CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

20-699/S-054, 057

Trade Name: Effexor XR

Generic Name: Venlafaxine HCL

Sponsor: Wyeth Pharmaceuticals

Approval Date: November 18, 2005

Indications: Treatment of long-term and short-term panic disorder

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APPLICATION NUMBER:

20-699/S-054, 057

CONTENTS

Reviews / Information Included in this NDA Review.	
Approval Letter	X
Other Action Letters	X
Labeling	X
REMS	
Summary Review	
Officer/Employee List	
Office Director Memo	
Cross Discipline Team Leader Review	
Medical Review(s)	X
Chemistry Review(s)	X
Environmental Assessment	X
Pharmacology Review(s)	
Statistical Review(s)	X
Microbiology Review(s)	
Clinical Pharmacology/Biopharmaceutics Review(s)	
Other Reviews	
Risk Assessment and Risk Mitigation Review(s)	
Proprietary Name Review(s)	
Administrative/Correspondence Document(s)	X

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APPLICATION NUMBER:

20-699/S-054, 057

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-699/S-054, 057

Wyeth Pharmaceuticals
Attention: Dr. Qingha (Sarah) Ji
Senior Regulatory Specialist
Worldwide Regulatory Affairs
P.O. Box 8299
Philadelphia, PA 19101

Dear Dr. Ji:

Please refer to your supplemental new drug applications dated September 29, 2004, received September 29, 2004, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Effexor XR (venlafaxine HCL) Extended-Release Capsules.

Your submission of September 23, 2005 constituted a complete response to our July 15, 2005 action letter.

These supplemental new drug applications provide for the use of Effexor XR in the treatment of long-term and short-term panic disorder.

We have completed our review of these applications, as amended. These applications are approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert).

Please submit an electronic version of the FPL according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA*. 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. Individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, designate these submissions "**FPL for approved supplement NDA 20-699/S-054, 057.**" Approval of these submissions by FDA is not required before the labeling is used.

Pediatric Research Equity Act (PREA)
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. We are waiving the pediatric study requirement for this application.

Promotional Materials
In addition, submit three copies of the introductory promotional materials that you propose to use for these products. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to this division/ the Division of Psychiatry Products 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, MD 20857

If you issue a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HFD-410
FDA
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Susan Player, Regulatory Project Manager, at (301) 796-2260.

Sincerely,

{See appended electronic signature page}

Thomas Laughren, M.D.
Director
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure

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

/s/

Thomas Laughren
11/18/2005 08:28:47 AM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-699/S-054, 057

OTHER ACTION LETTER(s)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

NDA 20-699/S-054, 057

Wyeth Pharmaceuticals, Inc.
Attention: Dr. Qinghua Ji
Sr. Regulatory Specialist, Worldwide Regulatory Affairs
P.O. Box 8299
Philadelphia, PA 19101

Dear Dr. Ji:

Please refer to your supplemental new drug applications dated September 29, 2004, received September 29, 2004, 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 submissions dated May 24, 2005, January 27, 2005, and December 9, 2004.

These supplemental new drug applications provide for the use of Effexor XR in the treatment of long-term and short-term panic disorder.

We have completed our review of these applications, as amended, and they are approvable. Before the applications may be approved, however, you must submit draft labeling for this drug. The attachment to this letter provides a draft of the labeling that the Agency asks you to adopt upon approval of these supplemental applications. Please also note that we have embedded throughout the text of the attached draft labeling several comments and further revisions of the labeling. We also ask that when you submit draft labeling, you include in the labeling all previous revisions, as reflected in the most recently approved package insert. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes and identify which version of labeling was used as the base document. If additional information relating to the safety or effectiveness of these drugs becomes available, revision of the labeling may be required.

In addition to the above labeling revisions, before your application may be approved we ask that you respond to the following outstanding information requests, as communicated in emails dated May 19, 2005, May 20, 2005, June 3, 2005, June 10, 2005, June 20, 2005, June 27, 2005, and June 28, 2005:

1. For the two positive short-term studies (398, 399) and the relapse prevention study (354), we noted discrepancies between the ITT population, as defined in the amended protocol, and the ITT population as defined in the study report. Please provide the ITT population definition that was used in your efficacy LOCF and OC analyses for each of these studies. In addition, for studies 398 and 354, it appears that protocol amendments clarifying the ITT population definition were submitted after study completion. Please provide your warrant that these definitions were not changed subsequent to the unblinding of the efficacy data if this was the case.

2. For each of the above three studies, please provide an enumeration and a line listing of patients (including study number, site number, and patient number), by treatment group, who were missing greater than 3 days of PAAS data[1] and who were included in the above efficacy ITT LOCF and OC analyses at each visit for both Effexor XR- and placebo-treated patients. This would apply, for example, to a patient for whom 6 days of PAAS data were missing in a 14 day analysis period. Further efficacy analyses may be required if this number is large.

3. We have reviewed your identification of suicide, suicide attempt (including overdoses), and suicidal ideation cases on page 89 of 223 of the Summary of Clinical Safety. In addition, we have reviewed your identification of overdose cases on page 180 of 223 of the summary of clinical safety. However, we discovered a serious adverse event case coded to a COSTART preferred term of depression that, according to the narrative summary, involved suicidal and homicidal ideation (Patient 35370-1066). This case was not included in your suicide ideation and behavior analysis. Please address this and recompute the incidence, by treatment group, of suicidal ideation and behavior for all patients in the pool of the four short-term, placebo-controlled trials.

4. In the SAS transport files (case report tabulations) for adverse events, we noticed numerous line entries that were missing both verbatim adverse events (AEX) and their associated COSTART preferred terms (AEPTX)[2]. In addition, there were several verbatim adverse events that were not coded to COSTART preferred terms[3], and at least one COSTART preferred term that was not associated with a verbatim adverse event[4]. Please explain these deficiencies.

5. For study 354, the submission states that 225 patients completed the open label period. However, after subtracting the number of discontinuations during the open-label treatment period (137) from the number who entered open-label (321), only 184 patients remain. Please explain this discrepancy.

6. It is unclear what patient dataset was used for Tables 2.7.4.3.2.1C and 2.7.4.3.2.2B of the Summary of Clinical Safety on pages 117 and 122, respectively. Please clarify. For example, are these tables based on only completers from the Safety ITT, an LOCF analysis of the Safety ITT, or some other patient sample?

7. Please provide a table that enumerates patients by mean daily dose and total duration of exposure for all 5 studies (studies 398, 399, 353, 391, and 354) combined. This should follow the format of Table 2.7.4.1.2.1.1.2A on page 11 of 223 in the Summary of Clinical Safety.

8. In reviewing your tables in Section 1.2 (Overall Extent of Exposure) of the Summary of Clinical Safety, we noted multiple tables (for example, Table 2.7.4.1.2.1.1.1A on page 7 of 223) in which it appears the mean daily dose for a 225 mg fixed dose group was 100-200 mg. Please explain this discrepancy.

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[1] Missing PAAS data refers to any missing PAAS data, and 3 days refers to any 3 days throughout a 14 day analysis period.
[2] For example, line 1 in the SAS transport file (case report tabulation) for adverse events in study 353 (Patient 000466)
[3] For example, line 432 in the SAS transport file (case report tabulation) for adverse events in study 353 (Patient 000556)
[4] For example, line 1196 in the SAS transport file (case report tabulation) for adverse events in study 391 (Patient 000653)

9. For study 354, provide the mean daily dose of Effexor XR at the end of the open-label phase for the 169 patients who comprised the efficacy ITT population for the double-blind phase of this trial.

10. For study 354, provide the mean time in continuous responder status during the open-label phase prior to randomization for these 169 patients. Responder status is defined by having at most one full-symptom panic attack per week and a CGI-I score of 1 or 2 compared to the assessment of open-label baseline.

11. We note that the QT interval was corrected for heart rate using Bazett's formula. To further assist in our analysis, please provide QT data using the Fredericia correction formula. This data should include a) mean ECG results for both the pool of studies 398, 399, and 353 and study 391 following the formats of Tables 2.7.4.4.4.1D and 2.7.4.4.4.1C on pages 162 and 161 of 223 of the Summary of Clinical Safety, respectively, and b) proportions of patients who met criteria for potentially clinically important ECG results following the format of Table 2.7.4.4.3.2.1C on page 151 of 223 of the Summary of Clinical Safety.

12. In your recently proposed labeling, under ADVERSE REACTIONS in the subsection of labeling entitled "Other Adverse Events Observed During the Premarketing Evaluation of Effexor and Effexor XR," it is our understanding that you have not incorporated adverse events that occurred during open label Effexor XR treatment for 84 patients in the relapse prevention study (study 354) who were randomized to placebo during the double-blind period. This section is intended to encompass all adverse experiences that emerged during treatment with active drug during any clinical trial, regardless of design. Therefore, for consistency with previous labeling for Effexor XR as well as with labeling for other antidepressant agents, it will be necessary to include serious adverse events experienced by these patients while they received open-label Effexor XR (if such events are not already included in Effexor XR labeling). Please incorporate a revision of this subsection to include these events.

Safety Update
It is our understanding that you have completed all five trials, and that all safety data for these trials has been submitted. Thus, a safety update based on these trials as described in 21 CFR 314.50(d)(5)(vi)(b) is not required. However, please provide us with an update of the worldwide published literature relevant to Effexor XR in Panic Disorder since March 4, 2004.

Request for Regulatory Update and Foreign Labeling
Also, please provide any new information on the regulatory status of Effexor XR worldwide. We require a review of the status of all actions with regard to this drug, either taken or pending before foreign regulatory authorities. Approval actions can be noted, but we also ask that you describe in detail any and all actions taken that have been negative, supplying a full explanation of the views of all parties and the resolution of the matter. It is only necessary to provide information that is more recent than that provided in your September 29, 2004 submission. Please note, however, that information regarding regulatory action in the U.K. which you submitted to us on December 3, 9, and 22, 2004, does not need to be resubmitted.

In addition, we request that you provide English translations of current approved foreign labeling not previously submitted.

Promotional Materials
Please submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to this division/ Division of Neuropharmacological Drug Products and two copies of both the promotional materials and the package inserts directly to:

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

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. If you do not follow one of these options, we will consider your lack of response a request to withdraw the applications under 21 CFR 314.65. 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.

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

If you have any questions, call Richardae C. Taylor, Pharm.D., Regulatory Project Manager, at (301) 594-5793.

Sincerely,
{See appended electronic signature page}

Thomas Laughren, M.D.
Acting Director
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure

47 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

_X_ Draft Labeling (b4)

_X_ Draft Labeling (b5)

_____ Deliberative Process (b5)

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

/s/

Thomas Laughren
7/15/05 02:49:12 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-699/S-054, 057

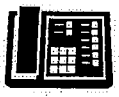
LABELING

Effexor® XR

(venlafaxine hydrochloride)
Extended-Release Capsules

℞ only

This product's label may have been revised after this insert was used in production. For further product information and current package insert, please visit www.wyeth.com or call our medical communications department toll-free at 1-800-934-5556.



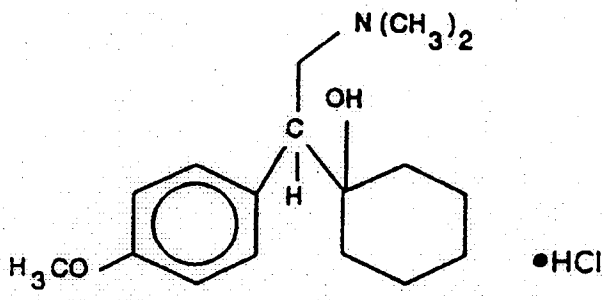
Suicidality in Children and Adolescents

Antidepressants increased the risk of suicidal thinking and behavior (suicidality) in short-term studies in children and adolescents with Major Depressive Disorder (MDD) and other psychiatric disorders. Anyone considering the use of Effexor XR or any other antidepressant in a child or adolescent must balance this risk with the clinical need. Patients who are started on therapy should be observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. Effexor XR is not approved for use in pediatric patients. (See WARNINGS and PRECAUTIONS, Pediatric Use.)

Pooled analyses of short-term (4 to 16 weeks) placebo-controlled trials of 9 antidepressant drugs (SSRIs and others) in children and adolescents with major depressive disorder (MDD), obsessive compulsive disorder (OCD), or other psychiatric disorders (a total of 24 trials involving over 4400 patients) have revealed a greater risk of adverse events representing suicidal thinking or behavior (suicidality) during the first few months of treatment in those receiving antidepressants. The average risk of such events in patients receiving antidepressants was 4%, twice the placebo risk of 2%. No suicides occurred in these trials.

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 $C_{17}H_{27}NO_2$ HCl. 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, hypromellose, iron oxide, and titanium dioxide.

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 to 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 to 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 to 150 mg/day (mean dose for completers was 136 mg/day) and an 8-week study utilizing Effexor XR doses in a range 75 to 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, adult 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), (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, adult 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 to 200 mg/day, on a b.i.d. 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 adult 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 to 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 to 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 to 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.

Panic Disorder

The efficacy of Effexor XR capsules as a treatment for panic disorder was established in two double-blind, 12-week, multicenter, placebo-controlled studies in adult outpatients meeting DSM-IV criteria for panic disorder, with or without agoraphobia. Patients received fixed doses of 75 or 150 mg/day in one study and 75 or 225 mg/day in the other study.

Efficacy was assessed on the basis of outcomes in three variables: (1) percentage of patients free of full-symptom panic attacks on the Panic and Anticipatory Anxiety Scale (PAAS); (2) mean change from baseline to endpoint on the Panic Disorder Severity Scale (PDSS) total score; and (3) percentage of patients rated as responders (much improved or very much improved) on the Clinical Global Impressions (CGI) Improvement scale. In these two trials, Effexor XR was significantly more effective than placebo in all three variables.

In the two 12-week studies described above, one evaluating Effexor XR doses of 75 and 150 mg/day and the other evaluating Effexor XR doses of 75 and 225 mg/day, efficacy was established for each dose. A dose-response relationship for effectiveness in patients with panic disorder was not clearly established in fixed-dose studies.

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.

In a longer-term study, adult outpatients meeting DSM-IV criteria for panic disorder who had responded during a 12-week open phase with Effexor XR (75 to 225 mg/day) were randomly assigned to continue the same Effexor XR dose (75, 150, or 225 mg) or switch to placebo for observation for relapse under double-blind conditions. Response during the open phase was defined as ≤ 1 full-symptom panic attack per week during the last 2 weeks of the open phase and a CGI Improvement score of 1 (very much improved) or 2 (much improved). Relapse during the double-blind phase was defined as having 2 or more full-symptom panic attacks per week for 2 consecutive weeks or having discontinued due to loss of effectiveness as determined by the investigators during the study. Randomized patients were in response status for a mean time of 34 days prior to being randomized. In the randomized phase following the 12-week open-label period, patients receiving continued Effexor XR experienced a significantly longer time to relapse.

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 adult 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 adult 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 (see **DOSAGE AND ADMINISTRATION**).

Generalized Anxiety Disorder

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

The efficacy of Effexor XR in the treatment of GAD was established in 8-week and 6-month placebo-controlled trials in adult 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, ie, 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**).

Panic Disorder

Effexor XR is indicated for the treatment of panic disorder, with or without agoraphobia, as defined in DSM-IV. Panic disorder is characterized by the occurrence of unexpected panic attacks and associated concern about having additional attacks, worry about the implications or consequences of the attacks, and/or a significant change in behavior related to the attacks.

Panic disorder (DSM-IV) is characterized by recurrent, unexpected panic attacks, ie, a discrete period of intense fear or discomfort, in which four (or more) of the following symptoms develop abruptly and reach a peak within 10 minutes: 1) palpitations, pounding heart, or accelerated heart rate; 2) sweating; 3) trembling or shaking; 4) sensations of shortness of breath or smothering; 5) feeling of choking; 6) chest pain or discomfort; 7) nausea or abdominal distress; 8) feeling dizzy, unsteady, lightheaded, or faint; 9) derealization (feelings of unreality) or depersonalization (being detached from oneself); 10) fear of losing control; 11) fear of dying; 12) paresthesias (numbness or tingling sensations); 13) chills or hot flushes.

The efficacy of Effexor XR in the treatment of panic disorder was established in two 12-week placebo-controlled trials in adult outpatients with panic disorder (DSM-IV). The efficacy of Effexor XR in prolonging time to relapse in panic disorder among responders following 12 weeks of open-label acute treatment was demonstrated in a placebo-controlled study (see **CLINICAL PHARMACOLOGY, Clinical Trials**). Nevertheless, 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

Clinical Worsening and Suicide Risk

Patients with major depressive disorder (MDD), both adult and pediatric, may experience worsening of their depression and/or the emergence of suicidal ideation and behavior (suicidality) or unusual changes in behavior, whether or not they are taking antidepressant medications, and this risk may persist until significant remission occurs. There has been a long-standing concern that antidepressants may have a role in inducing worsening of depression and the emergence of suicidality in certain patients. Antidepressants increased the risk of suicidal thinking and behavior (suicidality) in short-term studies in children and adolescents with Major Depressive Disorder (MDD) and other psychiatric disorders.

Pooled analyses of short-term placebo-controlled trials of 9 antidepressant drugs (SSRIs and others) in children and adolescents with MDD, OCD, or other psychiatric disorders (a total of 24 trials involving over 4400 patients) have revealed a greater risk of adverse events representing suicidal behavior or thinking (suicidality) during the first few months of treatment in those receiving antidepressants. The average risk of such events in patients receiving antidepressants was 4%, twice the placebo risk of 2%. There was considerable variation in risk among drugs, but a tendency toward an increase for almost all drugs studied. The risk of suicidality was most consistently observed in the MDD trials, but there were signals of risk arising from some trials in other psychiatric indications (obsessive compulsive disorder and social anxiety disorder) as well. **No suicides occurred in any of these trials.** It is unknown whether the suicidality risk in pediatric patients extends to longer-term use, i.e., beyond several months. It is also unknown whether the suicidality risk extends to adults.

All pediatric patients being treated with antidepressants for any indication should be observed closely for clinical worsening, suicidality, and unusual changes in behavior, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases. Such observation would generally include at least weekly face-to-face contact with patients or their family members or caregivers during the first 4 weeks of treatment, then every other week visits for the next 4 weeks, then at 12 weeks, and as clinically indicated beyond 12 weeks. Additional contact by telephone may be appropriate between face-to-face visits.

Adults with MDD or co-morbid depression in the setting of other psychiatric illness being treated with antidepressants should be observed similarly for clinical worsening and suicidality, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases.

The following symptoms, anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, and mania, have been reported in adult and pediatric patients being treated with antidepressants for major depressive disorder as well as for other indications, both psychiatric and nonpsychiatric. Although a causal link between the emergence of such symptoms and either the worsening of depression and/or the emergence of suicidal impulses has not been established, there is concern that such symptoms may represent precursors to emerging suicidality.

Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients whose depression is persistently worse, or who are experiencing emergent suicidality or symptoms that might be precursors to worsening depression or suicidality, especially if these symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms.

If the decision has been made to discontinue treatment, medication should be tapered, as rapidly as is feasible, but with recognition that abrupt discontinuation can be associated with certain symptoms (see **PRECAUTIONS** and **DOSAGE AND ADMINISTRATION, Discontinuation of Treatment with Effexor XR,** for a description of the risks of discontinuation of Effexor XR).

Families and caregivers of pediatric patients being treated with antidepressants for major depressive disorder or other indications, both psychiatric and nonpsychiatric, should be alerted about the need to monitor patients for the emergence of agitation, irritability, unusual changes in behavior, and the other symptoms described above, as well as the emergence of suicidality, and to report such symptoms immediately to health care providers. Such monitoring should include daily observation by families and caregivers. 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. Families and caregivers of adults being treated for depression should be similarly advised.

Screening Patients for Bipolar Disorder: A major depressive episode may be the initial presentation of bipolar disorder. It is generally believed (though not established in controlled trials) that treating such an episode with an antidepressant alone may increase the likelihood of precipitation of a mixed/manic episode in patients at risk for bipolar disorder. Whether any of the symptoms described above represent such a conversion is unknown. However, prior to initiating treatment with an antidepressant, patients with depressive symptoms should be adequately screened to determine if they are at risk for bipolar disorder; such screening should include a detailed psychiatric history, including a family history of suicide, bipolar disorder, and depression. It should be noted that Effexor XR is not approved for use in treating bipolar depression.

