Dear Mr. Bonk:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Effexor XR (venlafaxine HCl) Extended-release Capsules.

We also refer to your amendments dated September 22, 2000 (serial # 312), September 27, 2000 (serial # 317), and October 24, 2000 (serial # 321), containing statistical modifications to protocols 387, 390, 392, and 393 for your Phase 3 social anxiety disorder program.

We have completed the review of your amendments and have the following comments:

1. In order to test the null hypothesis that the regression lines for the treatment groups are parallel in the ANCOVA model, you state in your amendments that if the assumption of parallelism is rejected, the baseline covariate will not be entered into the model as a continuous variable but will be tricotomized and entered into the model as a categorical variable. Please elaborate on how the assumption of parallelism issue will be satisfied after tricotomizing the baseline covariate and how inferences will be made about the differences between two treatments' mean values when the regression lines are not parallel. In addition, please state the grouping criteria for tricotomizing the baseline covariate if it is needed.

2. You have specified two approaches to deal with missing items for the LSAS scale for the same data set. Since the two approaches seem to be independent, please provide a rationale as to why two approaches will be used on the same data set, or select one of the approaches to deal with missing data. We note that the second approach seems to be more reasonable as compared to the first approach except for the criteria 'If more than 50% of the patients have more than 10% of their items missing...'

If you should have any questions, please call Ms. Anna Marie Homonnay, Regulatory Project Manager, at (301) 594-5535.

Sincerely,

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

/s/

Russell Katz
12/5/00 09:28:02 AM

Homonna

NOV 29 1999

IND 41,412

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

Dear Mr. Bonk:

Reference is made to your Investigational New Drug Application (IND) for Effexor XR (venlafaxine HCl) Extended-release Capsules and your submission dated September 9, 1999 (N-204).

We have completed our review of Protocol No. 0600B4-387-US and have the following comments:

1. We note that you propose to use ANCOVA methodology to analyze the primary efficacy variable results. Although it is common statistical practice to assess the assumptions that underlie this test, such as normality and homogeneity of variance, such assessment is not addressed in this protocol. Thus, we ask that you specify how underlying assumptions will be evaluated, criteria for judging the applicability of ANCOVA to the resulting data, and alternative methods for analysis if these criteria are not met.

2. You propose that LSAS assessments that are missing up to 50% of the items will still be used for efficacy analysis. In such cases, the average of available items will be multiplied by the total number of items to obtain an LSAS total score. If a small number of items is missing for a small number of patients, it is likely that the inferred scores reasonably approximate the actual clinical status of the patient. However, as the number of patients missing a substantial number of items increases, the validity of the efficacy results becomes more questionable. Methods for handling missing data are a controversial issue with no clearly correct solution and it is difficult to mount a strong argument against your proposal. However, to assist us in later

evaluating the validity of the efficacy data, we ask that you provide a summary in the study report of which patients were missing more than 10% of the LSAS items in the primary analysis and, for each patient, how many items were missing.

If your should have any questions regarding these comments, please contact Ms. Anna M. Homonnay-Weikel, R.Ph., Regulatory Project Manager, at (301) 594-5535.

Sincerely yours,

11/29/99

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

Honorary

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

IND 41,412

NOV 29 1999

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

Adult Study

Dear Mr. Bonk:

Reference is made to your Investigational New Drug Application (IND) for Effexor XR (venlafaxine HCl) Extended-release Capsules and your submission dated September 9, 1999 (N-204).

We have completed our review of Protocol No. 0600B4-387-US and have the following comments:

1. We note that you propose to use ANCOVA methodology to analyze the primary efficacy variable results. Although it is common statistical practice to assess the assumptions that underlie this test, such as normality and homogeneity of variance, such assessment is not addressed in this protocol. Thus, we ask that you specify how underlying assumptions will be evaluated, criteria for judging the applicability of ANCOVA to the resulting data, and alternative methods for analysis if these criteria are not met.

2. You propose that LSAS assessments that are missing up to 50% of the items will still be used for efficacy analysis. In such cases, the average of available items will be multiplied by the total number of items to obtain an LSAS total score. If a small number of items is missing for a small number of patients, it is likely that the inferred scores reasonably approximate the actual clinical status of the patient. However, as the number of patients missing a substantial number of items increases, the validity of the efficacy results becomes more questionable. Methods for handling missing data are a controversial issue with no clearly correct solution and it is difficult to mount a strong argument against your proposal. However, to assist us in later

evaluating the validity of the efficacy data, we ask that you provide a summary in the study report of which patients were missing more than 10% of the LSAS items in the primary analysis and, for each patient, how many items were missing.

If your should have any questions regarding these comments, please contact Ms. Anna M. Homonnay-Weikel, R.Ph., Regulatory Project Manager, at (301) 594-5535.

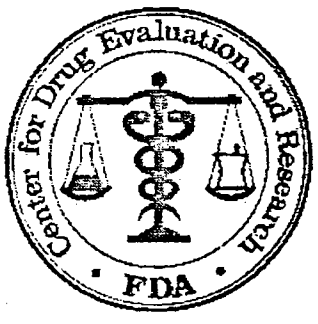
Sincerely yours,

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

facsimile
TRANSMITTAL

[redacted]

To: Ken Bonk
Sponsor: Wyeth Ayerst Laboratories
Fax #: (610) 964-5973
Re: EFFEXOR XR/Social Anxiety Disorder
Date: 11/29/99
Pages: (including cover sheet) 3



From the desk of...

Ms. Anna M. Homonnay-Weikel, R.Ph.
Project Manager
Division of Neuropharmacological Drug
Products / HFD-120
Food and Drug Administration
Rockville, Maryland 20857
301-594-5535
Fax: 301-594-2859

Homonnay

IND 41,412

SEP 24 1999

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

Dear Mr. Bonk:

Please refer to the meeting between representatives of your firm and FDA on August 19, 1999. The purpose of the meeting was to discuss your proposed clinical development program for an efficacy supplement for Effexor XR for the treatment of social anxiety disorder.

A copy of our minutes of that meeting is enclosed. These minutes are the official minutes of the meeting.

If you have any questions, contact Anna Marie Homonnay-Weikel, R.Ph., Project Manager, at (301) 594-5535.

Sincerely,

9/22/99

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

Enclosure

cc:
Orig IND
HFD-120/Homonnay

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GENERAL CORRESPONDENCE (MINUTES SENT)

2

PAGE(S) HAVE BEEN REDACTED IN FULL FROM THIS DOCUMENT

REASON:

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__X__ b(4) CCI

_____ b(4) TS

__X__ b(5) Deliberative Process; Attorney Client and Attorney Work Product Privilege

_____ b(6) Personal Privacy

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