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 treatment is associated with sustained increases in blood pressure in some patients. Among patients treated with 75 to 375 mg/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 to 225 mg/day of Effexor XR in premarketing GAD studies, 0.5% (5/1011) experienced sustained hypertension. Among patients treated with 75 to 225 mg/day of Effexor XR in premarketing Social Anxiety Disorder studies, 1.4% (4/277) experienced sustained hypertension. Among patients treated with 75 to 225 mg/day of Effexor XR in premarketing panic disorder studies, 0.9% (9/973) experienced sustained hypertension. Experience with the immediate-release venlafaxine showed that sustained hypertension was dose-related, increasing from 3% to 7% at 100 to 300 mg/day to 13% at doses above 300 mg/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 to 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 to 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 to 225 mg/day up to 12 weeks, a final on-drug mean increase in SDBP of 1.3 mm Hg was observed for Effexor XR-treated patients compared with a mean decrease of 1.3 mm Hg for placebo-treated patients. In placebo-controlled premarketing panic disorder studies with Effexor XR 75 to 225 mg/day up to 12 weeks, 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 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 to 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 to 25 mm Hg, SDBP up to 8 weeks; 8 to 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). In premarketing panic disorder studies up to 12 weeks, 0.5% (5/1001) of the Effexor XR-treated patients discontinued treatment because of elevated blood pressure. In these patients, the blood pressure increases were in a modest range (7 to 19 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

Discontinuation of Treatment with Effexor XR

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 in major 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.

During marketing of Effexor XR, other SNRIs (Serotonin and Norepinephrine Reuptake Inhibitors), and SSRIs (Selective Serotonin Reuptake Inhibitors), there have been spontaneous reports of adverse events occurring upon discontinuation of these drugs, particularly when abrupt, including the following: dysphoric mood, irritability, agitation, dizziness, sensory disturbances (e.g. paresthesias such as electric shock sensations), anxiety, confusion, headache, lethargy, emotional lability, insomnia, hypomania, tinnitus, and seizures. While these events are generally self-limiting, there have been reports of serious discontinuation symptoms.

Patients should be monitored for these symptoms when discontinuing treatment with Effexor XR. A gradual reduction in the dose rather than abrupt cessation is recommended whenever possible. If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, then resuming the previously prescribed dose may be considered. Subsequently, the physician may continue decreasing the dose but at a more gradual rate (see **DOSAGE AND ADMINISTRATION**).

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, Social Anxiety Disorder, and panic disorder studies, as shown in Table 1.

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

	Major Depressive Disorder		GAD		Social Anxiety Disorder		Panic Disorder	
Symptom	Effexor XR n = 357	Placebo n = 285	Effexor XR n = 1381	Placebo n = 555	Effexor XR n = 277	Placebo n = 274	Effexor XR n = 1001	Placebo n = 662
Insomnia	17%	11%	15%	10%	23%	7%	17%	9%
Nervousness	10%	5%	6%	4%	11%	3%	4%	6%

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.

In panic disorder trials, insomnia and nervousness led to drug discontinuation in 1% and 0.1%, respectively, of the patients treated with Effexor XR up to 12 weeks.

Changes in Weight

Adult Patients: A loss of 5% or more of body weight occurred in 7% of Effexor XR-treated and 2% of placebo-treated patients in the short-term placebo-controlled major depressive disorder trials. The discontinuation rate for weight loss associated with Effexor XR was 0.1% in major depressive disorder studies. In placebo-controlled GAD studies, a loss of 7% or more of body weight occurred in 3% of Effexor XR patients and 1% of placebo patients who received treatment for up to 6 months. The discontinuation rate for weight loss was 0.3% for patients receiving Effexor XR in GAD studies for up to eight weeks. In placebo-controlled Social Anxiety Disorder trials, 3% of the Effexor XR-treated and 0.4% of the placebo-treated patients sustained a loss of 7% or more of body weight during up to 12 weeks of treatment. None of the patients receiving Effexor XR in Social Anxiety Disorder studies discontinued for weight loss. In placebo-controlled panic disorder trials, 3% of the Effexor XR-treated and 2% of the placebo-treated patients sustained a loss of 7% or more of body weight during up to 12 weeks of treatment. None of the patients receiving Effexor XR in panic disorder studies discontinued for weight loss.

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

Pediatric Patients: Weight loss has been observed in pediatric patients (ages 6-17) receiving Effexor XR. In a pooled analysis of four eight-week, double-blind, placebo-controlled, flexible dose outpatient trials for major depressive disorder (MDD) and generalized anxiety disorder (GAD), Effexor XR-treated patients lost an average of 0.45 kg (n = 333), while placebo-treated patients gained an average of 0.77 kg (n = 333). More patients treated with Effexor XR than with placebo experienced a weight loss of at least 3.5% in both the MDD and the GAD studies (18% of Effexor XR-treated patients vs. 3.6% of placebo-treated patients; p<0.001). Weight loss was not limited to patients with treatment-emergent anorexia (see **PRECAUTIONS, General,** *Changes in Appetite*).

The risks associated with longer-term Effexor XR use were assessed in an open-label study of children and adolescents who received Effexor XR for up to six months. The children and adolescents in the study had increases in weight that were less than expected based on data from age- and sex-matched peers. The difference between observed weight gain and expected weight gain was larger for children (<12 years old) than for adolescents (>12 years old).

Changes in Height

Pediatric Patients: During the eight-week placebo-controlled GAD studies, Effexor XR-treated patients (ages 6-17) grew an average of 0.3 cm (n = 122), while placebo-treated patients grew an average of 1.0 cm (n = 132); p=0.041. This difference in height increase was most notable in patients younger than twelve. During the eight-week placebo-controlled MDD studies, Effexor XR-treated patients grew an average of 0.8 cm (n = 146), while placebo-treated patients grew an average of 0.7 cm (n = 147). In the six-month open-label study, children and adolescents had height increases that were less than expected based on data from age- and sex-matched peers. The difference between observed growth rates and expected growth rates was larger for children (<12 years old) than for adolescents (>12 years old).

Changes in Appetite

Adult Patients: Treatment-emergent anorexia was more commonly reported for Effexor XR-treated (8%) than placebo-treated patients (4%) in the pool of short-term, double-blind, placebo-controlled major depressive disorder studies. The discontinuation rate for anorexia associated with Effexor XR was 1.0% in major depressive disorder studies. Treatment-emergent anorexia was more commonly reported for Effexor XR-treated (8%) than placebo-treated patients (2%) in the pool of short-term, double-blind, placebo-controlled GAD studies. The discontinuation rate for anorexia was 0.9% for patients receiving Effexor XR for up to 8 weeks in GAD studies. Treatment-emergent anorexia was more commonly reported for Effexor XR-treated (20%) than placebo-treated patients (2%) in the pool of short-term, double-blind, placebo-controlled Social Anxiety Disorder studies. The discontinuation rate for anorexia was 0.4% for patients receiving Effexor XR for up to 12 weeks in Social Anxiety Disorder studies. Treatment-emergent anorexia was more commonly reported for Effexor XR-treated (8%) than placebo-treated patients (3%) in the pool of short-term, double-blind, placebo-controlled panic disorder studies. The discontinuation rate for anorexia was 0.4% for patients receiving Effexor XR for up to 12 weeks in panic disorder studies.

Pediatric Patients: Decreased appetite has been observed in pediatric patients receiving Effexor XR. In the placebo-controlled trials for GAD and MDD, 10% of patients aged 6-17 treated with Effexor XR for up to eight weeks and 3% of patients treated with placebo reported treatment-emergent anorexia (decreased appetite). None of the patients receiving Effexor XR discontinued for anorexia or weight loss.

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 premarketing panic disorder studies, 0.1% of Effexor XR-treated patients and 0.0% 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 marketed drugs 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 panic disorder studies, 1 seizure occurred among 1,001 Effexor XR-treated patients. 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.

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 in major 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, 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, and for 661 patients who received Effexor XR and 395 patients who received placebo in three 10- to 12-week double-blind, placebo-controlled trials in panic disorder. The mean change from baseline in corrected QT interval (QTc) 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 corrected QT interval (QTc) for Effexor XR-treated patients in the GAD studies did not differ significantly from that with placebo. The mean change from baseline in QTc 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). The mean change from baseline in QTc for Effexor XR-treated patients in the panic disorder studies was increased relative to that for placebo-treated patients (increase of 1.5 msec for Effexor XR and decrease of 0.7 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). The mean change from baseline in heart rate for Effexor XR-treated patients in the panic disorder studies was significantly higher than that for placebo (a mean increase of 3 beats per minute for Effexor XR and a mean decrease of less than 1 beat per minute for placebo).

In a flexible-dose study, with Effexor doses in the range of 200 to 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 (eg, 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 to 70 mL/min) or cirrhosis of the liver, the clearances of venlafaxine and its active metabolites were decreased, thus prolonging the elimination half-lives of these substances. A lower dose may be necessary (see **DOSAGE AND ADMINISTRATION**). Effexor XR, like all drugs effective in the treatment of major depressive disorder, should be used with caution in such patients.

Information for Patients

Prescribers or other health professionals should inform patients, their families, and their caregivers about the benefits and risks associated with treatment with Effexor XR and should counsel them in its appropriate use. A patient Medication Guide About Using Antidepressants in Children and Teenagers is available for Effexor XR. The prescriber or health professional should instruct patients, their families, and their caregivers to read the Medication Guide and should assist them in understanding its contents. Patients should be given the opportunity to discuss the contents of the Medication Guide and to obtain answers to any questions they may have. The complete text of the Medication Guide is reprinted at the end of this document.

Patients should be advised of the following issues and asked to alert their prescriber if these occur while taking Effexor XR.

Clinical Worsening and Suicide Risk: Patients, their families, and their caregivers should be encouraged to be alert to the emergence of anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, mania, other unusual changes in behavior, worsening of depression, and suicidal ideation, especially early during antidepressant treatment and when the dose is adjusted up or down. Families and caregivers of patients should be advised to observe for the emergence of such symptoms on a day-to-day basis, since changes may be abrupt. Such symptoms should be reported to the patient's prescriber or health professional, especially if they are severe, abrupt in onset, or were not part of the patient's presenting symptoms. Symptoms such as these may be associated with an increased risk for suicidal thinking and behavior and indicate a need for very close monitoring and possibly changes in the medication.

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, coadministration 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 (see also *CNS-Active Drugs*, below).

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 enzyme systems.

Drugs Metabolized by Cytochrome P450 Isoenzymes

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

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

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

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

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

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

CYP2C9: Venlafaxine did not inhibit CYP2C9 in vitro. In vivo, venlafaxine 75 mg by mouth every 12 hours did not alter the pharmacokinetics of a single 500 mg dose of tolbutamide or the CYP2C9 mediated formation of 4-hydroxy-tolbutamide.

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. Based on the mechanism of action of venlafaxine and the potential for serotonin syndrome, caution is advised when venlafaxine is co-administered with other drugs that may affect the serotonergic neurotransmitter systems, such as triptans, serotonin reuptake inhibitors (SRIs), or lithium.

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 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

Neonates exposed to Effexor XR, other SNRIs (Serotonin and Norepinephrine Reuptake Inhibitors), or SSRIs (Selective Serotonin Reuptake Inhibitors), late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding. Such complications can arise immediately upon delivery. Reported clinical findings have included respiratory distress, cyanosis, apnea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycemia, hypotonia, hypertonia, hyperreflexia, tremor, jitteriness, irritability, and constant crying. These features are consistent with either a direct toxic effect of SSRIs and SNRIs or, possibly, a drug discontinuation syndrome. It should be noted that, in some cases, the clinical picture is consistent with serotonin syndrome (see **PRECAUTIONS-Drug Interactions-***CNS-Active Drugs*). When treating a pregnant woman with Effexor XR during the third trimester, the physician should carefully consider the potential risks and benefits of treatment (see **DOSAGE AND ADMINISTRATION**).

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 the pediatric population have not been established (see **BOX WARNING** and **WARNINGS, Clinical Worsening and Suicide Risk**). Two placebo-controlled trials in 766 pediatric patients with MDD and two placebo-controlled trials in 793 pediatric patients with GAD have been conducted with Effexor XR, and the data were not sufficient to support a claim for use in pediatric patients.

Anyone considering the use of Effexor XR in a child or adolescent must balance the potential risks with the clinical need.

Although no studies have been designed to primarily assess Effexor XR's impact on the growth, development, and maturation of children and adolescents, the studies that have been done suggest that Effexor XR may adversely affect weight and height (see **PRECAUTIONS, General**, *Changes in Height* and *Changes in Weight*). Should the decision be made to treat a pediatric patient with Effexor XR, regular monitoring of weight and height is recommended during treatment, particularly if it is to be continued long term. The safety of Effexor XR treatment for pediatric patients has not been systematically assessed for chronic treatment longer than six months in duration.

In the studies conducted in pediatric patients (ages 6-17), the occurrence of blood pressure and cholesterol increases considered to be clinically relevant in pediatric patients was similar to that observed in adult patients. Consequently, the precautions for adults apply to pediatric patients (see **WARNINGS, Sustained Hypertension**, and **PRECAUTIONS, General**, *Serum Cholesterol Elevation*).

Geriatric Use

Approximately 4% (14/357), 6% (77/1381), 2% (6/277), and 2% (16/1001) of Effexor XR-treated patients in placebo-controlled premarketing major depressive disorder, GAD, Social Anxiety Disorder, and panic 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®, on data up to 12 weeks from a pool of two controlled clinical trials in Social Anxiety Disorder, and on data up to 12 weeks from a pool of four controlled clinical trials in panic 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. Approximately 7% of the 1,001 patients who received Effexor XR capsules in placebo-controlled clinical trials for panic disorder discontinued treatment due to an adverse experience, compared with 6% of the 662 placebo-treated patients in those studies. The most common events leading to discontinuation and considered to be drug-related (ie, leading to discontinuation in at least 1% of the Effexor XR-treated patients at a rate at least twice that of placebo for any 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		Panic Disorder Indication	
	Effexor XR n = 357	Placebo n = 285	Effexor XR n = 1381	Placebo n = 555	Effexor XR n = 277	Placebo n = 274	Effexor XR n = 1001	Placebo n = 662
Body as a Whole								
Asthenia	--	--	3%	<1%	1%	<1%	1%	0%
Headache	--	--	--	--	2%	<1%	--	--
Digestive System								
Nausea	4%	<1%	8%	<1%	4%	0%	2%	<1%
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%	1%	<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	--	--	--	--	3%[5]	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. Two of the panic disorder studies were flexible dose and two were fixed 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, 5, and 6 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), of Social Anxiety Disorder (up to 12 weeks; dose range of 75 to 225 mg/day), and of panic disorder (up to 12 weeks; dose range of 37.5 to 225 mg/day), respectively, in 2% or more of patients treated with Effexor XR (venlafaxine hydrochloride) 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, 5, and 6:

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.

Panic 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 4 placebo-controlled trials for the panic disorder indication (Table 6): gastrointestinal complaints (anorexia, constipation, dry mouth), CNS complaints (somnolence, tremor), abnormalities of sexual function (abnormal ejaculation), and sweating.

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)
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%

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

[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%

Body System Preferred Term	% Reporting Event Effexor XR (n = 1381)	 Placebo (n = 555)
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]

	% Reporting Event	
Body System Preferred Term	**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/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%

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

[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).

Table 6
Treatment-Emergent Adverse Event Incidence in Short-Term Placebo-Controlled Effexor XR Clinical Trials in Panic Disorder Patients[1,2]

	% Reporting Event	
Body System Preferred Term	**Effexor XR** (n = 1001)	**Placebo** (n = 662)
Body as a Whole		
Asthenia	10%	8%
Cardiovascular System		
Hypertension	4%	3%
Vasodilatation[3]	3%	2%
Digestive System		
Nausea	21%	14%
Dry mouth	12%	6%
Constipation	9%	3%
Anorexia[4]	8%	3%
Nervous System		
Insomnia	17%	9%
Somnolence	12%	6%
Dizziness	11%	10%
Tremor	5%	2%
Libido Decreased	4%	2%
Skin		
Sweating	10%	2%
Urogenital System		
Abnormal Ejaculation[5,6]	8%	<1%
Impotence[6]	4%	<1%
Orgasmic Dysfunction[7,8]	2%	<1%

[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, abnormal vision, accidental injury, anxiety, back pain, diarrhea, dysmenorrhea, dyspepsia, flu syndrome, headache, infection, nervousness, pain, paresthesia, pharyngitis, rash, rhinitis, and vomiting.
[2] <1% means greater than zero but less than 1%.
[3] Mostly "hot flushes."
[4] Mostly "decreased appetite" and "loss of appetite."
[5] Includes "delayed or retarded ejaculation" and "anorgasmia."
[6] Percentage based on the number of males (Effexor XR = 335, placebo = 238).
[7] Includes "anorgasmia" and "delayed orgasm."
[8] Percentage based on the number of females (Effexor XR = 666, placebo = 424).

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 a mean final on-therapy increase in pulse rate of approximately 4 beats per minute, compared with an increase of 1 beat per minute for placebo. Effexor XR treatment for up to 12 weeks in premarketing placebo-controlled panic disorder trials was associated with a mean final on-therapy increase in pulse rate of approximately 1 beat per minute, compared with a decrease of less than 1 beat per minute 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 to 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 of 7.4 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 decreases of 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. Effexor XR treatment for up to 12 weeks in premarketing placebo-controlled panic disorder trials was associated with mean final on-therapy increases in serum cholesterol concentration of approximately 5.8 mg/dL compared with a mean final decrease of 3.7 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 ≥50 mg/dL from baseline and to a value ≥261 mg/dL, or 2) an average on-therapy increase in serum cholesterol ≥50 mg/dL from baseline and to a value ≥261 mg/dL, were recorded in 5.3% of venlafaxine-treated patients and 0.0% of placebo-treated patients (see **PRECAUTIONS-General-***Serum Cholesterol Elevation*).

ECG Changes

In a flexible-dose study, with Effexor doses in the range of 200 to 375 mg/day and mean dose greater than 300 mg/day, the mean change in heart rate was 8.5 beats per minute compared with 1.7 beats per minute for placebo.

(See the *Use in Patients with Concomitant Illness* 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 1,381 patients in Phase 3 GAD studies, 277 patients in Phase 3 Social Anxiety Disorder studies, and 1314 patients in Phase 3 panic disorder studies. In addition, in premarketing assessment of Effexor, multiple doses were administered to 2897 patients in Phase 2 to Phase 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 6670 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, 5, and 6, 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, bradycardia, extrasystoles, hypotension, peripheral vascular disorder (mainly cold feet and/or cold hands), syncope, thrombophlebitis; **Rare:** aortic aneurysm, arteritis, first-degree atrioventricular block, bigeminy, bundle branch block, capillary fragility, cerebral ischemia, coronary artery disease, congestive heart failure, heart arrest, hematoma, cardiovascular disorder (mitral valve and circulatory disturbance), mucocutaneous hemorrhage, myocardial infarct, pallor, sinus arrhythmia.

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:** abdominal distension, biliary pain, cheilitis, cholecystitis, cholelithiasis, esophageal spasms, duodenitis, hematemesis, gastroesophageal reflux disease, gastrointestinal hemorrhage, gum hemorrhage, hepatitis, ileitis, jaundice, intestinal obstruction, liver tenderness, parotitis, periodontitis, proctitis, rectal disorder, salivary gland enlargement, increased salivation, soft stools, tongue discoloration.

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

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

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

Musculoskeletal system - **Frequent:** arthralgia; **Infrequent:** arthritis, arthrosis, bone spurs, bursitis, leg cramps, myasthenia, tenosynovitis; **Rare:** bone pain, pathological fracture, muscle cramp, muscle spasms, musculoskeletal stiffness, 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, manic reaction, myoclonus, neuralgia, neuropathy, psychosis, seizure, abnormal speech, stupor, suicidal ideation; **Rare:** abnormal/changed behavior, adjustment disorder, akinesia, alcohol abuse, aphasia, bradykinesia, buccoglossal syndrome, cerebrovascular accident, feeling drunk, loss of consciousness, delusions, dementia, dystonia, energy increased, facial paralysis, abnormal gait, Guillain-Barre Syndrome, homicidal ideation, hyperchlorhydria, hypokinesia, hysteria, impulse control difficulties, libido increased, motion sickness, neuritis, nystagmus, paranoid reaction, paresis, psychotic depression, reflexes decreased, reflexes increased, 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, contact dermatitis, dry skin, eczema, maculopapular rash, psoriasis, urticaria; **Rare:** brittle nails, erythema nodosum, exfoliative dermatitis, lichenoid dermatitis, hair discoloration, skin discoloration, furunculosis, hirsutism, leukoderma, miliaria, petechial rash, pruritic rash, pustular rash, vesiculobullous rash, seborrhea, skin atrophy, skin hypertrophy, skin striae, sweating decreased.

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

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

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 torsade de pointes; epidermal necrosis/Stevens-Johnson Syndrome, erythema multiforme, extrapyramidal symptoms (including dyskinesia and 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), neutropenia, night sweats, pancreatitis, pancytopenia, panic, prolactin increased, pulmonary eosinophilia, renal failure, rhabdomyolysis, serotonin syndrome, shock-like electrical sensations or tinnitus (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 (eg, 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.

There were 2 reports of acute overdose with Effexor XR in panic disorder trials. One patient took 0.675 g of Effexor XR once, and the other patient took 0.45 g of Effexor XR for 2 days. No signs or symptoms were associated with either overdose, and no actions were taken to treat them.

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 (eg, prolongation of QT interval, bundle branch block, QRS prolongation), sinus and ventricular tachycardia, bradycardia, hypotension, altered level of consciousness (ranging from somnolence to coma), rhabdomyolysis, 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, or it may be administered by carefully opening the capsule and sprinkling the entire contents on a spoonful of applesauce. This drug/food mixture should be swallowed immediately without chewing and followed with a glass of water to ensure complete swallowing of the pellets.

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 to 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 **PRECAUTIONS-General-***Use in Patients with Concomitant Illness.*)

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 Illness* 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 Illness* section of **PRECAUTIONS**.)

Panic Disorder

It is recommended that initial single doses of 37.5 mg/day of Effexor XR be used for 7 days. In clinical trials establishing the efficacy of Effexor XR in outpatients with panic disorder, initial doses of 37.5 mg/day for 7 days were followed by doses of 75 mg/day and subsequent weekly dose increases of 75 mg/day to a maximum dose of 225 mg/day. Although a dose-response relationship for effectiveness in patients with panic disorder was not clearly established in fixed-dose studies, certain patients not responding to 75 mg/day 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 7 days. (See the *Use in Patients with Concomitant Illness* 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), eg, 37.5 mg venlafaxine two-times-a-day to 75 mg Effexor XR once daily. However, individual dosage adjustments may be necessary.

Special Populations

Treatment of Pregnant Women During the Third Trimester

Neonates exposed to Effexor XR, other SNRIs, or SSRIs, late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding (see **PRECAUTIONS**). When treating pregnant women with Effexor XR during the third trimester, the physician should carefully consider the potential risks and benefits of treatment. The physician may consider tapering Effexor XR in the third trimester.

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 to 70 mL/min) compared with normal subjects (see **CLINICAL PHARMACOLOGY**), it is recommended that the total daily dose be reduced by 25% to 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, Social Anxiety Disorder, or panic 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 with major depressive disorder, Generalized Anxiety Disorder, Social Anxiety Disorder, or panic 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 periods of up to 52 weeks on the same dose (100 to 200 mg/day, on a b.i.d. 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.

In a study of panic disorder in which patients responding during 12 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), patients continuing Effexor XR experienced a significantly longer time to relapse than patients randomized to placebo. The need for continuing medication in patents with panic disorder who improve with Effexor XR treatment should be periodically reassessed.

Discontinuing Effexor XR

Symptoms associated with discontinuation of Effexor XR, other SNRIs, and SSRIs, have been reported (see **PRECAUTIONS**). Patients should be monitored for these symptoms when discontinuing treatment. A gradual reduction in the dose rather than abrupt cessation is recommended whenever possible. If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, then resuming the previously prescribed dose may be considered. Subsequently, the physician may continue decreasing the dose but at a more gradual rate. 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.

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).

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 of Wyeth Pharmaceuticals.

Medication Guide
About Using Antidepressants in Children and Teenagers

What is the most important information I should know if my child is being prescribed an antidepressant?

Parents or guardians need to think about 4 important things when their child is prescribed an antidepressant:

1. There is a risk of suicidal thoughts or actions.
2. How to try to prevent suicidal thoughts or actions in your child.
3. You should watch for certain signs if your child is taking an antidepressant.
4. There are benefits and risks when using antidepressants.

1. There is a Risk of Suicidal Thoughts or Actions

Children and teenagers sometimes think about suicide, and many report trying to kill themselves.

Antidepressants increase suicidal thoughts and actions in some children and teenagers. But suicidal thoughts and actions can also be caused by depression, a serious medical condition that is commonly treated with antidepressants. Thinking about killing yourself or trying to kill yourself is called *suicidality* or *being suicidal.*

A large study combined the results of 24 different studies of children and teenagers with depression or other illnesses. In these studies, patients took either a placebo (sugar pill) or an antidepressant for 1 to 4 months. ***No one committed suicide in these studies***, but some patients became suicidal. On sugar pills, 2 out of every 100 became suicidal. On the antidepressants, 4 out of every 100 patients became suicidal.

For some children and teenagers, the risks of suicidal actions may be especially high. These include patients with:

- Bipolar illness (sometimes called manic-depressive illness)
- A family history of bipolar illness
- A personal or family history of attempting suicide

If any of these are present, make sure you tell your healthcare provider before your child takes an antidepressant.

2. How to Try to Prevent Suicidal Thoughts and Actions

To try to prevent suicidal thoughts and actions in your child, pay close attention to changes in her or his moods or actions, especially if the changes occur suddenly. Other important people in your child's life can help by paying attention as well (e.g., your child, brothers and sisters, teachers, and other important people). The changes to look out for are listed in Section 3, on what to watch for.

Whenever an antidepressant is started or its dose is changed, pay close attention to your child.

After starting an antidepressant, your child should generally see his or her healthcare provider:

- Once a week for the first 4 weeks
- Every 2 weeks for the next 4 weeks
- After taking the antidepressant for 12 weeks
- After 12 weeks, follow your healthcare provider's advice about how often to come back
- More often if problems or questions arise (see Section 3)

You should call your child's healthcare provider between visits if needed.

3. You Should Watch for Certain Signs If Your Child is Taking an Antidepressant

Contact your child's healthcare provider ***right away*** if your child exhibits any of the following signs for the first time, or if they seem worse, or worry you, your child, or your child's teacher:

- Thoughts about suicide or dying
- Attempts to commit suicide
- New or worse depression
- New or worse anxiety
- Feeling very agitated or restless
- Panic attacks
- Difficulty sleeping (insomnia)
- New or worse irritability
- Acting aggressive, being angry, or violent
- Acting on dangerous impulses
- An extreme increase in activity and talking
- Other unusual changes in behavior or mood

Never let your child stop taking an antidepressant without first talking to his or her healthcare provider. Stopping an antidepressant suddenly can cause other symptoms.

4. There are Benefits and Risks When Using Antidepressants

Antidepressants are used to treat depression and other illnesses. Depression and other illnesses can lead to suicide. In some children and teenagers, treatment with an antidepressant increases suicidal thinking or actions. It is important to discuss all the risks of treating depression and also the risks of not treating it. You and your child should discuss all treatment choices with your healthcare provider, not just the use of antidepressants.

Other side effects can occur with antidepressants (see section below).

Of all the antidepressants, only fluoxetine (Prozac®) has been FDA approved to treat pediatric depression.

For obsessive compulsive disorder in children and teenagers, FDA has approved only fluoxetine (Prozac®), sertraline (Zoloft®), fluvoxamine, and clomipramine (Anafranil®).*

Your healthcare provider may suggest other antidepressants based on the past experience of your child or other family members.

Is this all I need to know if my child is being prescribed an antidepressant?

No. This is a warning about the risk for suicidality. Other side effects can occur with antidepressants. Be sure to ask your healthcare provider to explain all the side effects of the particular drug he or she is prescribing. Also ask about drugs to avoid when taking an antidepressant. Ask your healthcare provider or pharmacist where to find more information.

* Prozac® is a registered trademark of Eli Lilly and Company
Zoloft® is a registered trademark of Pfizer Pharmaceuticals
Anafranil® is a registered trademark of Mallinckrodt Inc.

This Medication Guide has been approved by the U.S. Food and Drug Administration for all antidepressants.

Wyeth®

Wyeth Pharmaceuticals Inc.
Philadelphia, PA 19101

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-699/S-054, 057

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	NDA
Submission Number	20-699/S054 & 20-699/S057
Submission Code	SE1
Letter Date	September 29, 2004
Stamp Date	September 29, 2004
PDUFA Goal Date	July 29, 2005
Reviewer Name	Michelle M. Chuen, M.D.
Review Completion Date	June 10, 2005
Established Name	Venlafaxine HCl Extended Release Capsules
Trade Name	Effexor XR
Therapeutic Class	Serotonin and norepinephrine reuptake inhibitor
Applicant	Wyeth Pharmaceuticals, Inc.
Priority Designation	S
Formulation	37.5, 75, and 150mg Capsules
Dosing Regimen	75-225 mg/day
Indication	Panic Disorder
Intended Population	Adults with Panic Disorder

Table of Contents

1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

Based on the data available at the time of completion of this review, it is recommended that this supplement be granted approvable status. There are a number of requests[1] to which the sponsor has not yet responded. These responses will be reviewed in an addendum. Final approval is contingent on satisfactory responses to the concerns conveyed in these requests and mutual agreement on labeling (see section 9.4).

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

There are no additional recommendations.

1.2.2 Required Phase 4 Commitments

There are no additional recommendations.

1.2.3 Other Phase 4 Requests

There are no additional recommendations.

[1] These requests are summarized as follows: 1) clarification of discrepancy between the number of Study 354 safety population patients described in the submission and the number of Study 354 safety population patients incorporated into a revision the other adverse events section of labeling, 2) clarification of ITT population definition used in study analyses, 3) warrant that ITT population definition changes were not made after unblinding, 4) enumeration and line listing of patients with greater than 3 days of missing PAAS data who were included in the efficacy analyses (further efficacy analyses may be required if this number is large), 5) recomputation of incidence of suicidal ideation and behavior for all patients in the pool of short-term studies, 6) explanation of line entries in adverse event case report tabulations missing both verbatim and preferred terms, 7) explanation of verbatim adverse events that were not coded to preferred terms, 8) explanation of preferred term missing an associated verbatim adverse event, 9) clarification of discrepancy in number of patients completing the open label period in Study 354, 10) clarification of patient dataset used in Tables 2.7.4.3.2.1C and 2.7.4.3.2.2B of the Summary of Clinical Safety, 11) enumeration of mean daily dose and total duration of exposure for all 5 studies combined, and 12) clarification of tables in which mean daily dose for a 225 mg fixed dose group was 100-200 mg.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

The safety and efficacy of oral venlafaxine ER in the treatment of patients with panic disorder is based on studies 398, 399, 353, 391, and 354. Studies 398 and 399 are 12-week fixed dose studies (75 or 150 mg/day and 75 mg or 225 mg/day, respectively) and studies 353 and 391 are 10-week flexible dose studies (75, 150, or 225 mg/day). Study 354 consisted of a 12-week open-label period (flexible dosing with 75, 150, or 225 mg/day) followed by a 6-month double-blind period at the open-label dose. In the 4 short-term studies, safety was evaluated in 1001 venlafaxine ER patients and 662 placebo patients. In the relapse prevention study, safety was evaluated in 313 patients.

1.3.2 Efficacy

The sponsor has provided evidence from two adequate, well-controlled studies that support the claim of short-term efficacy for the use of venlafaxine ER in panic disorder (studies 398 and 399) in dosage ranges of 75 to 225 mg/day. Studies 353 and 391 failed to demonstrate efficacy. The primary efficacy variable in all four studies was the proportion of patients free of full-symptom panic attacks at endpoint.

Study 354 demonstrated that venlafaxine ER short-term panic disorder responders randomized to continue venlafaxine ER experienced a significantly longer time to relapse than patients randomized to placebo.

1.3.3 Safety

A total of 1314 patients received Effexor XR and had safety data in these five trials. Information regarding mean daily dose and duration of exposure to Effexor XR is pending submission from the sponsor at this time. This submission revealed safety findings consistent with the previously observed safety profile of venlafaxine.

1.3.4 Dosing Regimen and Administration

Study 398 was a fixed dose study of venlafaxine ER that examined doses of 75 and 150 mg/day versus placebo in the treatment of panic disorder. Both dose groups produced a significant difference over placebo. Dosing for venlafaxine ER began at 37.5 mg/day for the first week of treatment, and all patients were increased to 75 mg/day during the second week. During week 3, high-dose patients had their dosage increased to 150 mg.

Study 399 was a fixed dose study of venlafaxine ER that examined doses of 75 and 225 mg/day versus placebo in the treatment of panic disorder. Both dose groups produced a significant difference over placebo. Dosing for venlafaxine ER began at 37.5 mg/day for the first week of treatment, and all patients were increased to 75 mg/day during the second week. High-dose

patients had their dosage increased to 150 mg daily during the third week and to 225mg during the fourth week.

For the above two studies, the interval for dose incrementation is inconsistent with the dosing instructions proposed by the sponsor for labeling. See Section 9.4 for details.

In these two fixed dose trials, there was evidence of a significant treatment effect for the low dose (75mg) ($p<0.001$), and results at the two higher doses were similar in both robustness ($p<0.001$) and magnitude of effect size (54.4% and 59.7% for 75 mg and 150mg and 64.7% and 70.0% for 75 mg and 225 mg). Thus, it is not clear that there is any significant therapeutic advantage of the 150mg and 225mg doses over the 75mg dose.

Dosing in study 354 was flexible (75, 150, or 225mg) during open-label treatment with the open-label dose continued during double-blind therapy. Since patients were not randomized to fixed doses in this trial, no assessment of dose-response for delaying relapse of panic disorder was possible.

1.3.5 Drug-Drug Interactions

There were no serious adverse events that suggested drug-drug interactions. There were no drug-drug interaction studies in the submission.

1.3.6 Special Populations

Gender did not appear to significantly affect treatment response as measured by percentage of patients free of full-symptom panic attacks. There was insufficient information to determine the effect of age or race on outcome. Please see Section 6.1.4 for further details.

The sponsor was granted a full pediatric waiver. Please see Section 2.5 for further details.

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

Effexor (venlafaxine hydrochloride) has been approved for treatment of major depressive disorder. Effexor XR (venlafaxine hydrochloride extended-release capsule) is a marketed serotonin and norepinephrine reuptake inhibitor which has been approved for the treatment of major depressive disorder, generalized anxiety disorder, and social phobia.

The sponsor is now seeking approval for treatment of adults with panic disorder (PD) with a dosing regimen of 75 to 225 mg/day based on the results of 5 completed clinical studies (2 short-term fixed-dose, 2 short-term flexible-dose, and 1 relapse prevention).

2.2 Currently Available Treatment for Indications

The five moieties approved in the U.S. for the treatment of panic disorder are: two benzodiazepines (alprazolam [IR and XR] and clonazepam), and 3 SSRI's (sertraline, paroxetine, and fluoxetine).

2.3 Availability of Proposed Active Ingredient in the United States

Venlafaxine hydrochloride is a marketed drug which was first approved on December 28, 1993. The extended-release capsule was approved on October 20, 1997. There have been no major toxicities identified to date, and the only safety issues identified have been sustained hypertension, increased heart rate, and increased risk of suicidal behavior in pediatric patients based on premarketing clinical studies.

2.4 Important Issues With Pharmacologically Related Products

There are no other important issues with pharmacologically related products.

2.5 Presubmission Regulatory Activity

An end-of-Phase 2 meeting request to discuss the development of Effexor XR in the treatment of PD was submitted October 31, 2000, and the meeting was held on December 4, 2000. At the meeting, the sponsor requested a full pediatric waiver. Although the Agency granted a partial waiver for children under 12 years of age and a deferral to allow submission of results after sNDA submission for short-term adult trials, we required one placebo-controlled clinical trial in the adolescent population. Other issues addressed included: 1) the inclusion of PD patients having secondary diagnoses such as MDD or GAD, 2) the acceptability of the PAAS as the primary efficacy measure, 3) recommendations regarding statistical analyses, 4) developing a plan for pooling centers before unblinding, and 5) labeling.

On August 30, 2001, the Agency provided feedback by letter on three adult panic disorder protocols (353-US, 354-US, 399-US), which included comments related to statistical issues, including key secondary efficacy variables, urine drug screening, and definition of relapse. In addition, the Agency provided feedback by letter on protocol 355-US on October 11, 2001, which also related to statistical issues and urine drug screening. On October 17, 2001, the sponsor submitted a response to the Agency's comments, which was agreed upon by the Agency in a letter dated November 7, 2001.

On December 9, 2002, the Agency provided recommendations by letter to Amendment 2 of protocol 398-EU submitted on September 10, 2002, relating to statistical issues and patient diary.

On December 17, 2002, the sponsor made a second request for a full pediatric waiver (Serial No. 622) due to enrollment difficulties. The Agency responded via phone conversation, stating that

consideration would be given to the request, after reinstatement of the "Pediatric Rule".[2] On April 5, 2004, the sponsor submitted a third request for a full pediatric waiver. The decision was made to grant a full pediatric waiver, and the Agency informed the sponsor via the Filing Letter dated December 8, 2004.

On January 15, 2003, a pre-sNDA package for Effexor XR in the treatment of PD was submitted to the FDA for review and comment, which FDA provided by email on February 26, 2003.[1] FDA's comments related to a literature search, pooling of safety data, and analyses of safety and efficacy by demographic subgroups.

On February 12, 2004, the Agency responded via letter to the sponsor's proposal to change the definition of relapse, and thereby the primary efficacy variable in protocol 354 (US, CA, EU, and AU versions). The Agency agreed to this proposal, with a minor modification in wording.

This sNDA was submitted to the Agency on September 29, 2004. The Filing Meeting was held on November 10, 2004 and it was concluded that this supplement was fileable. The User Fee due date is June 29, 2005. For User Fee purposes, two separate submissions were required since the sponsor requested approval for both acute (S-054) and longer-term indications (S-057).

2.6 Other Relevant Background Information

Effexor XR has not been withdrawn in any country for any reason, and the sponsor has not submitted any marketing authorization applications to foreign regulatory agencies seeking approval for the use of Effexor XR in the treatment of panic disorder.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

An Environmental Assessment was requested since approval of this supplement will likely increase the use of Effexor XR. This assessment was completed by Florian Zielinski, Environmental Officer, Center for Drug Evaluation and Research, on January 27, 2005. It was concluded that Effexor XR can be used and disposed of without any expected adverse environmental effects and a Finding of No Significant Impact (FONSI) was recommended.

3.2 Animal Pharmacology/Toxicology

There is no new animal pharmacology/toxicology data in this submission.

[2] Based on information submitted by the sponsor. Internal documentation could not be located

3.3 Statistical Review and Evaluation

Ohidul Siddiqui, Ph.D., is the statistical reviewer for this supplement. His written review is pending completion at this time. Based on a draft of his review, he has indicated that among the four short-term studies, the results of the two fixed-dose studies (398 and 399) demonstrated efficacy. He also indicated that the long-term maintenance study demonstrated the significant efficacy of venlafaxine ER (dose range of 75 to 225 mg) in delaying the relapse of panic disorder.

3.4 DSI Clinical Site Inspections

The Division of Scientific Investigations (DSI) inspected 2 sites from the relapse prevention trial, study 354: site 354013 (David Sheehan, M.D.) and site 354081 (Evan Zimmer, M.D.). The results of these inspections were communicated in a Clinical Inspection Summary completed by Robert S. Stasko, M.D., DSI Medical Officer, on May 9, 2005.

In summary, 8 subjects' records from the open-label trial and 3 from the double-blind phase (26 subjects were screened, 12 were enrolled for the open-label phase, 8 completed the open-label phase, 6 were randomized into the double-blind phase, and none completed the double-blind phase) from site 354013 were audited by DSI. A number of minor regulatory deviations were noted at this site, to include violation of inclusion criteria ("responder") in 2 patients enrolled in the double-blind phase, and lack of serum pregnancy test documentation prior to acceptance of two subjects into the open-label phase. This site was classified as VAI (minor deviations from regulations, data acceptable).

At site 354081, 8 records (25 entered and 12 completed the study) were audited. A number of minor regulatory deviations were noted at this site, including insufficient documentation to ensure that qualified study personnel performed screening evaluations to determine eligibility of 4 subjects. This site was classified as VAI (minor deviations from regulations, data acceptable).

Overall, data from these sites appeared to be acceptable for use in support of this NDA supplement.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

The safety and efficacy of venlafaxine ER in the treatment of adult patients with panic disorder is based on studies 398, 399, 353, 391, and 354. Studies 398 and 399 are 12-week fixed dose studies and studies 353 and 391 are 10-week flexible dose studies. Study 354 consisted of a 12-week open-label period followed by a 6-month double-blind period.

4.2 Tables of Clinical Studies

A total of five clinical trials in adult panic disorder comprise this supplement. These trials are summarized in the table below.

TABLE 4.2.1: EFFEXOR XR PANIC DISORDER STUDIES

Fixed-Dose Short-Term Studies	
398	Multicenter, randomized, double-blind, parallel-group, placebo- and paroxetine-controlled, fixed-dose study in 664 adult outpatients with panic disorder treated with venlafaxine ER (75 or 150 mg once daily), paroxetine 40 mg once daily, or placebo over 12 weeks, followed by a taper period of 2 weeks.
399	Multicenter, randomized, double-blind, parallel-group, placebo- and paroxetine-controlled, fixed-dose study in 653 adult outpatients with panic disorder treated with venlafaxine ER (75 or 225 mg once daily), paroxetine 40 mg once daily, or placebo over 12 weeks, followed by a taper period of 2 weeks.
Flexible-Dose Short-Term Studies	
353	Multicenter, double-blind, placebo-controlled, randomized, parallel-group, flexible-dose study in 343 adult outpatients with panic disorder treated with venlafaxine ER (75, 150, or 225 mg once daily) or placebo over 10 weeks, followed by a taper period of 2 weeks.
391	Multicenter, double-blind, placebo-controlled, randomized, parallel-group, flexible-dose study in 361 adult outpatients with panic disorder treated with venlafaxine ER (75, 150, or 225 mg once daily) or placebo over 10 weeks, followed by a taper period of 2 weeks.
Relapse Prevention Study	
354	Multicenter, placebo-controlled, randomized, parallel-group, flexible-dose study with 4 periods (2-week baseline, 12-week open-label, 6-month double-blind, and 2-week taper) in 321 adult outpatients with panic disorder treated with venlafaxine ER (75, 150, or 225 mg once daily) during the open-label period and venlafaxine ER (75, 150, or 225 mg once daily) or placebo during the double-blind period.

4.3 Review Strategy

A listing of the items examined during the course of this review is provided in Table 4.3. The progress report for the adolescent study (355), which was discontinued due to enrollment difficulties, will be examined for major safety findings only.

TABLE 4.3.1: ITEMS UTILIZED IN THE REVIEW	
Submission Date	**Items Reviewed**
September 29, 2004	Study Reports: Studies 398, 399, 353, 391, and 354 Proposed Labeling Financial Disclosure Certification Application Summary Case Report Tabulations (.xpt files) Case Report Forms
January 27, 2005	Response to FDA Request for Information
May 24, 2005	Response to FDA Request for Information

4.4 Data Quality and Integrity

The efficacy data from the three positive trials were examined by the statistician, Ohidul Siddiqui, and there were no outliers or sites identified that were felt to be driving the efficacy results. The Division of Scientific Investigations (DSI) chose 2 U.S. sites from the long-term study (354) for inspection: Evan Zimmer, M.D. and David Sheehan, M.D. This was based on the number of enrollments and the last date of inspection. The 2 positive short-term studies (398 and 399) were done in either Eastern Europe or South America, with very small sites and strong efficacy p values, and thus were not selected for inspection. Results of the DSI inspections are described in section 3.4.

I conducted an audit of adverse event safety data by comparing Case Report Forms (CRF's), Narrative Summaries, and adverse event line listings for consistency of adverse event information across these three documents in a random sample of 10 patients. Results are described in section 7.2.8 of this review.

4.5 Compliance with Good Clinical Practices

Studies 353, 391, and 398 were conducted according to the Declaration of Helsinki and its amendments active at the time the studies were conducted. Study 354 was conducted according to the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with Good Clinical Practice and the applicable regulatory requirements. Study 399 was conducted according to the ethical principles that have their origin in the Declaration of Helsinki (with the exception of the paragraph concerning the use of placebo) and that are consistent with Good Clinical Practice and the applicable regulatory requirements.

4.6 Financial Disclosures

For purposes of this NDA supplement, all five studies (398, 399, 353, 391, and 354) are considered "covered clinical stud[ies]" in accordance with 21 CFR 54.2 (e).

Among the clinical investigators in this study, 13 were identified by Wyeth as having financial arrangements that require disclosure:

———— ., the principal investigator at study site —— received significant payments (in excess of $25,000) from the sponsor for participation as a visiting professor, honoraria, and travel. It is unlikely that these arrangements biased the study results since this was a double-blind trial and —— site contributed only ~ patients of the —[3] patients in the study. b(6)

———— , the principal investigator at study site —— received significant payments (in excess of $25,000) from the sponsor for participation as a visiting professor, honoraria, and travel. It is unlikely that these arrangements biased the study results since this was a double-blind trial and — site contributed only – patients of the — patients in the study. b(6)

———— ., the sub-investigator at study site —— received significant payments (in excess of $25,000) from the sponsor for participation as a visiting professor, honoraria, and travel. It is unlikely that these arrangements biased the study results since this was a double-blind trial and — site contributed – patients of the — patients in the study. b(6)

———— the principal investigator at study site —— received significant payments (in excess of $25,000) from the sponsor for participation as a visiting professor, honoraria, and travel. It is unlikely that these arrangements biased the study results since this was a double-blind trial and — site contributed only – patients of the — patients in the study. b(6)

———— , the principal investigator at study site —— , received significant payments (in excess of $25,000) from the sponsor for participation as a visiting professor, honoraria, and travel. It is unlikely that these arrangements biased the study results since this was a double-blind trial and — site contributed only – patients of the —— patients in the study, with ———— supervising randomization of ———— b(6)

———— the principal investigator at study site —— received significant payments (in excess of $25,000) from the sponsor for participation as a visiting professor, honoraria, and travel. It is unlikely that these arrangements biased the study results since this was a double-blind trial and — site contributed only – patients of the —— patients in the study. b(6)

———— the sub-investigator at study site —— received significant payments (in excess of $25,000) from the sponsor for participation as a visiting professor, CME,

[3] Number of patients based on ————
[4] Number of patients based on b(6)

honoraria, and travel. It is unlikely that these arrangements biased the study results since this was a double-blind trial and — site contributed only — patients of the — patients in the study.

b(6)

———————— , the primary investigator at study site ——, received significant payments (in excess of $25,000) from the sponsor for honoraria and travel. It is unlikely that these arrangements biased the study results since this was a double-blind trial and — site contributed only — patients of the — patients in the study.

———————— the primary investigator at study site ——— received significant payments (in excess of $25,000) from the sponsor for participation as a visiting professor, honoraria, and travel. It is unlikely that these arrangements biased the study results since this was a double-blind trial and — site contributed only — atients (about — of the — atients in the study.

b(6)

———————— ., the primary investigator at study site ——, received significant payments (in excess of $25,000) from the sponsor for honoraria and travel. It is unlikely that these arrangements biased the study results since this was a double-blind trial and — site contributed only — patients of the — patients in the study.

———————— ., a subinvestigator at study site ——— eceived significant payments (in excess of $25,000) from the sponsor for unrestricted grants to fund ongoing research, honoraria, and travel. It is unlikely that these arrangements biased the study results since this was a double-blind trial and — site contributed only — patient of the — patients in the study.

b(6)

———————— ., the principal investigator at study site — , received significant payments (in excess of $25,000) from the sponsor for participation at investigators' meetings. It is unlikely that these arrangements biased the study results since — site contributed only — patient of the — patients in the study.

———————— ., a subinvestigator at study site ———, received significant payments (in excess of $25,000) from the sponsor for honoraria and travel. It is unlikely that these arrangements biased the study results since this was a double-blind trial and — site contributed only — patients of the ——patients in the study.

b(6)

A total of one clinical investigator in these trials was identified by the sponsor as not having provided financial disclosure information. The sponsor certified that due diligence had been exercised to obtain financial disclosure information from the non-responder and, despite this, the required information could not be obtained. The investigator was identified as ———— subinvestigator at site ——— was noted that the company received no response and that the investigator was no longer with the facility. This site enrolled — patients into the open-label phase and — patients entered the double-blind phase.

b(6)

[5] Number of patients based on ————————

5 CLINICAL PHARMACOLOGY

5.1 Pharmacokinetics

No new pharmacokinetic data are presented in this sNDA.

5.2 Pharmacodynamics

No new pharmacodynamic data are presented in this sNDA.

5.3 Exposure-Response Relationships

See Section 8.1 for a discussion of efficacy dose response and Section 7.1.5.6 for a discussion of safety dose response.

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

This supplemental application seeks to establish the safety and efficacy of venlafaxine ER in adult outpatients with panic disorder.

6.1.1 Methods

The sponsor has conducted four multicenter studies to evaluate the short term efficacy of venlafaxine ER in the treatment of adult outpatients with panic disorder (PD). In addition, they have conducted one relapse prevention study to evaluate the efficacy of venlafaxine ER in delaying time to relapse in open label responders.

6.1.2 General Discussion of Endpoints

At the pre-phase 3 meeting for panic disorder on 12/4/00, the Panic and Anticipatory Anxiety Scale (PAAS) was considered acceptable as the primary efficacy variable for the four short-term venlafaxine ER panic disorder studies. Assessing panic attack frequency via the PAAS was considered to correlate well with the effects of pharmacotherapy on the course of panic disorder. The primary efficacy metric was the percentage of patients free of full-symptom panic attacks at endpoint (last on-therapy visit prior to taper).

For the relapse prevention study (354), FDA expressed concern regarding the sponsor's plan to use a primary variable of percentage-to-relapse, stating that normally time-to-relapse is the primary outcome measure for relapse studies. The sponsor asked about adding the alternate criterion that, in the investigator's judgment, a treatment change is indicated, and FDA

responded that this could result in many patients being terminated early, thereby making it difficult to separate venlafaxine XR from placebo. Nevertheless, FDA stated that the new criterion was not unreasonable. FDA also mentioned that the definition of relapse within the protocol synopsis currently was very severe. In their protocol for the relapse prevention study, the sponsor selected time to relapse as the primary outcome measure, with relapse defined as either a) ≥ 2 panic attacks per week for 2 consecutive weeks,[6] or b) discontinuation due to loss of effectiveness as determined by the investigators during the study.

Regarding key secondary variables, FDA stated that efficacy measures, such as the Panic Disorder Severity Scale (PDSS), could be classified as key secondary variables, if they were declared upfront in the protocol and FDA agreed in advance with the sponsor that each is a legitimate and clinically relevant outcome. The protocols for three of the short-term studies (398, 399, and 353) identified PDSS total score and response rate on the Clinical Global Impressions improvement (CGI-I) subscale, defined as a score of 1 or 2 as key secondary variables, which were considered acceptable. One of the short-term studies (391) and the relapse prevention study (354) did not identify any key secondary variables.

6.1.3 Study Design

Two studies (398, 399) were randomized, double-blind, placebo- and paroxetine-controlled, parallel-group, fixed-dose trials of about 12 weeks duration. Study 398 used venlafaxine ER doses of 75 and 150 mg/day and a paroxetine dose of 40mg. Study 399 used doses of 75 and 225 mg/day and a paroxetine dose of 40mg.

Two studies (353, 391) were randomized, double-blind, placebo-controlled, parallel-group, flexible-dose trials of about 10 weeks duration utilizing doses of 75, 150, or 225 mg/day.

The fifth study, study 354, consisted of 4 phases in a relapse prevention design:

1) a 14-day baseline period
2) a 12-week open-label treatment phase using flexible doses of venlafaxine ER (75, 150, or 225 mg/day)
3) randomization of venlafaxine ER responders to same-dose venlafaxine ER or placebo for 6 months of double-blind study treatment
4) taper period

Each of these 5 studies will be reviewed separately in Section 10.1.

[6] To enter the double-blind portion of the study, patients must have ≤ 1 full-symptom panic attack per week during the last 2 weeks of open label treatment.

6.1.4 Efficacy Findings

Predictors of Response
The sponsor performed subset analyses to evaluate the effect of the following variables on treatment response for the pool of the short-term studies. A demographic analysis for study 354 was not provided.

- Age (<50 vs. ≥50 years old)
- Gender
- Ethnicity
- Baseline severity of panic attacks
- Presence or absence of agoraphobia at the final on-therapy evaluation

None of these variables appeared to significantly affect treatment response as measured by percentage of patients free of full-symptom panic attacks. The appendices in Section 10.4 present data based on these subgroups. Of note, due to relatively small numbers of patients ≥50 years old and relatively small number of non-white patients, there is insufficient information to determine the effect of age or race on outcome.

Size of Treatment Effect
Treatment effect size was examined in terms of the percentage of patients who were free of full panic attacks at endpoint. Results are summarized in Table 6.1.4.1 below for studies 398, 399, 353, and 391.

TABLE 6.1.4.1: TREATMENT EFFECT SIZE AS EXPRESSED BY THE PROPORTION OF PATIENTS FREE OF FULL PANIC ATTACKS AT ENDPOINT

Study	Venlafaxine XR (%)	Placebo (%)	Difference (Drug-Placebo) (%)
398 (75 mg)	54.4	35.3	19.1
398 (150 mg)	59.7	35.3	24.4
399 (75 mg)	64.7	47.8	16.9
399 (225 mg)	70.0	47.8	22.2
353	51.6	43.2	8.4
391	56.3	53.6	2.7

The sponsor has provided evidence from two adequate, well-controlled studies that supports the claim of short-term efficacy for the use of venlafaxine ER in panic disorder (studies 398 and 399).

Studies 353 and 391 failed to convincingly demonstrate the superiority of venlafaxine ER over placebo in this condition.

The results of the four short-term studies are summarized in Table 6.1.4.2 below.

TABLE 6.1.4.2: SUMMARY OF EFFICACY RESULTS (STATISTICAL SIGNIFICANCE OF DRUG/PLACEBO DIFFERENCES AT FINAL ON-THERAPY ASSESSMENT

Variable	Dataset	Study					
		398 75 mg dose	398 150 mg dose	399 75 mg dose	399 225 mg dose	353	391
% patients with zero full attacks	LOCF	**	**	**	**	ns	ns
	OC	tr	*	tr	**	*	ns
Mean Δ in PDSS total score	LOCF	**	**	**	**	**	NA
	OC	*	**	*	**	**	NA
CGI-I responders	LOCF	**	**	**	**	*	NA
	OC	**	**	**	**	**	NA

Codes: ns= not significant ($p>0.10$)
tr= trend ($0.05<p\leq0.10$)
* = significant ($0.01<p\leq0.05$)
**= highly significant ($p\leq0.01$)
NA= not applicable

Duration of Treatment
No study addressing the long-term efficacy of venlafaxine ER in panic disorder has been completed. Study 354 examined the efficacy of venlafaxine ER in a double-blind extension in which short-term responders were randomized to venlafaxine ER (75, 150, or 225 mg/day) or placebo. Patients randomized to venlafaxine ER were significantly less likely to relapse than patients randomized to placebo (relapse rates of 22.5% vs. 50.0%, respectively; $p<0.001$).

6.1.5 Clinical Microbiology

Since venlafaxine ER is a solid oral formulation, this section is not applicable.

6.1.6 Efficacy Conclusions

In summary, the sponsor has provided evidence from two adequate, well-controlled studies that support the claim of short-term efficacy for the use of venlafaxine ER in adults with panic disorder (studies 398 and 399) in dosage ranges of 75 to 225 mg/day.

Study 354 demonstrated that venlafaxine ER short-term panic disorder responders randomized to continue venlafaxine ER experienced a significantly longer time to relapse than patients randomized to placebo.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

This evaluation of the safety of venlafaxine ER in panic disorder (PD) is based on five completed studies: two short-term fixed dose trials (398 and 399), two short-term flexible dose trials (353 and 391), and one long-term trial (354). Please see Table 4.2 for a summary of these investigations.

Adverse events which were classified as serious were evaluated from all five clinical trials. Common adverse events, laboratory data, vital sign changes, and ECG findings were evaluated within the pool of the four short-term trials.

Study 355, conducted in adolescents with panic disorder, was prematurely terminated due to an insufficient patient population. Forty-eight patients were enrolled, 31 completed, and 17 dropped out. There were no deaths, overdoses, or IND Safety Reports from this trial. No further safety findings are reported and this study will not be further discussed in this review since the sponsor is not seeking a pediatric indication.

7.1.1 Deaths

No patient died during or immediately following any of the 4 short-term studies (398, 399, 353, and 391).

One (1) patient died during study 354: Patient 35453-1382 was a 43-year old woman who was treated with venlafaxine ER in the open-label period. She had been diagnosed with asthma in 1999, and at baseline had elevated alkaline phosphatase levels. Her liver function tests continued to increase, and on study day 21, the patient was referred to a consultant physician. Subsequent testing suggested lung cancer with liver metastases, and the patient died on study day 34.

7.1.2 Other Serious Adverse Events

A serious adverse event was defined by the sponsor as any adverse drug experience suggesting a significant hazard, contraindication, side effect, or precaution, including those that are fatal or life threatening, permanently disabling, requiring or prolonging inpatient hospitalization, or resulting in congenital anomalies or cancer. Additionally, important medical events that may not result in death, be life threatening, or require hospitalization may have been considered serious adverse events when, based upon appropriate medical judgment, the events may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

A total of 29 venlafaxine ER-treated patients and 12 placebo patients in studies 398, 399, 353, 391, and 354 experienced non-fatal adverse events classified as serious. These patients are listed in Tables 7.1.2.1 and 7.1.2.2 below.

The Narrative Summaries for the venlafaxine ER patients were reviewed. In the short-term studies, nine serious adverse events are considered possibly related to venlafaxine ER treatment: suicide attempt, accidental overdose, deep thrombophlebitis, colitis, depression, convulsion NOS, vertigo, manic reaction, and metrorrhagia.

Depression is frequently comorbid with panic disorder and, thus, is not considered an unexpected event in this population. The accidental overdose seems unlikely related to drug. The cases of metrorrhagia appear to be abnormal bleeding, and abnormal bleeding is already listed in precautions of current Effexor XR labeling. The case of vertigo occurred on the second day of the taper period. Vertigo is already listed in precautions under discontinuation of treatment. The case of deep thrombophlebitis occurred in a patient after arthroscopy of the knee, which may have predisposed her to developing thrombophlebitis. The case coded as colitis was a diagnosis of diverticulosis, which is unlikely related to drug.

I searched the verbatim terms of all adverse events of the short-term studies for events possibly related to convulsion or manic reaction. There were no cases of convulsion NOS or manic reaction in the placebo-treated group (0/662). The incidence of convulsion NOS in the venlafaxine-treated group was 0.1% (1/1001). The incidence of manic reaction in the venlafaxine-treated group was 0.1% (1/1001). The differences between placebo and venlafaxine ER incidences were not statistically significant (2-tailed Fisher's exact p-value= 1.000).

Regarding the suicide attempt, an analysis of suicidal behavior has been requested from the sponsor and is pending at this time.

TABLE 7.1.2.1:
VENLAFAXINE ER-TREATED PATIENTS WITH SERIOUS ADVERSE EVENTS
STUDIES 398, 399, 353, 391, & 354

Patient	Age	Sex	Days to Onset	Dose (mg/day)	Serious Adverse Event
Short-Term Studies					
35332-0469	24	F	19	92.9	Suicide attempt
39122-0841	40	M	42	177.2	Accidental overdose
39868-3352	49	F	52	67.4	Accidental injury and hemorrhage
39104-0122	44	F	13	131.3	Deep thrombophlebitis
35316-1464	30	F	21	46.4	Gastroenteritis
39117-0653	48	M	3	60.0	Colitis
39937-0875	36	F	95	174.0	Diarrhea
35370-1066	38	M	70	185.4	Depression
35372-2880	24	M	44	136.0	Convulsion NOS
39117-0672	48	M	6	52.5	Panic attack
39816-0772	27	F	66	72.7	Vertigo
39948-1140	26	M	57	187.5	Manic reaction
35327-0393	29	F	76	126.1	Unintended pregnancy
35338-0558	31	F	76	133.0	Unintended pregnancy
35365-0989	25	F	49	151.5	Unintended pregnancy
39115-0569	57	F	30	130.2	Metrorrhagia
39129-1126	22	F	38	60.0	Unintended pregnancy
39845-2209	22	F	66	71.6	Metrorrhagia
39929-0683	27	F	64	186.6	Pregnancy NOS
39937-0873	30	F	79	68.2	Unintended pregnancy
39949-1177	22	F	84/119[7]	71.0	Unintended pregnancy/Spontaneous abortion NOS

[7] These two serious adverse events occurred on days 84 and 119, respectively.

Relapse Prevention Study					
35454-1436	24	F	92/110[8]	189.3	Abdominal pain/Suicide attempt
35413-2771	36	F	62	160.8	Adjustment disorder with mixed features
35448-1134	35	F	5	37.5	Anxiety
35456-1540	31	F	26	113.9	Anxiety
35402-0019	23	F	15	57.5	Unintended pregnancy
35444-0933	20	F	80	151.2	Unintended pregnancy
35454-1436	24	F	87	189.3	Unintended pregnancy
35422-0318	28	F	208	144.0	Accidental exposure

TABLE 7.1.2.2: PLACEBO-TREATED PATIENTS WITH SERIOUS ADVERSE EVENTS STUDIES 398, 399, 353, 391, & 354

Patient	Age	Sex	Days to Onset	Dose (mg/day)	Serious Adverse Event
39116-0602	32	M	7	Placebo	Infection
35307-0095	52	F	14	Placebo	Chest pain, agitation, and accidental injury
39104-0134	21	F	6	Placebo	Vascular purpura
39115-0570	59	M	2	Placebo	Myocardial infarct
35347-0720	19	F	45	Placebo	Depression
39852-2551	49	F	15	Placebo	Agitation
35305-0062	62	F	31	Placebo	Skin carcinoma
35304-0049	30	F	2	Placebo	Unintended pregnancy
35316-0240	24	F	32	Placebo	Unintended pregnancy
35316-1475	28	F	45	Placebo	Abnormal laboratory test
39103-0083	25	F	32	Placebo	Unintended pregnancy
39933-0774	28	F	85	Placebo	Unintended pregnancy

[8] These two serious adverse events occurred on days 84 and 119, respectively.

7.1.3 Dropouts and Other Significant Adverse Events

7.1.3.1 Overall profile of dropouts

In the pool of the 4 short-term studies (398, 399, 353, and 391), overall dropout rates were roughly comparable between treatment groups [25% (168/662) of placebo patients and 21% (215/1001) of venlafaxine ER patients]. Dropout rates primarily due to adverse events [5% (33/662) of placebo patients and 6% (63/1001) of venlafaxine ER patients], failure to return [4% (27/662) of placebo patients and 4% (38/1001) of venlafaxine ER patients], and unsatisfactory response [9% (59/662) of placebo patients and 4% (45/1001) of venlafaxine patients] were also roughly comparable.

7.1.3.2 Adverse events associated with dropouts

In the pool of the 4 short-term studies (398, 399, 353, and 391), adverse experiences were either the primary or secondary reason for discontinuation of treatment in 21% (N=215/1001) of the venlafaxine ER-treated patients compared to 25% (N=168/662) of the placebo patients.

Appendix 10.5.1 in Section 10.5 presents the incidence of dropouts due to adverse experiences in the 4 pooled short-term studies. There were four adverse experiences that led to dropout in at least 1% of venlafaxine ER patients at a rate higher than that for placebo patients: asthenia, nausea, anxiety, and insomnia. No single adverse event led to dropout in greater than 2% of the venlafaxine ER group. The overall profile of adverse events leading to dropout in these studies was not substantially different from that observed with studies for other Effexor XR indications[9], and no adverse events leading to dropout were serious adverse events.

A tabulation of treatment-emergent adverse events that led to dropout in study 354 was examined.[10] There were no adverse events leading to dropout that have not been previously observed in association with venlafaxine or that were serious adverse events.

7.1.3.3 Other significant adverse events

No other clinically significant adverse events were detected.

7.1.4 Other Search Strategies

We have asked the sponsor to do a separate suicidal ideation and behavior analysis. The results are still pending at this time.

[9] See Table 2 in Effexor XR labeling.
[10] Supportive Tables ST 10-12 and ST 10-13 of the Study Report for study 354

7.1.5 Common Adverse Events

7.1.5.1 Eliciting adverse events data in the development program

Adverse event information was based on symptoms reported by the patient or signs observed by the investigator during physical examination and clinical evaluation. All such events were recorded in the adverse event case report forms (CRFs) as follows: the specific event or condition, whether the event was present during the prestudy period, the dates of occurrence, chronicity, severity, relationship to study drug, specific countermeasures, and outcome.

Standard coding terms for a thesaurus of adverse reaction terms (COSTART) were used to categorize the reported or verbatim adverse events. The investigators' descriptive terminology was preserved ("verbatim" report) and made available.

Treatment-emergent adverse events were any negative events, to include laboratory findings, that were experienced by the patient and were not seen before the first dose of open-label or double-blind study medication was taken or that were reported before treatment and worsened during treatment.

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

The sponsor provided a thesaurus for the coding of all adverse events in the safety database. This listing was examined to assess the adequacy of coding. There are a number of verbatim terms not coded to preferred terms, and one preferred term unassociated with a verbatim term. The sponsor was asked to explain these findings. Otherwise, no important deficiencies were found.

7.1.5.3 Incidence of common adverse events

Table 7.1.5.3.1 enumerates the incidence of treatment-emergent adverse events that occurred in 2% or more of patients treated with venlafaxine ER in the four short-term studies where the incidence in patients treated with venlafaxine ER was greater than the incidence for the respective placebo-treated patients.

TABLE 7.1.5.3.1: TREATMENT-EMERGENT ADVERSE EVENT INCIDENCE IN SHORT-TERM STUDIES

	% Reporting Event	
Body System Preferred Term	**Effexor XR** (n = 1001)	**Placebo** (n = 662)
Body as a Whole		
Asthenia	10%	8%
Cardiovascular System		
Hypertension	4%	3%
Vasodilatation[3]	3%	2%
Digestive System		
Nausea	21%	14%
Dry mouth	12%	6%
Constipation	9%	3%
Anorexia[4]	8%	3%
Nervous System		
Insomnia	17%	9%
Somnolence	12%	6%
Dizziness	11%	10%
Tremor	5%	2%
Libido Decreased	4%	2%
Skin		
Sweating	10%	2%
Urogenital System		
Abnormal Ejaculation[5,6]	8%	<1%
Impotence[6]	4%	<1%
Orgasmic Dysfunction[7,8]	2%	<1%

[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, abnormal vision, accidental injury, anxiety, back pain, diarrhea, dysmenorrhea, dyspepsia, flu syndrome, headache, infection, nervousness, pain, paresthesia, pharyngitis, rash, rhinitis, and vomiting.
[2] <1% means greater than zero but less than 1%.
[3] Mostly "hot flushes."
[4] Mostly "decreased appetite" and "loss of appetite."
[5] Includes "delayed or retarded ejaculation" and "anorgasmia."
[6] Percentage based on the number of males (Effexor XR = 335, placebo = 238).
[7] Includes "anorgasmia" and "delayed orgasm."
[8] Percentage based on the number of females (Effexor XR = 666, placebo = 424).

7.1.5.4 Common adverse event tables

Please see Section 7.1.5.3.

7.1.5.5 Identifying common and drug-related adverse events

Adverse events that are considered common and drug-related (i.e., reported in at least 5% of the venlafaxine ER patients at a rate at least twice that in the placebo group) are: anorexia, constipation, dry mouth, somnolence, tremor, sweating, and abnormal ejaculation/orgasm.

All of these events were reported as common and drug related in the original Effexor XR depression, generalized anxiety disorder, and social anxiety disorder NDA safety databases.[11]

7.1.5.6 Additional analyses and explorations

Demographic Effects on Adverse Event Incidence
The sponsor performed a subgroup analysis of demographic variables (age <50 or ≥50, gender, and race white or nonwhite) on the reporting rates of the above common, drug related events based on pooled data from the 4 short-term studies (398, 399, 353, and 391) and also from the relapse prevention study (354). For each variable, the venlafaxine ER:placebo odds ratio was computed for each subgroup followed by a Breslow-Day Chi-Square test for homogeneity across subgroups.

For the pooled short-term studies, there was a significant difference of reporting rates across subgroups for four adverse events. Constipation was reported much more frequently among those aged ≥50 (drug:placebo OR=17.69 among age ≥50 and 2.65 among age <50, Breslow p-value = 0.0444) and among whites (OR=5.47 among whites and 1.27 among nonwhites, Breslow-Day p-value=0.0041). Somnolence was reported more frequently among those aged ≥50 (OR=16.79 among age ≥50 and 1.85 among age <50; Breslow p-value=0.0135). Anorexia was reported more frequently among women (OR=4.06 among women and 1.11 among men; Breslow p-value 0.0146). Sweating was reported more frequently among nonwhites (OR=31.14 among nonwhites and 3.38 among whites, Breslow-Day p-value 0.0379).

These differences are difficult to interpret due to the lack of randomization to subgroups which would, in theory, control for all the other factors that could possibly be contributing to these differences in adverse event incidence. Additionally, there is difficulty interpreting the p-values given the multiplicity of comparisons.

Dose-Relatedness
The sponsor pooled short-term (12 week) data from the two fixed dose panic disorder trials (398 and 399) to evaluate the relationship between dose and the reporting incidence of treatment-emergent adverse events. Events examined were those reported by at least 1% of venlafaxine ER

[11] See Effexor XR labeling.

patients in any dose group. Dose groups were: 75mg (N=326), 150mg (N=168), and 225mg (N=166).

There appears to be a dose-related trend for treatment-emergent adverse events of anorexia, dry mouth, insomnia, decreased libido, and abnormal ejaculation/orgasm. For all other adverse events there does not appear to be a dose response or it's unclear.

7.1.6 Less Common Adverse Events

I reviewed tables of all adverse events in both the pool of the 4 short-term studies[12] and in the relapse prevention study[13] and did not find any adverse events that were considered serious adverse events but not already classified as serious.

7.1.7 Laboratory Findings

7.1.7.1 Overview of laboratory testing in the development program

Routine hematology, chemistry, and urinalysis testing was done at screening and at final on-therapy for all four short-term studies.

7.1.7.2 Standard analyses and explorations of laboratory data

7.1.7.2.1 Analyses focused on measures of central tendency

Mean Change from Baseline in Laboratory Tests
Mean changes from baseline were computed for several laboratory variables[14] in the pool of short-term studies. Results are displayed in Table 2.7.4.3.2.1C of the Summary of Clinical Safety.

For the pool of short-term studies, mean changes from baseline to final on-therapy assessment were statistically significantly different between venlafaxine ER and placebo for sodium, chloride, creatinine, AST, alkaline phosphatase, cholesterol, HDL cholesterol, and LDL cholesterol. Data are presented in Table 7.1.7.2.1.1 below.[15]

[12] Supportive Table ST 2-1 of the Summary of Clinical Safety
[13] Supportive Table ST 2-11 of the Summary of Clinical Safety
[14] Sodium, chloride, BUN, creatinine, AST, alkaline phosphatase, cholesterol, HDL cholesterol, LDL cholesterol, triglycerides, glucose, and total protein
[15] Changes for other variables were not significantly different between drug and placebo.

TABLE 7.1.7.2.1.1: MEAN CHANGES FROM BASELINE FOR SERUM SODIUM, CHLORIDE, CREATININE, AST, ALKALINE PHOSPHATASE, CHOLESTEROL, HDL CHOLESTEROL, AND LDL CHOLESTEROL (SHORT-TERM STUDIES 398, 399, 353, AND 391): DOUBLE-BLIND PERIOD[16]

	Placebo		Venlafaxine ER		p-value
	N	Mean Δ	N	Mean Δ	
Sodium	544	-0.1	803	-0.8	≤ 0.05
Chloride	544	0.1	803	-0.7	≤ 0.05
Creatinine	543	-0.088	803	-1.381	≤ 0.05
AST	531	0	787	2.2	≤ 0.05
Alk. Phosphatase	544	0.2	805	4.9	≤ 0.05
Cholesterol	437	-0.09462[17]	694	0.14898[18]	≤ 0.05
HDL cholesterol	435	0.01	692	0.05	≤ 0.05
LDL cholesterol	422	-0.1122	669	0.07554	≤ 0.05

The mean changes in sodium, chloride, creatinine, AST, alkaline phosphatase, cholesterol, HDL cholesterol, and LDL cholesterol were small and unlikely to be clinically significant.

7.1.7.2.2 Analyses focused on outliers or shifts from normal to abnormal

Potentially Clinically Significant Laboratory Changes
Criteria for potentially clinically important (PCI) laboratory test results are displayed in Appendix 10.5.2 in Section 10.5. The proportions of patients who met these criteria for pooled 4 short-term studies are provided in Table 2.7.4.3.1.2.1C in the Summary of Clinical Safety.

The proportions were comparable between the venlafaxine ER group and placebo group for all laboratory parameters in the pooled short-term studies. For high triglycerides, proportions were 16% (112/719) in the venlafaxine ER group and 12% (56/402) in the placebo group. The difference was not significant (chi-square=2.57, p=0.11).

7.1.7.2.3 Marked outliers and dropouts for laboratory abnormalities

Dropouts due to Laboratory Abnormalities
No venlafaxine ER patients in the short-term studies dropped out due to laboratory abnormalities.

7.1.7.3 Additional analyses and explorations

No laboratory parameters warranted additional exploration.

[16] Units are as follows: sodium (mmol/L), chloride (mmol/L), creatinine (μmol/L), AST (U/L), alk phosphatase (mU/mL), cholesterol (mmol/L), HDL cholesterol (mmol/L), LDL cholesterol (mmol/L)
[17] Equivalent to -3.66 mg/dL
[18] Equivalent to 5.76 mg/dL

7.1.7.4 Special assessments

The above analyses revealed no evidence of any particular toxicity manifested as a laboratory test abnormality.

7.1.8 Vital Signs

7.1.8.1 Overview of vital signs testing in the development program

Vital Sign Assessments
For the short-term studies (398, 399, 353, 391), supine pulse and supine and standing blood pressure were measured at screening, baseline, at each visit during double-blind treatment and at poststudy.

7.1.8.2 Selection of studies and analyses for overall drug-control comparisons

7.1.8.3 Standard analyses and explorations of vital signs data

7.1.8.3.1 Analyses focused on measures of central tendencies

Mean Change from Baseline in Vital Sign Measures
For the short-term studies, the mean changes from baseline to various study visits in standing and supine systolic and diastolic blood pressure, supine pulse, and weight are displayed by visit in Table 2.7.4.4.2.1C of the summary of clinical safety. For most variables, statistically significant differences between venlafaxine ER and placebo occurred only transiently during the study.

For the pool of short-term studies, mean changes from baseline to final on-therapy assessment were statistically different between venlafaxine ER and placebo for supine diastolic BP, supine pulse rate, and weight. Data are presented in Table 7.1.8.3.1.1 below.[19]

[19] Changes for other variables were not significantly different between drug and placebo.

TABLE 7.1.8.3.1.1: MEAN CHANGES FROM BASELINE IN BLOOD PRESSURE, PULSE, AND WEIGHT (SHORT-TERM STUDIES 398, 399, 353, AND 391): DOUBLE-BLIND PERIOD					
	Placebo		Venlafaxine ER		p-value
	N	Mean Δ	N	Mean Δ	
Supine Diastolic BP (mm Hg)	650	-1.06	973	0.25	≤ 0.05
Supine Pulse Rate (beats/min)	650	-0.15	973	1.41	≤ 0.05
Weight (kg)	561	0.01	844	-0.29	≤ 0.05

The mean changes in supine diastolic BP, supine pulse rate, and weight were small and unlikely to be clinically significant.

7.1.8.3.2 Analyses focused on outliers or shifts from normal to abnormal

Potentially Clinically Significant Vital Sign Changes
The proportions of venlafaxine ER and placebo patients in the short-term studies who met these criteria are displayed in Appendix 10.5.3 in Section 10.5.

In the pooled short-term studies, the proportions were comparable between the venlafaxine ER group and placebo group for all vital sign measurements except for a decrease in standing systolic BP of ≥20 mm Hg and ≤ 90 mm Hg (4% in the venlafaxine ER group and 2% in the placebo group). However, the difference was not statistically significant (chi-square p-value =0.09).

There were no PCI changes among venlafaxine ER patients that were at least 5% and twice that among placebo patients.

Sustained Increases in Supine Diastolic Blood Pressure
The incidence of sustained increases in supine diastolic blood pressure (SDBP) was computed for the short-term studies. A sustained increase in SDBP was defined as a treatment-emergent increase in SDBP of at least 10 mm Hg from baseline to an on-therapy value ≥90 mm Hg for at least 3 consecutive visits.

In the short-term studies, 0.9% (9/973) of venlafaxine ER and 0.6% (4/650) of placebo patients had sustained increases in SDBP. This difference is not statistically significant (chi-square=0.46, p=0.50).

7.1.8.3.3 Marked outliers and dropouts for vital sign abnormalities

Dropouts due to Vital Sign Abnormalities
In the short-term studies, the proportions of patients who experienced a change in vital signs or weight that led to premature discontinuation are displayed in Table 7.1.8.3.3.1 below. The incidence for dropout due hypertension was slightly higher in the venlafaxine ER group than in the placebo group. The difference was not statistically significant (p=0.71, 2-tailed Fishers exact test). In the venlafaxine ER patients who dropped out due to hypertension, the maximum increase from baseline ranged from 7 to 19 mm Hg for supine diastolic blood pressure, and from 10 to 34 mm Hg for supine systolic blood pressure.

TABLE 7.1.8.3.3.1: DROPOUTS DUE TO VITAL SIGN OR WEIGHT CHANGES

Abnormality	Venlafaxine ER (N=1001)	Placebo (N=662)
Tachycardia	1 (0.1%)	1 (0.2%)
Hypertension	5 (0.5%)	2 (0.3%)

7.1.8.4 Additional analyses and explorations

No further explorations were deemed necessary.

7.1.9 Electrocardiograms (ECGs)

7.1.9.1 Overview of ECG testing in the development program, including brief review of preclinical results

ECG Assessments
Standard 12-lead electrocardiograms were performed at screening and at final on-therapy for all four short-term studies. QTc was the QT interval corrected for heart rate using Bazett's formula.

7.1.9.2 Selection of studies and analyses for overall drug-control comparisons

7.1.9.3 Standard analyses and explorations of ECG data

7.1.9.3.1 Analyses focused on measures of central tendency

Mean Change from Baseline in ECG parameters
For the short-term studies, mean changes from baseline to final on-therapy assessment were computed for the venlafaxine ER and placebo treatment groups. Study 391 was not pooled with

the other 4 studies due to differences in ECG interpretation methodologies.[20] Results are displayed in Tables 2.7.4.4.4.1C and –D of the Summary of Clinical Safety.

For the pool of the 3 short-term studies, mean changes from baseline to final on-therapy assessment were statistically significantly different between venlafaxine ER and placebo for heart rate, PR interval, QRS interval, QT interval, and QTc interval. For study 391, mean changes from baseline to final on-therapy assessment were statistically significantly different between venlafaxine ER and placebo for heart rate, PR interval, and QTc interval. Data are presented in Tables 7.1.9.3.1.1 and 7.1.9.3.1.2 below.[21]

TABLE 7.1.9.3.1.1: MEAN CHANGES FROM BASELINE FOR QUANTITATIVE ECG VARIABLES (SHORT-TERM STUDIES 398, 399, AND 353): DOUBLE-BLIND PERIOD

	Placebo		Venlafaxine ER		p-value
	N	Mean Δ	N	Mean Δ	
Heart rate (beats/ min)	395	-0.41	661	3.48	≤ 0.05
PR interval (ms)	395	1.20	660	-1.74	≤ 0.05
QRS interval (ms)	395	0.35	661	-0.68	≤ 0.05
QT interval (ms)	395	0.32	661	-8.51	≤ 0.05
QTc interval (ms)	395	-0.65	661	1.47	≤ 0.05

TABLE 7.1.9.3.1.2: MEAN CHANGES FROM BASELINE FOR QUANTITATIVE ECG VARIABLES (SHORT-TERM STUDY 391): DOUBLE-BLIND PERIOD

	Placebo		Venlafaxine ER		p-value
	N	Mean Δ	N	Mean Δ	
Heart rate (beats/ min)	143	-1.45	130	3.38	≤ 0.001
PR interval (ms)	142	1.72	128	-4.58	0.010
QTc interval (ms)	143	-4.32	129	4.02	0.035

The changes in heart rate, PR interval, QRS interval, QT interval, and QTc interval were generally small and unlikely to be clinically significant. However, in Study 391, the drug/placebo difference in QTc was over 8 msec which is large but still less than a 10 msec difference at which we might get concerned.

[20] See pages 148 of 223 in the Summary of Clinical Safety for details of the interpretation methodologies.
[21] Changes for other variables were not significantly different between drug and placebo.

7.1.9.3.2 Analyses focused on outliers or shifts from normal to abnormal

Potentially Clinically Significant ECG Changes
Criteria for potentially clinically important (PCI) ECG results are displayed in Appendix 10.5.4 in Section 10.5. The proportions of patients who met these criteria for pooled 4 short-term studies are provided in Table 2.7.4.4.3.2.1C in the Summary of Clinical Safety.

The proportions were comparable between the venlafaxine ER group and placebo group for all ECG results. There were no PCI changes among venlafaxine ER patients that were at least 5% and twice that among placebo patients.

7.1.9.3.3 Marked outliers and dropouts for ECG abnormalities

Dropouts due to ECG Abnormalities
No venlafaxine ER patients in the short-term studies dropped out due to ECG abnormalities.

7.1.9.4 Additional analyses and explorations

No ECG parameters warranted additional exploration.

7.1.10 Human Reproduction and Pregnancy Data

There were no studies in this submission designed specifically to assess safety in human reproduction and pregnancy. A review of serious adverse events revealed a total of 10 pregnancies during the short-term and relapse prevention studies. Of these 10 pregnancies follow-up information was available for 7 pregnancies. These pregnancies resulted in the delivery of 3 healthy infants, 1 elective termination (with intact fetus on pathology evaluation), 1 therapeutic abortion, and 2 miscarriages.

7.1.11 Overdose Experience

There were 3 cases of overdose during these studies.

1. One patient "probably" took 6 extra capsules of venlafaxine ER 75mg. There were no symptoms or signs associated with this possible overdose, and no clinically important ECG or laboratory abnormalities were reported.
2. Another patient over-medicated with 450 mg venlafaxine ER for 2 days instead of 225 mg daily. There were no associated adverse events and the patient recovered without incident.
3. The 4-year-old child of a patient ingested 2 capsules of venlafaxine ER 75mg. The child was monitored for 1 month with no adverse effects noted.

7.1.12 Postmarketing Experience

There is no postmarketing data in this submission. This was discussed at the November 10, 2004 Filing Meeting, and submission of this information was deemed unnecessary.

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

7.2.1.1 Study type and design/patient enumeration

TABLE 7.2.1.1.1: EFFEXOR XR PANIC DISORDER STUDIES, INCLUDING SAFETY POPULATION ENUMERATION

Fixed-Dose Short-Term Studies	
398	Multicenter, randomized, double-blind, parallel-group, placebo- and paroxetine-controlled, fixed-dose study in 664 adult outpatients with panic disorder treated with venlafaxine ER (75 or 150 mg once daily), paroxetine 40 mg once daily, or placebo over 12 weeks, followed by a taper period of 2 weeks. Safety population consisted of 163 patients assigned to placebo, 166 patients assigned to venlafaxine ER 75 mg, and 168 patients assigned to venlafaxine 150 mg.
399	Multicenter, randomized, double-blind, parallel-group, placebo- and paroxetine-controlled, fixed-dose study in 653 adult outpatients with panic disorder treated with venlafaxine ER (75 or 225 mg once daily), paroxetine 40 mg once daily, or placebo over 12 weeks, followed by a taper period of 2 weeks. Safety population consisted of 162 patients assigned to placebo, 160 patients assigned to venlafaxine ER 75 mg, and 166 patients assigned to venlafaxine ER 225 mg.
Flexible-Dose Short-Term Studies	
353	Multicenter, double-blind, placebo-controlled, randomized, parallel-group, flexible-dose study in 343 adult outpatients with panic disorder treated with venlafaxine ER (75, 150, or 225 mg once daily) or placebo over 10 weeks, followed by a taper period of 2 weeks. Safety population consisted of 159 patients assigned to placebo and 164 patients assigned to venlafaxine ER.
391	Multicenter, double-blind, placebo-controlled, randomized, parallel-group, flexible-dose study in 361 adult outpatients with panic disorder treated with venlafaxine ER (75, 150, or 225 mg once daily) or placebo over 10 weeks, followed by a taper period of 2 weeks. Safety population consisted of 178 patients assigned to placebo and 177 venlafaxine ER.
Relapse Prevention Study	
354	Multicenter, placebo-controlled, randomized, parallel-group, flexible-dose study with 4 periods (2-week baseline, 12-week open-label, 6-month double-blind, and 2-week taper) in 321 adult outpatients with panic disorder treated with venlafaxine ER (75, 150, or 225 mg once daily) during the open-label period and venlafaxine ER (75, 150, or 225 mg once daily) or placebo during the double-blind period. Safety population consisted of 313 patients.

7.2.1.2 Demographics

TABLE 7.2.1.2.1 : SHORT-TERM STUDIES 398, 399, 353, AND 391 BASELINE DEMOGRAPHICS, SAFETY POPULATION								
TX (n)	Age (yrs)		Sex (%)		Race (%)			
	Mean	Range	Male	Female	White	Black	Hispanic	Other
Ven ER (1001)	37.1	18-84	33	67	77	2	20	1
Placebo (662)	37.3	18-74	36	64	80	3	16	1

TABLE 7.2.1.2.1 : RELAPSE PREVENTION STUDY 354 BASELINE DEMOGRAPHICS, SAFETY POPULATION								
TX (n)	Age (yrs)		Sex (%)		Race (%)			
	Mean	Range	Male	Female	White	Black	Hispanic	Other
Ven ER (313)	37.2	18-70	32	68	86	4	8	3

7.2.1.3 Extent of exposure (dose/duration)

We have asked the sponsor to submit an enumeration of mean daily dose and total duration of exposure for all 5 studies combined. The results are still pending at this time.

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

7.2.2.1 Other studies

There was one relapse prevention study (Study 354) that was not pooled with the other studies in comprising the primary safety database due to a difference in study design.

7.2.2.2 Postmarketing experience

There is no postmarketing data in this submission. This was discussed at the November 10, 2004 Filing Meeting, and submission of this information was deemed unnecessary.

7.2.2.3 Literature

A literature search was done for published papers relevant to Ef(f)exor ER and panic disorder through 04 March 2004.

A search of 5 major biomedical and pharmaceutical databases (MEDLINE, BIOSIS, Current Contents, Derwent Drug File, and EMBASE) was conducted through OVID, in addition to the Wyeth Product and Publications Database.

These databases provide complementary information resources and, at Wyeth, cover the time periods from 1996 to week 04 of February 2004 (MEDLINE); 1985 to week 11 of 2004 (BIOSIS); 1996 to week 10 of 2004 (Current Contents); 1964 to week 09 of 2004 (Derwent Drug File); 1988 to week 09 of 2004 (EMBASE); and week 01 of March 2003 to week 01 of March 2004 (Wyeth Product and Publications).

7.2.3 Adequacy of Overall Clinical Experience

Overall clinical experience was adequate.

7.2.4 Adequacy of Routine Clinical Testing

Routine clinical testing was adequate.

7.2.5 Adequacy of Metabolic, Clearance, and Interaction Workup

There were no studies addressing metabolic, clearance, or interaction in this submission.

7.2.6 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

There are no recommendations for further study.

7.2.7 Assessment of Quality and Completeness of Data

An audit of the Case Report Forms (CRF's), Narrative Summaries, and adverse event data listings was conducted for 10 patients whom I randomly selected from the database for this supplement (5% of the 201 patients with submitted CRF's).[22] The adverse event data listings examined were adverse.xpt for each of the 4 studies selected. Narrative Summaries were only available for patients who died, had serious adverse events, had laboratory test values, vital signs, or ECG results of clinical importance, or who discontinued from the study because of a clinically important adverse event. Thus, only CRF's and data listings were examined for 9 of the 10 patients selected, and the CRF, Narrative Summary, and adverse event data listing were examined for patient 391EU/015/0570.

[22] This consisted of 1 patient from study 353 (353US/014/0197), 2 patients from study 354 (354EU/043/0890 and 354US/007/0102), 3 patients from study 391 (391EU/004/0132, 391EU/015/0570, and 391EU/044/1721), and 4 patients from study 398 (398EU/011/0510, 398EU/044/2156, 398EU/062/3061, and 398EU/076/3753).

An examination of the adverse event information across these sources for each of the 10 patients revealed reasonable consistency and completeness.

In addition, the Division of Scientific Investigations (DSI) inspected two sites from study 354. The results of these inspections are presented in Section 3.4 above. Overall, the data from these two sites appeared to be acceptable for use in support of this NDA supplement.

7.2.8 Additional Submissions, Including Safety Update

There was no safety update because all studies were completed at the time of submission.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

This submission revealed only findings consistent with the previously observed safety profile of venlafaxine.

7.4 General Methodology

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

7.4.1.1 Pooled data vs. individual study data

The 4 short-term studies (398, 399, 353, and 391) were pooled to estimate the incidence of adverse events.

7.4.2 Explorations for Predictive Factors

7.4.2.1 Explorations for dose dependency for adverse findings

Please see Section 7.1.5.6

7.4.2.2 Explorations for drug-demographic interactions

Please see Section 7.1.5.6.

7.4.3 Causality Determination

Adverse events were considered common and possibly drug-related if they were reported in at least 5% of the venlafaxine ER patients at a rate at least twice that in the placebo group within the pool of the four short-term trials.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

Study 398 was a fixed dose study of venlafaxine ER that examined doses of 75 and 150 mg/day versus placebo in the treatment of panic disorder. Both dose groups produced a significant difference over placebo.

Study 399 was a fixed dose study of venlafaxine ER that examined doses of 75 and 225 mg/day versus placebo in the treatment of panic disorder. Both dose groups produced a significant difference over placebo.

Dosing for venlafaxine ER began at 37.5 mg/day for the first week of treatment, and all patients were increased to 75 mg/day during the second week. In study 398, after week 2, patients could have their dosage increased to 150 mg daily based upon the investigator's judgment regarding therapeutic efficacy and tolerability. In study 399, patients were randomized to 75 mg and 225 mg treatment groups. For the 225 mg treatment group, dosage was increased by 75 mg increments every 7 days. This is inconsistent with the dosing instructions proposed by the sponsor for labeling. See Section 9.4 for details.

Based on drug/placebo comparisons there was evidence of a significant treatment effect for the low dose ($p<0.001$), and results at the two higher doses were similar in both robustness ($p<0.001$) and magnitude of effect size (54.4% and 59.7% for 75 mg and 150mg and 64.7% and 70.0% for 75 mg and 225 mg). Therefore, there appears to be no substantial advantage of the higher doses (150 and 225 mg) over the lower dose (75mg).

8.2 Drug-Drug Interactions

There were no serious adverse events that suggested drug-drug interactions. There were no drug-drug interaction studies in the submission.

8.3 Special Populations

Please see Section 6.1.4.

8.4 Pediatrics

The sponsor was granted a full pediatric waiver. Please see Section 2.5 for further details.

8.5 Advisory Committee Meeting

This submission was not presented to the Psychopharmacologic Drugs Advisory Committee.

8.6 Literature Review

The sponsor's Medical Monitor for panic disorder warranted that he reviewed the worldwide literature review and that no relevant papers or issues that would adversely affect the conclusions about the safety profile of Effexor XR were found.

8.7 Postmarketing Risk Management Plan

There are no additional recommendations.

9 OVERALL ASSESSMENT

9.1 Conclusions

This submission revealed only safety findings consistent with the previously observed safety profile of venlafaxine.

The sponsor has provided evidence from two adequate, well-controlled studies that support the claim of short-term efficacy for the use of venlafaxine ER in panic disorder (studies 398 and 399) in dosage ranges of 75 to 225 mg/day.

Study 354 demonstrated that venlafaxine ER short-term panic disorder responders randomized to continue venlafaxine ER experienced a significantly longer time to relapse than patients randomized to placebo.

9.2 Recommendation on Regulatory Action

Based on the data available at the time of completion of this review, it is recommended that this supplement be granted approvable status. There are a number of requests[23] to which the sponsor has not yet responded. These responses will be reviewed in an addendum. Final approval is

[23] See footnote in Section 1.1 for a list of the specific requests.

contingent on satisfactory responses to the concerns conveyed in these requests and mutual agreement on labeling (see section 9.4).

9.3 Recommendation on Postmarketing Actions

There are no recommendations for postmarketing actions.

9.3.1 Risk Management Activity

There are no recommendations for risk management beyond those already labeled (e.g., blood pressure monitoring).

9.3.2 Required Phase 4 Commitments

There are no recommendations for Phase 4 commitments from a clinical perspective.

9.3.3 Other Phase 4 Requests

There are no other Phase 4 requests.

9.4 Labeling Review

The following labeling changes to Effexor XR labeling were proposed by the sponsor in the original submission of this supplement.

CLINICAL PHARMACOLOGY/Clinical Trials/Panic Disorder
This section has been added to describe the two positive short-term studies in panic disorder (398 and 399). The summary of the efficacy results for these two studies is acceptable, with a few exceptions:

1. The statement "Efficacy was assessed on the basis of outcomes in three variables..." should be modified to state "Efficacy was assessed on the basis of outcomes of a primary variable of percentage of patients free of full-symptom panic attacks on the Panic and Anticipatory Anxiety Scale (PAAS) and 2 key secondary variables of mean change from baseline to endpoint on the Panic Disorder Severity Scale (PDSS) total score and percentage of patients rated as responders (much improved or very much improved) on the Clinical Global Impressions (CGI) Improvement scale."
2. The statement "Relapse during the double-blind phase was defined..." should be modified to state "Relapse during the double-blind...due to loss of effectiveness as determined by the investigators during the study."
3. The statement "[redacted] should be modified to state "In the randomized phase following the 12-week open-label period, patients receiving continued venlafaxine ER experienced a significantly longer time to relapse." b(4)

Since studies 353 and 391 were considered failed, I do not object to omitting mention of these studies here. Since an active comparator was not included in these two studies, lack of assay sensitivity as the reason for the failed results cannot be ruled out.

INDICATIONS AND USAGE/Panic Disorder

This section has been added to describe the indication of panic disorder. The statement '[redacted] should be modified to state "The efficacy of Effexor XR in prolonging time to relapse in panic disorder following 12 weeks of open-label acute treatment was demonstrated in a relapse prevention study". b(4)

WARNINGS/Sustained Hypertension
This section has been modified to reflect updated short-term study data. The added information is accurate.

PRECAUTIONS/General/Insomnia and Nervousness
This section has been modified to reflect updated short-term study data. The added information is accurate.

PRECAUTIONS/General/Changes in Weight
This section has been modified to reflect updated short-term study data. The added information is accurate.

PRECAUTIONS/General/Changes in Appetite
This section has been modified to reflect updated short-term study data. The added information is accurate.

PRECAUTIONS/General/Activation of Mania/Hypomania
This section has been modified to reflect updated short-term study data. The added information is accurate.

PRECAUTIONS/General/Seizures
This section has been modified to reflect updated short-term study data. The added information is accurate.

PRECAUTIONS/General/Use in Patients with Concomitant Illness
This section has been modified to reflect updated short-term study data. The added information is accurate.

PRECAUTIONS/Geriatric Use
This section has been modified to reflect updated short-term study data. The added information is accurate.

ADVERSE REACTIONS

The trials in the short-term panic disorder study pool have been added.

ADVERSE REACTIONS/Adverse Findings Observed in Short-Term, Placebo-Controlled Studies with Effexor XR/Adverse Events Associated with Discontinuation of Treatment
This section has been modified to reflect updated short-term study data. The added information is accurate.

ADVERSE REACTIONS/Adverse Findings Observed in Short-Term, Placebo-Controlled Studies with Effexor XR/Adverse Events Occurring at an Incidence of 2% or More Among Effexor XR-Treated Patients
This section has been modified to reflect updated short-term study data. The added information is accurate.

ADVERSE REACTIONS/Adverse Findings Observed in Short-Term, Placebo-Controlled Studies with Effexor XR/Vital Sign Changes
This section has been modified to reflect updated short-term study data. The added information is accurate.

ADVERSE REACTIONS/Adverse Findings Observed in Short-Term, Placebo-Controlled Studies with Effexor XR/Laboratory Changes
This section has been modified to reflect updated short-term studydata. The added information is accurate.

ADVERSE REACTIONS/Other Adverse Events Observed During the Premarketing Evaluation of Effexor and Effexor XR
We have requested that the sponsor revise this information to include adverse events observed during study 354. The sponsor submitted revised labeling along with a table of adverse event incidence. However, the number of patients added to the dataset is inconsistent with the number of patients in the safety population of Study 354, and the sponsor's response to our request for clarification is still pending.

OVERDOSAGE/Human Experience
This section has been modified to reflect updated short-term study data and relapse prevention data (i.e., 12-week open label and 6 month double-blind data from the relapse prevention study). The added information is accurate.

DOSAGE AND ADMINISTRATION/Initial Treatment
A section for panic disorder has been added. The added information does not reflect the dosing regimen used for the studies in the sponsor's submission. In order to reflect the dosing regimen used in the studies, the paragraph under Panic Disorder should be modified to state:

> "It is recommended that initial single doses of 37.5 mg/day of Effexor XR be used for 7 days. In clinical trials establishing the efficacy of Effexor XR in outpatients with panic

disorder, initial doses of 37.5 mg/day for 7 days were followed by doses of 75 mg/day and subsequent weekly dose increases of 75 mg/day to a maximum dose of 225 mg/day. Although a dose-response relationship for effectiveness in patients with panic disorder was not clearly established in fixed-dose studies, certain patients not responding to 75 mg/day may benefit from dose increase 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 7 days. (See the Use in Patients with Concomitant Illness section of PRECAUTIONS.)"

DOSAGE AND ADMINISTRATION/Maintenance Treatment
This section has been modified to reflect updated relapse prevention data. The paragraph should be modified to state:

"In patients with panic disorder, one study in which patients responding during 12 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), patients continuing Effexor XR experienced a significantly longer time to relapse than patients randomized to placebo. The need for continuing medication in patients with panic disorder who improve with Effexor XR treatment should be periodically reassessed."

9.5 Comments to Applicant

See summary of requests to sponsor in section 1.1 of this review.

Michelle M. Chuen, M.D.
June 10, 2005

cc: NDA 20-699
HFD-120/Division File
HFD-120/MChuen
/GDubitsky
/TLaughren
/PAndreason
/PDavid
/RTaylor

10 APPENDICES

10.1 Review of Individual Study Reports

Study 398[24]

Investigators/Sites
Seventy investigators conducted this study at 71 sites in Europe.[25] Investigators and sites are listed in the Appendix 10.3.1 in Section 10.3 extracted from the sponsor's submission.

Objectives
By protocol, the objectives of this trial were to compare the efficacy, safety, and tolerability of venlafaxine ER capsules with placebo over 12 weeks in the treatment of outpatients with PD.

Patient Sample
Important inclusion criteria were:

- outpatients
- age ≥18 years
- history of DSM-IV panic disorder, with or without agoraphobia, for at least 3 months
- CGI severity of illness score ≥4
- ≥8 full panic attacks during the 4 week period prior to screening, ≥4 full panic attacks during the 2 week placebo lead-in
- Covi Anxiety Scale total score greater than the Raskin Depression Scale total score

The following were relevant exclusion criteria:

- treatment with venlafaxine or paroxetine within 3 months
- medical disease that might compromise the study or be detrimental to the patient
- pregnancy, lactation, or sexual activity without contraception
- use of herbal products intended for anxiety, insomnia, or depression within 14 days
- myocardial infarction within 6 months
- history or presence of a seizure disorder or clinically significant head trauma
- psychotic illness, bipolar affective disorder, or organic brain disease
- primary diagnosis of DSM-IV major depressive disorder or generalized anxiety disorder
- screening or baseline HAM-D score ≥18
- screening or baseline HAM-D item 1 score >2
- screening or baseline Raskin Depression Scale score>3 on any single item or baseline Raskin total score >9
- use of fluoxetine or antipsychotics within 30 days
- use of benzodiazepines ≥4 days a week within 14 days

[24] Note that important protocol changes are incorporated into my description of the protocol.
[25] There was one physician who was the principal investigator at two sites.

- other antidepressants, non-benzodiazepine anxiolytics, lithium, or sedative-hypnotics within 14 days
- cognitive behavioral therapy within 30 days or introduction or change in intensity of formal psychotherapy within 60 days
- ECT within 6 months
- history or presence of raised intraocular pressure or narrow angle glaucoma

Design
This was a multicenter, randomized, double-blind, parallel group comparison of two fixed doses of venlafaxine ER and one fixed dose of paroxetine with placebo. After a 14 ± 3 day placebo lead-in period, eligible patients were randomized to one of two doses of venlafaxine ER (75 or 150 mg/day), paroxetine 40 mg/day, or placebo for 12 weeks of treatment followed by a taper period of up to 14 days. Patients returned for a poststudy evaluation 4 to 10 days after taking the last dose of test article.

Study drug was administered with food once daily in the morning as identically-appearing capsules. Dosing was administered according to the schedule below:

TABLE 10.1.1: DOSING SCHEDULE

Study Interval	Ven ER 75mg	Ven ER 150mg	Paroxetine (mg/day)
Days 1-7	37.5	37.5	10
Days 8-14	75	75	20
Days 15-21	75	150	30
Days 22-84	75	150	40

Patients were permitted to take up to 10 mg of zaleplon or zolpidem at night up to 3 times per week for the first 14 days of the study.

Efficacy Assessments
The protocol-defined primary efficacy variable was full-symptom panic attack (attack with 4 or more symptoms) frequency from the PAAS (Panic and Anticipatory Anxiety Scale), which was extracted from the panic diary and assessed at baseline and on days 7, 14, 21, 28, 42, 56, 70, and 84.

The two key secondary variables were mean change from baseline in PDSS total score (measured at baseline and on days 14, 28, 42, 56, 70 and 84) and the response rate on the CGI-I subscale (measured at baseline and on days 7, 14, 21, 28, 42, 56, 70, and 84).

Efficacy Analysis
The intent-to-treat (ITT) patients were those who:

- had a baseline PAAS evaluation
- had at least one double-blind on-therapy evaluation (defined as a period ≥7 days of double-blind PAAS data) of the primary efficacy variable during visits 3 to 10 (i.e., weeks 1 to 12) and within 3 days of stopping nontaper test article

Of note, the protocol does not include "during visits 3 to 10" in its definition of the ITT population. In addition, the protocol states only that a "baseline evaluation" is necessary for inclusion in the ITT population.

The primary outcome measure was the percentage of patients free of full-symptom panic attacks at the end of the study period (final on-therapy observation). This variable was analyzed with categorical methods using a logistic regression model with treatment group and location as factor. If the treatment effect was significant, the treatment by location interaction term was explored, and tested at an alpha level of 0.10.

The first key secondary variable (total score on the PDSS) was analyzed using an ANCOVA model with treatment group and center as factors and baseline total score as a covariate. The second key efficacy variable (response rate on the CGI-I subscale defined as a score of 1 or 2) was analyzed using the Fisher's exact test.

Comparisons for the primary efficacy variable will be with each venlafaxine ER treatment group versus placebo. The Hochberg[26] step-up method was used to control the overall error rate of 0.05. By this method, the p-values corresponding to the hypotheses of primary interest are ordered from largest to smallest ($p_1 \geq p_2$). The larger is then compared to the nominal alpha level (0.05) and, if it is smaller than alpha, both doses are considered efficacious. If the largest is not smaller than alpha, then the next largest is compared to alpha/2 (0.025). If it is smaller than alpha/2, then it is considered efficacious.[27]

A sequential testing strategy with a pre-specified order of testing was used to control for multiplicity in the primary and two key secondary efficacy variables. This was applied separately for each dose of venlafaxine compared to placebo. If the comparison of venlafaxine vs. placebo was significant at the α=0.05 level for the primary efficacy variable, then the subsequent pairwise comparison for the first of the two key secondary efficacy variables (total score from PDSS) was be made and was declared significant if p-value ≤ 0.05. The second of the two key secondary efficacy variables (response rate on the CGI-I scale) was considered significant if both of the previous comparisons were significant and p-value ≤ 0.05.

For the PAAS, in each two week (14 day) analysis period, if more than 50% of PAAS data (8 days or more) are missing, the evaluation was considered missing for this two week period. For the PDSS, if more than 50% of the items are missing, then the total score was not used in the

[26] Hochberg, Y. A sharper Bonferroni procedure for multiple tests of significance. Biometrika 1988; 75: 800-802.
[27] Note that the description of the Hochberg method was not included in the sponsor's submission.

analysis. If less than or equal to 50% of the items are missing, then the average of the available items was multiplied by the total number of items to get an inferred score.

Baseline Demographics
The table below displays the demographic characteristics of the ITT patient sample by treatment group. No patient under age 18 or over age 70 participated in this study. There were no major differences between the 4 treatment groups with respect to age, gender, or race. Of note, the vast majority of patients were white.

TABLE 10.1.2 : STUDY 398[28]
BASELINE DEMOGRAPHICS, ITT POPULATION

TX (n)	Age (yrs)		Sex (%)		Race (%)	
	Mean	Range	Male	Female	White	Arabic
Ven ER 75 mg (158)	36.2	19-70	34	66	100	0
Ven ER 150 mg (159)	37.7	18-70	30	70	100	0
Paroxetine (161)	37.6	19-69	35	64	100	0
Placebo (156)	37.7	18-69	31	69	99	1

Baseline Severity of Illness
Treatment groups had no major differences with respect to mean baseline full-symptom panic attacks from PAAS (mean scores of 9.1 in placebo patients, 11.0 in venlafaxine ER 75 mg patients, 11.4 in venlafaxine ER 150 mg patients, and 11.5 in paroxetine patients).

Patient Disposition
A total of 664 patients were included in the database. One of these patients returned the study drug unused and thus had no data. An additional 29 patients who did not have a primary efficacy evaluation during the double-blind period were not included in the ITT population. The ITT population included 634 patients (156 placebo patients, 158 ven ER 75 mg patients, 159 ven ER 150 mg patients, and 161 paroxetine patients).

The numbers of ITT patients in-study over time are displayed in Appendix 10.3.2 in Section 10.3. At week 12, 85% (134/158) of venlafaxine ER 75 mg patients, 84% (133/159) of venlafaxine ER 150 mg patients, and 77% (120/156) of placebo patients completed the study. Based on the safety population, overall dropout rates were roughly comparable [19% (32/166) of venlafaxine ER 75 mg patients, 21% (35/168) of venlafaxine ER 150 mg patients, and 25% (41/163) of placebo patients]. Based on the safety population, dropout rates due to lack of

[28] Figures may not add up to 100% due to rounding.

efficacy were also roughly comparable [7% (4/166) of venlafaxine ER 75 mg patients, 2% (4/168) of venlafaxine 150 mg patients, and 9% (14/163) of placebo patients].

Dosing Information
This was a fixed dose study.

Concomitant Medications
Up to 10 mg of zaleplon or zolpidem, ≤3 times per week, was permitted at bedtime through study day 14. Nonpsychopharmacologic drugs with psychotropic effects were permitted only if the patient had been receiving a stable dose of the drug for at least 3 months before study day 1 and was expected to continue taking the drug without dose changes. Other psychopharmacologic drugs and ECT were prohibited. Formal psychotherapy (other than cognitive behavioral therapy) was permitted if it was not introduced or changed in intensity within 60 days of study day 1.

With respect to the percentages of double blind safety population patients[29] using various concomitant medications during the study, there were no major differences between treatment groups (64% in placebo patients, 64% in ven ER 75 mg patients, 59% in ven ER 150 mg patients, and 63% in paroxetine patients), and the most frequently used were analgesics and antipyretics, and nonsteroidal anti-inflammatory/antirheumatic products. Based on the safety population, there were 6/163 (4%) patients in the placebo group, 1/166 (1%) patient in the venlafaxine ER 75 mg group, and 3/168 (2%) patients in the venlafaxine ER 150 mg group identified as protocol violators because of prohibited medication use.

Efficacy Results
Efficacy data displays may be found in the Appendices 10.3.2 to 10.3.5 in Section 10.3.

For the percentage of patients free of full-symptom panic attack analysis, the differences were statistically significant in favor of venlafaxine ER at final on-therapy assessment for both doses. The OC analysis was consistent with the LOCF analysis.

For the mean change from baseline in PDSS total score, the differences between adjusted mean change from baseline were statistically significant in favor of venlafaxine ER from week 6 onward. The OC analysis was consistent with the LOCF analysis.

Response rate on the CGI-I subscale was also significantly greater in the venlafaxine ER groups from week 6 onward. The OC analysis was consistent with the LOCF analysis.

There was no evidence of a center-by-therapy interaction in this trial according to a May 25, 2005 email from the statistician, Ohidul Siddiqui.

Conclusions
The results of study 398 provide adequate evidence of the anti-panic efficacy of venlafaxine ER in doses of 75 mg and 150 mg/day versus placebo over 12 weeks of treatment.

[29] This information was not provided for the ITT population.

Study 399[30]

Investigators/Sites
Thirty-nine investigators conducted this study at 39 sites in Latin America. Investigators and sites are listed in Appendix 10.3.6 extracted from the sponsor's submission.

Objectives
By protocol, the objective of this trial was to determine the efficacy, safety, and tolerability of venlafaxine ER versus placebo in the treatment of adult outpatients with panic disorder.

Patient Sample
Important inclusion criteria were:

- outpatients
- age ≥18 years
- history of DSM-IV panic disorder, with or without agoraphobia, for at least 3 months
- CGI severity of illness score ≥4
- ≥8 full panic attacks during the 4 week period prior to screening, ≥4 full panic attacks during the 2 week placebo lead-in
- Covi Anxiety Scale total score greater than the Raskin Depression Scale total score

The following were relevant exclusion criteria:

- treatment with venlafaxine or paroxetine within 6 months
- medical disease that might compromise the study or be detrimental to the patient
- pregnancy, lactation, or sexual activity without contraception
- use of herbal products intended for anxiety, insomnia, or depression within 14 days
- myocardial infarction within 6 months
- history or presence of a seizure disorder or clinically significant head trauma
- psychotic illness, bipolar affective disorder, or organic brain disease
- primary diagnosis of DSM-IV major depressive disorder or generalized anxiety disorder
- screening or baseline HAM-D score ≥18
- screening or baseline HAM-D item 1 score >2
- screening or baseline Raskin Depression Scale score>3 on any single item or baseline Raskin total score >9
- use of fluoxetine or antipsychotics within 30 days
- use of benzodiazepines ≥4 days a week within 14 days
- other antidepressants, non-benzodiazepine anxiolytics, lithium, or sedative-hypnotics within 14 days
- cognitive behavioral therapy within 30 days or introduction or change in intensity of formal psychotherapy within 60 days
- ECT within 6 months
- history or presence of raised intraocular pressure or narrow angle glaucoma

[30] Note that important protocol changes are incorporated into my description of the protocol.

Design
This was a multicenter, randomized, double-blind, placebo- and paroxetine-controlled, parallel group fixed dose study. After a 14 ± 3 day placebo lead-in period, eligible patients were randomized to venlafaxine ER (75mg or 225mg treatment groups), paroxetine, or placebo for 12 weeks of treatment. This was followed by a taper period of up to 14 days. Patients returned for a post-study evaluation 4-10 days after taking the last dose of study drug.

Study drug was administered as identical-appearing capsules once in the morning with food. Venlafaxine ER was supplied as 37.5 and 75mg capsules and paroxetine as 10 and 20mg capsules. The dosing schedule for the active drug groups is depicted in Table 10.1.3 below.

TABLE 10.1.3: DOSING SCHEDULE

Study Days	Treatment Group		
	Ven 75	Ven 225	Paroxetine
1-7	37.5mg	37.5mg	10mg
8-14	75mg	75mg	20mg
15-21	75mg	150mg	30mg
22-84	75mg	225mg	40mg

Efficacy Assessments
The protocol-defined primary efficacy variable was full-symptom panic attack (attack with 4 or more symptoms) frequency from the PAAS (Panic and Anticipatory Anxiety Scale), which was extracted from the panic diary and assessed at baseline and on days 7, 14, 21, 28, 42, 56, 70, and 84.

The two key secondary variables were PDSS total score (measured at baseline and on days 14, 28, 42, 56, 70, and 84weeks) and the response rate on the CGI-I subscale (measured on days 7, 14, 21, 28, 42, 56, 70, and 84).

Efficacy Analysis
The intent-to-treat (ITT) patients were those who:

- had a baseline evaluation
- had at least one double-blind on-therapy evaluation (defined as a period ≥7 days of double-blind PAAS data) of the primary efficacy variable within 3 days of stopping nontaper test article
- took at least one dose of study medication

Of note, the last criterion for inclusion in the ITT population ("took at least one dose of study medication") was not included in the protocol.

The primary outcome measure was the percentage of patients free of full-symptom panic attacks at the end of the study period (final on-therapy observation). This variable was analyzed with categorical methods using a logistic regression model with treatment group and country as factors and baseline severity as covariate. Severity was determined by a dichotomization of the median number of full-symptom panic attacks at baseline from all patients in the analysis. Patients with a baseline full-symptom panic attack frequency that was greater than or equal to the median number of full-symptom panic attacks for all patients in the analysis were considered as a more severe group relative to those patients who were below the median. If the treatment effect was significant, the treatment by country interaction term was explored, and tested at the alpha level of 0.10.

The first key secondary variable (total score on the PDSS) was analyzed using an ANCOVA model with treatment group and country as factors and baseline total score as covariate. The second key efficacy variable (response rate on the CGI-I scale) was analyzed using the Fishers exact test.

Comparisons for the primary efficacy variable will be with each venlafaxine ER treatment group versus placebo. The Hochberg[31] step-up method was used to control the overall error rate of 0.05. By this method, the p-values corresponding to the hypotheses of primary interest are ordered from largest to smallest ($p_1 \geq p_2$). The larger is then compared to the nominal alpha level (0.05) and, if it is smaller than alpha, both doses are considered efficacious. If the larger is not smaller than alpha, then the next largest is compared to alpha/2 (0.025). If it is smaller than alpha/2, then it is considered efficacious.[32]

A sequential testing strategy with a pre-specified order of testing was used to control for multiplicity in the primary and two key secondary efficacy variables. This was applied separately for each dose of venlafaxine compared to placebo. If the comparison of venlafaxine vs. placebo was significant at the α=0.05 level for the primary efficacy variable, then the subsequent pairwise comparison for the first of the two key secondary efficacy variables (total score from PDSS) was made and was declared significant if p-value ≤ 0.05. The second of the two key secondary efficacy variables (response rate on the CGI-I scale) was only considered significant if both of the previous comparisons were significant and p-value ≤ 0.05.

For the PAAS, in each two week (14 day) analysis period, if more than 50% of PAAS data (8 days or more) are missing, the evaluation was considered missing for this two week period. For the PDSS, if more than 50% of the items are missing, then the total score was not used in the analysis. If less than or equal to 50% of the items are missing, then the average of the available items was multiplied by the total number of items to get an inferred score.

[31] Hochberg, Y. A sharper Bonferroni procedure for multiple tests of significance. Biometrika 1988; 75: 800-802.
[32] Note that the description of the Hochberg method was not included in the sponsor's submission.

Baseline Demographics
Table 10.1.4 displays the demographic characteristics of the ITT patient sample by treatment group. No patient under age 18 or over age 72 participated in this study. There were no major differences between the 4 treatment groups with respect to age, gender, or race.

TABLE 10.1.4 : STUDY 399[33]
BASELINE DEMOGRAPHICS, ITT POPULATION

TX (n)	Age (yrs)		Sex (%)		Race (%)			
	Mean	Range	Male	Female	White	Hispanic	Black	Native American
Ven ER 75 mg (156)	35.8	19-66	35	65	47	51	1	1
Ven ER 225 mg (160)	37.1	18-72	33	68	47	53	0	0
Paroxetine (151)	37.5	18-72	33	68	54	46	0	0
Placebo (157)	35.1	19-60	31	69	52	48	0	0

Baseline Severity of Illness
Treatment groups had no major differences with respect to mean baseline full-symptom panic attacks from PAAS (mean scores of 11.1 in placebo patients, 15.7 in venlafaxine ER 75 mg patients, 12.1 in venlafaxine ER 150 mg patients, and 14.9 in paroxetine patients).

Patient Disposition
A total of 653 patients were included in the database. Four of these patients had no data. Study drug was dispensed to 3 of these 4 patients who returned the medication unused, and study drug was not dispensed to the one other patient. An additional 25 patients who did not have primary efficacy evaluation during the double-blind period were not included in the ITT population. The ITT population included 624 patients (157 placebo patients, 156 ven ER 75 mg patients, 160 ven ER 150 mg patients, and 151 paroxetine patients).

The numbers of ITT patients in-study over time are displayed in Appendix 10.3.7 in Section 10.3. At week 12, 87% (135/156) of venlafaxine ER 75 mg patients, 87% (139/160) of venlafaxine ER 225 mg patients, and 76% (119/157) of placebo patients completed the study. Based on the safety population, overall dropout rates were slightly higher in the placebo group [15% (24/160) of venlafaxine ER 75 mg patients, 17% (29/166) of venlafaxine ER 225 mg patients, and 27% (43/162) of placebo patients]. Based on the safety population, dropout rates due to lack of efficacy were also higher in the placebo group [5% (8/160) of venlafaxine ER 75 mg patients, 6% (10/166) of venlafaxine ER 225 mg patients, and 12% (19/162) of placebo patients].

[33] Figures may not add up to 100% due to rounding.

Dosing Information
This was a fixed dose study.

Concomitant Medications
Up to 10 mg of zaleplon or zolpidem, ≤3 times per week, was permitted at bedtime through study day 14. Other psychopharmacologic drugs and ECT were prohibited. Nonpsychopharmacologic drugs with psychotropic effects were permitted only if the patient had been receiving a stable dose of the drug for at least 3 months before study day 1 and was expected to continue taking the drug without dose changes. Formal psychotherapy (other than cognitive behavioral therapy) was permitted if it was not introduced or changed in intensity within 60 days of study day 1.

With respect to the percentages of double blind safety population patients[34] using various concomitant medications during the study, there were no major differences between treatment groups (56% in placebo patients, 58% in ven ER 75 mg patients, 50% in ven ER 225 mg patients, and 45% in paroxetine patients), and the most frequently used were analgesics and antipyretics. Based on the safety population, there were 3/162 (2%) patients in the placebo group, 4/143 (3%) patients in the ven ER 75 mg group, and 3/153 (2%) patients in the ven ER 225 mg group identified as protocol violators because of prohibited medication use.

Efficacy Results
Efficacy data displays may be found in the Appendices 10.3.7 to 10.3.10.

For the percentage of patients free of full-symptom panic attack analysis, the differences were statistically significant in favor of venlafaxine ER at final on-therapy assessment for both doses. The OC analysis was consistent with the LOCF analysis except at the last visit where there was merely a trend for superiority of the low dose over placebo.

For the mean change from baseline in PDSS total score, the differences between adjusted mean change from baseline were statistically significant in favor of venlafaxine ER from week 4 onward for the 75 mg dose group and from week 2 onward for the 225 mg dose group. The OC analysis was consistent with the LOCF analysis.
Response rate on the CGI-I subscale was significantly greater in the venlafaxine ER groups from week 3 onward. The OC analysis was consistent with the LOCF analysis.

There was no evidence of a center-by-therapy interaction in this trial according to a May 25, 2005 email from the statistician, Ohidul Siddiqui.

Conclusions
The results of study 399 provide adequate evidence of the efficacy of venlafaxine ER in doses of 75 and 225 mg/day versus placebo over 12 weeks of treatment.

[34] This information was not provided for the ITT population.

Study 353[35]

Investigators/Sites
This study was conducted at 56 sites in the U.S. and Canada by 55 investigators. Investigators and sites are listed in Appendix 10.3.11.[36]

Objectives
By protocol, the objective of this trial was to determine the efficacy, safety, and tolerability of a flexible dose of venlafaxine ER capsules over 10 weeks in the treatment of adult outpatients with panic disorder (PD).

Patient Sample
Important inclusion criteria were:

- Outpatients
- Age ≥18 years
- Meeting DSM-IV criteria for PD with sufficient symptoms to require anxiolytic therapy, a minimum of 8 full-symptom panic attacks during the 4 weeks before screening, and a minimum of 4 full-symptom panic attacks during the 14±3 day placebo lead-in period
- Minimum CGI severity of illness item score of 4
- Covi Anxiety Scale total score greater than the Raskin Depression Scale total score.

Relevant exclusion criteria were:

- Treatment with venlafaxine or ECT within 6 months
- Use of any herbal products intended to treat anxiety, insomnia, or depression, regular use of benzodiazepines, or use of psychopharmacologic drugs (except zaleplon) within 14 days
- Use of triptans or fluoxetine within 30 days
- DSM-IV diagnosis of MDD or GAD that is considered by the investigator as being primary
- Other clinically significant Axis I or Axis II disorder within 6 months
- Drug or alcohol dependence or abuse within 1 year of study day 1
- Regular use of alcohol exceeding 24 ounces of beer/day or the equivalent
- Cognitive behavioral therapy within 30 days
- Introduction or change in intensity of formal psychotherapy within 60 days
- HAM-D total score ≥ 18
- HAM-D item 1 score > 2
- Raskin Depression Scale score > 3 on any single item or total score > 9

[35] Note that important protocol changes are incorporated into my description of the protocol.
[36] Not included in the table are investigators who did not enroll any subjects: Stephen Roger Dager, M.D., Marc Hertzman, M.D., Lawson R. Wulsin, M.D., Susan Eder, M.D., and Louis C. Kirby, II, M.D.

Design
This was a randomized, double-blind, placebo-controlled, parallel-group flexible dose study. After a 14±3 day placebo lead-in period, eligible patients were randomized to treatment with venlafaxine ER or placebo for up to 10 weeks of therapy followed by a taper period of up to 14 days. Patients returned for a poststudy evaluation 4 to 10 days after taking the last dose of test article.

Study medication was to be taken once daily in the morning as identically-appearing capsules. Dosing was flexible and administered according to the schedule shown below:

Days	Venlafaxine ER (mg/day)
1-4	37.5
5-14	75
15-21	75 or 150
22-70	75 or 150 or 225
Taper Week 1	0 or 75 or 150
Taper Week 2	0 or 75

Efficacy Assessments
The protocol-defined primary efficacy variable was full-symptom panic attack frequency from the PAAS (Panic and Anticipatory Anxiety Scale), which was extracted from the panic diary and assessed at baseline and on days 7, 14, 21, 28, 42, 56, and 70. The two key secondary variables were the PDSS (Panic Disorder Severity Scale) total score (assessed at baseline and on days 14, 28, 42, 56, and 70) and the CGI-I score (assessed on days 7, 14, 21, 28, 42, 56, and 70).

Efficacy Analysis
The efficacy intent-to-treat (ITT) patients were those who:

- had a baseline evaluation
- had at least one double-blind on-therapy evaluation (defined as a period ≥7 days of double-blind PAAS data) of the primary efficacy variable and within 3 days of stopping nontaper test article

The primary outcome measure was the percentage of patients free of full-symptom panic attacks at the end of the study period (final on-therapy observation). This variable was analyzed with categorical methods using logistic regression model with treatment group and site as factors. If the treatment effect was significant, the treatment by site interaction term was explored, and tested at the alpha level of 0.10. Sites were pooled prior to unblinding to form centers with a minimum of 8 patients at week 10 per center. This method was employed to allow for inclusion of center in the statistical model as a factor, which replaced the investigator site in all statistical models which consider site as one of the effects.

The first key secondary variable, PDSS total score, was analyzed using an analysis of covariance model (ANCOVA) with treatment group and site as factors and baseline total score as a covariate. The second key secondary variable (response rate on the CGI-I subscale defined as a score of 1 or 2) was analyzed using the Fisher's exact test.

A sequential testing strategy with a pre-specified order of testing, was used to control for the two key secondary efficacy variables. If the comparison of venlafaxine ER vs. placebo was significant at the α=0.05 level for the primary efficacy variable, then the subsequent pairwise comparison for the first of the two key secondary efficacy variables (total score from PDSS) was made and was declared significant if p-value ≤ 0.05. The second of the two key secondary efficacy variables (response rate on the CGI-I scale) was only considered significant if both of the previous comparisons were significant and p value ≤ 0.05.

For the PAAS, in each two week (14 day) analysis period, if more than 50% of PAAS data (8 days or more) are missing, the evaluation was considered missing for this two week period. For the PDSS, if more than 50% of the items are missing, then the total score was not used in the analysis. If less than or equal to 50% of the items are missing, then the average of the available items was multiplied by the total number of items to get an inferred score.

Baseline Demographics
Table 10.1.5 below displays the demographic characteristics of the ITT patient sample by treatment group. No patient under age 18 or over age 71 participated in this study. There were no major differences between the two treatment groups with respect to age, gender, or race except for a slightly higher percentage of males in the placebo group compared to the drug group.

TABLE 10.1.5: STUDY 353[37]
BASELINE DEMOGRAPHICS, ITT POPULATION

TX	Age (yrs)		Sex (%)		Race (%)			
(n)	Mean	Range	Male	Female	White	Hispanic	Black	Other
Ven ER (155)	36.0	18-71	28	72	68	16	12	4
Placebo (155)	36.7	18-69	41	59	66	21	10	3

Baseline Severity of Illness
Treatment groups had no major differences with respect to mean baseline full-symptom panic attacks from PAAS (mean scores of 13.3 in venlafaxine ER patients and 12.1 in placebo patients).

Patient Disposition
A total of 343 patients were randomized in this study. Twenty of these patients had no data after baseline. Another 13 were excluded from the ITT dataset because they did not have at least 7 days of on-therapy PAAS data. Thus, 310 patients comprised the ITT sample (155 ven ER and 155 placebo patients).

The numbers of ITT patients in-study over time are displayed in Appendix 10.3.12 in Section 10.3. At week 10, 71% (110/155) of venlafaxine ER patients and 74% (115/155) of placebo

[37] Figures may not add up to 100% due to rounding.

patients completed the study. Based on the safety population, overall dropout rates were roughly comparable [34% (55/164) of venlafaxine ER patients and 27% (27/159) of placebo patients]. Based on the safety population, dropout rates due to lack of efficacy [5% (8/164) of venlafaxine ER patients and 6% (9/159) of placebo patients] were almost equal.

Dosing Information
Dosing information is displayed in the following table.

TABLE 10.1.6: MEAN DAILY DOSE OF VENLAFAXINE ER FOR PATIENTS BY TIME INTERVAL DURING THE DOUBLE-BLIND PERIOD

Time Interval on Therapy[a] (Days)	n	Daily Dose[b] Mean±SD (mg)
1-7	164	52.3±4.9
8-14	155	76.1±6.5
15-21	142	125.6±33.8
22-28	136	169.6±48.3
29-42	127	183.2±48.8
43-56	121	188.8±47.7
57-70	110	188.3±49.1
>70	36	194.4±47.9

a: On-therapy period includes the double-blind period, excluding taper doses.
b: Mean daily dose including days of missed dose.
Data from CDR 4-2 (21 Feb 2003).

Concomitant Medications
Up to 10 mg of zaleplon, ≤3 times per week, was permitted at bedtime through study day 14. Nonpsychopharmacologic drugs with psychotropic effects were permitted only if the patient had been receiving a stable dose of the drug for at least 3 months before study day 1 and was expected to continue taking the drug without dose changes. Other psychopharmacologic drugs and ECT were prohibited.

With respect to the percentages of double blind safety population patients[38] using various concomitant medications during the study, there were no major differences between treatment groups (81% in placebo patients and 79% in ven ER patients), and the most frequently used were nonsteroidal anti-inflammatory/antirheumatic products and other analgesics and antipyretics. Based on the safety population there were 4/159 (2%) patients in the placebo group and 4/164 (2%) patients in the venlafaxine ER group identified as protocol violators because of prohibited medication use.

Efficacy Results
Efficacy data displays may be found in Appendices 10.3.12 to 10.3.14 in Section 10.3.

For the percentage of patients free of full-symptom panic attack analysis, the differences were not statistically significant in the LOCF analysis. The OC analysis was consistent with the

38 This information was not provided for the ITT population.

LOCF analysis up to day 43, with neither analysis showing drug superiority up to that point. After day 43, the differences were in favor of venlafaxine ER only in the OC analysis.

For the PDSS total score, the differences between adjusted mean change from baseline were statistically significant in favor of venlafaxine ER from week 4 onward. The OC analysis was consistent with the LOCF analysis.

Response rate on the CGI-I subscale was also significantly greater in the venlafaxine ER groups from week 4 onward. The OC analysis was consistent with the LOCF analysis, except at week 8 when the difference was not significant for the OC analysis.

There was no evidence of a center-by-therapy interaction in this trial according to a May 25, 2005 email from the statistician, Ohidul Siddiqui.

Conclusions
The results of study 353 do not provide adequate evidence of the anti-panic efficacy of venlafaxine ER versus placebo over 10 weeks of treatment. The positive OC analysis is not persuasive since it excludes dropouts, thus potentially biasing the study results in favor of drug.

Study 391[39]

Investigators/Sites
Fifty investigators conducted this study at 50 sites in Canada and Europe. Investigators and sites are listed in Appendix 10.3.15 extracted from the sponsor's submission.

Objectives
By protocol, the objective of this trial was to determine the anxiolytic efficacy, safety, and tolerability of a flexible dose of venlafaxine ER capsules administered for 10 weeks in the treatment of adult outpatients with PD in a placebo-controlled phase III study.

Patient Sample
Important inclusion criteria were:

- outpatients
- age ≥18 years
- DSM-IV-defined panic disorder, with or without agoraphobia, for at least 6 months
- symptoms require anxiolytic drug therapy
- CGI severity of illness score ≥4
- ≥4 full panic attacks during the 4 week period prior to prestudy visit, ≥2 full panic attacks during the 2 week placebo lead-in
- Covi Anxiety Scale total score greater than the Raskin Depression Scale total score

[39] Note that important protocol changes are incorporated into my description of the protocol.

The following were relevant exclusion criteria:

- treatment with venlafaxine within 6 months
- medical disease that might compromise the study or be detrimental to the patient
- pregnancy, lactation, or plans to become pregnant
- use of herbal products intended for anxiety or depression within 14 days
- myocardial infarction within 6 months
- history or presence of a seizure disorder or clinically significant head trauma
- psychotic illness, bipolar affective disorder, or organic brain disease
- primary diagnosis of DSM-IV major depressive disorder, generalized anxiety disorder, or any other clinically important Axis I or Axis II disorder, current or predominant within 6 months of study day 1
- prestudy HAM-D score ≥15
- prestudy HAM-D item 1 score >2
- screening or baseline Raskin Depression Scale score>3 on any single item or Raskin total score >9
- use of fluoxetine or antipsychotics within 30 days
- regular use of benzodiazepines, sumatriptan, naratriptan, zolmitriptan, or drugs for migraine treatment with a similar mechanism of action within 30 days
- other antidepressants, lithium, stimulants, or sedative-hypnotics within 14 days
- formal psychotherapy or cognitive behavioral therapy within 30 days
- ECT within 6 months
- history or presence of raised intraocular pressure or narrow angle glaucoma

Design

This was a multi-center, randomized, double-blind, placebo-controlled, parallel-group flexible dose study. After a 14±3 day placebo lead-in period, eligible patients were randomized to treatment with venlafaxine ER or placebo for up to 10 weeks of therapy followed by a taper period of up to 14 days. Patients returned for a poststudy evaluation 4 to 10 days after taking the last dose of test article.

Study medication was to be taken once daily in the morning as identically-appearing capsules. Dosing was flexible and administered according to the schedule shown below:

Days	Venlafaxine ER (mg/day)
1-5	37.5
5-14	75
15-21	75 or 150
22-70	75 or 150 or 225
Taper Week 1	0 or 75 or 150
Taper Week 2	0 or 75

Efficacy Assessments

The protocol-defined primary efficacy variable scale was the PAAS (Panic and Anticipatory Anxiety Scale), which was assessed at baseline and on days 7, 14, 21, 28, 42, 56, and 70. There were no key secondary variables identified.

Efficacy Analysis
The efficacy intent-to-treat (ITT) patients were those who:

- had a baseline evaluation
- had at least one double-blind on-therapy evaluation (defined as a period ≥7 days of double-blind PAAS data) of the primary efficacy variable during visits 3 to 9 (weeks 1 to 10) and within 3 days of stopping nontaper test article

The primary outcome measure was the percentage of patients free of full-symptom panic attacks at the end of the study period (final on-therapy observation). This variable was analyzed with categorical methods (logistic regression) with treatment group and site as factors. Due to the large number of sites in this study, sites with 5 or less patients will be combined to allow for the inclusion of site in the model as a factor.

For the PAAS, in each two week (14 day) analysis period, if more than 50% of PAAS data (8 days or more) are missing, the evaluation was considered missing for this two week period.

Baseline Demographics
Table 10.1.7 below displays the demographic characteristics of the ITT patient sample by treatment group. No patient under age 18 or over age 84 participated in this study. There were no major differences between the two treatment groups with respect to age, gender, or race.

TABLE 10.1.7 : STUDY 391[40]
BASELINE DEMOGRAPHICS, ITT POPULATION

TX	Age (yrs)		Sex (%)		Race (%)			
(n)	Mean	Range	Male	Female	White	Black	Asian	Other
Ven ER (167)	39.5	18-84	39	61	98	1	1	0
Placebo (176)	39.5	18-74	41	59	98	2	0	1

Baseline Severity of Illness
Treatment groups had no major differences with respect to mean baseline full-symptom panic attacks from PAAS (mean scores of 12.4 in venlafaxine ER patients and 11.1 in placebo patients).

[40] Figures may not add up to 100% due to rounding.

Patient Disposition

A total of 361 patients were randomized in this study. Six of these patients had no data after baseline. Another 12 were excluded from the ITT dataset because they had some efficacy data but did not have a primary efficacy evaluation on therapy. Thus, 343 patients comprised the ITT sample (167 ven ER and 176 placebo patients). Of note, efficacy data from site 39127 were excluded from the ITT efficacy analyses in the body of the report due to poor compliance with Good Clinical Practices, which the sponsor states was discovered during monitoring visits. This review utilizes efficacy data for the entire ITT population contained in the supplemental documentation.

The numbers of ITT patients in-study over time are displayed in Appendix 10.3.16 in Section 10.3. At week 10, 82% (137/167) of venlafaxine ER patients and 80% (141/176) of placebo patients completed the study. Based on the safety population, overall dropout rates were comparable [23% (40/177) of venlafaxine ER patients and 23% (41/178) of placebo patients]. Based on the safety population, dropout rates due to lack of efficacy were roughly comparable [5% (8/177) of venlafaxine ER patients and 10% (17/178) of placebo patients].

Dosing Information

Dosing information is displayed in the following table.

TABLE 10.1.8: NUMBER OF PATIENTS WHO RECEIVED VENLAFAXINE ER ACCORDING TO MEAN DAILY DOSE FOR EACH TIME PERIOD OF EXPOSURE IN DOUBLE-BLIND PERIOD

Treatment	Venlafaxine ER Mean Daily Dose,[b] mg (n=177)			
Days on Therapy[a]	0-50	>50-100	>100-200	Total
>0	11	52	114	177
>7	2	50	114	166
>14	0	42	114	156
>21	0	39	114	153
>28	0	37	112	149
>42	0	37	108	145
>56	0	34	106	140
>70	0	22	51	73

a: On-therapy period is double-blind period, excludes taper dose.
b: Mean daily dose including days of missed dose.
Data from CDR 4-2A (25 Jul 2002).

Concomitant Medications

Nonpsychopharmacologic drugs with psychotropic effects were permitted only if the patient had been receiving a stable dose of the drug for at least 3 months before study day 1. Psychopharmacologic drugs, introduction or change in intensity of formal psychotherapy (regularly scheduled sessions employing specific techniques), cognitive behavioral therapy, and ECT were prohibited.

With respect to the percentages of double blind safety population patients[41] using various concomitant medications during the study, there were no major differences between treatment groups (76% in placebo patients and 76% in ven ER patients), and the most frequently used were nonsteroidal anti-inflammatory/antirheumatic products and other analgesics and antipyretics. There were 6 patients in the placebo group and 14 patients in the venlafaxine ER group identified as protocol violators because of prohibited medication use.

Efficacy Results
Efficacy data displays may be found in Appendices 10.3.16 to 10.3.17.

For the percentage of patients free of full-symptom panic attack analysis, the differences were not statistically significant in the LOCF analysis. The OC analysis was consistent with the LOCF analysis .

There was no evidence of a center-by-therapy interaction in this trial according to a May 25, 2005 email from the statistician, Ohidul Siddiqui.

Conclusions
The results of study 353 do not provide adequate evidence of the anti-panic efficacy of venlafaxine ER versus placebo over 10 weeks of treatment.

Study 354[42]

Investigators/Sites
Fifty-two investigators conducted this study at 52 sites in Australia, Canada, Europe, and the U.S. Investigators and sites are listed in Appendix 10.3.18 extracted from the sponsor's submission.

Objectives
The primary objective is to compare the long-term safety and efficacy of venlafaxine ER to placebo in the prevention of relapse in outpatients with panic disorder (PD).

Patient Sample
Important inclusion criteria were:

- Outpatients
- Age ≥18 years
- Meeting DSM-IV criteria for PD with sufficient symptoms to require anxiolytic therapy, a minimum of 6 full-symptom panic attacks during the 2 weeks before screening, and a minimum of 3 full-symptom panic attacks per week for the 2 weeks prior to baseline
- Minimum CGI severity of illness item score of 4
- Covi Anxiety Scale total score greater than the Raskin Depression Scale total score

41 This information was not provided for the ITT population.
42 Note that important protocol changes are incorporated into my description of the protocol.

Relevant exclusion criteria were:

- DSM-IV major depressive disorder, or generalized anxiety disorder that is considered primary (i.e., causing a higher degree of distress or impairment than panic disorder); patients with secondary depression or GAD will be considered
- clinically significant Axis I or Axis II disorder current or predominant within 6 months of the study other than panic disorder
- screening or baseline MADRS score >22
- herbal products intended for anxiety, insomnia, or depression within 14 days of the study
- fluoxetine, antipsychotics, or specified migraine treatments within 30 days of the study
- other antidepressants within 14 days of the trial
- anxiolytics and benzodiazepines within 7 days of the trial
- cognitive behavioral therapy within 30 days or the introduction or change in intensity of formal psychotherapy within 60 days of the study
- history or presence of clinically important medical disease

Design

This study consisted of four phases:

1) 14 day (± 3 days) baseline period
2) 12 week open label treatment period
3) 6 month randomized, double-blind, placebo-controlled treatment period
4) taper phase

Eligible patients entered open label treatment. During the open label phase, venlafaxine ER was administered according to the following schedule:

Week #	Total Daily Dose
1	37.5mg
2	75mg
3	75 or 150mg
4-12	75, 150, or 225mg

All study medication was taken once daily in the morning. After the first two weeks, the dose was increased only if clinically necessary. Dose changes were not to occur after week 8 (day 56).

To enter the double-blind portion of the study, patients must have completed the 12 week open label treatment phase with no significant ongoing adverse events and meet criteria for response, i.e., at most one full-symptom panic attack per week during the last two weeks of open label treatment and a CGI-I score of 1 or 2 compared to the assessment of open-label baseline. Patients eligible for double-blind therapy were randomized to either continue venlafaxine ER or be switched to placebo for up to an additional 6 months. Those who received open label venlafaxine ER 150 or 225 mg/day and were randomized to placebo were tapered over the first 7 or 14 days, respectively, of the double-blind period.

At the completion of double-blind treatment or upon withdrawal from the study, patients receiving venlafaxine ER 150 or 225 mg/day were tapered by 75 mg/day per week during a taper period of 2 weeks.

Efficacy Assessments
The primary efficacy endpoint was the time to relapse for patients who entered the double-blind maintenance phase of the study. The time to relapse was based on panic frequency extracted from the PAAS. Relapse was defined as having a full symptom (defined as ≥ 4 symptoms) panic attack frequency of ≥ 2 panic attacks per week for 2 consecutive weeks or, to have been discontinued from the double-blind phase due to loss of effectiveness as determined by the investigators during the study. The time until relapse was assessed from the first day of the randomized double-blind maintenance phase (study day 85).

Efficacy Analysis
The efficacy intent-to-treat (ITT) patients were those who:

- had a baseline evaluation
- had at least one on-therapy evaluation (defined as a period ≥ 7 days of double-blind PAAS data) of the primary efficacy variable within 3 days of stopping nontaper test article
- took at least one dose of double-blind test article

Of note, the study report does not include the last criteria ("took at least one dose of double-blind test article") in its definition of the ITT population. Also, instead of "within 3 days of stopping nontaper test article" in the second criteria, the study report states "during visits 3 to 11 (days 7 to 98)".

The primary efficacy endpoint (time to relapse for patients who entered the double-blind maintenance phase of the study) was analyzed using survival (Kaplan-Meier) analysis. Survival curves were compared using a log-rank test. Because of the large number of sites in this study, the study sites were collapsed into geographic regions in the statistical model with the site as an effect.

For the PAAS and primary analysis, in each week (7 days), if more than 50% of PAAS data (4 days or more) was missing, the evaluation was considered missing for the week.

Baseline Demographics
Table 10.1.9 below displays the demographic characteristics of the ITT patient sample by treatment group. No patient under age 18 or over age 82 participated in this study. There were no major differences between the two treatment groups with respect to age, gender, or race except for a slightly higher percentage of males in the placebo group.

TABLE 10.1.9 : STUDY 354[43]
BASELINE DEMOGRAPHICS, DOUBLE-BLIND PERIOD, ITT POPULATION

TX	Age (yrs)		Sex (%)		Race (%)			
(n)	Mean	Range	Male	Female	White	Hispanic	Black	Other
Ven ER (89)	37.4	18-62	26	74	91	7	1	1
Placebo (80)	39.1	20-70	35	65	84	11	3	2

Baseline Severity of Illness
Treatment groups had no major differences with respect to mean baseline full-symptom panic attacks from PAAS (mean scores of 0.35 in venlafaxine ER patients and 0.39 in placebo patients).

Patient Disposition
A total of 321 patients entered the open-label phase and were dispensed study medication. Eight (8) of these did not have data for the open-label phase (3 returned the medication unused and 5 were lost to follow-up). A total of 137 (44%) patients discontinued treatment in the open-label treatment period, mostly due to adverse event (34/313), unsatisfactory response (27/313), and protocol violation (8/313). Thus, by the undersigned reviewer's calculations, 184 patients completed the open-label treatment period. However, according to the sponsor, 225 patients completed the open-label treatment period.

176 patients were randomized to double-blind (84 to placebo and 92 to venlafaxine ER). Seven (7) patients in the double-blind phase had some efficacy data but did not have a sufficient number of on-therapy primary efficacy evaluations during the double-blind period to qualify for inclusion in the ITT population. Thus, 169 patients comprised the efficacy ITT population (89 ven ER and 80 placebo patients).

The numbers of ITT patients in-study over time are displayed in Appendix 10.3.19 in Section 10.3. At week 26, 61% (54/89) of venlafaxine ER patients and 35% (28/80) of placebo patients completed the study. Based on the safety population, overall dropout rates were much higher in the placebo group [39% (36/92) of venlafaxine ER patients and 64% (54/84) of placebo patients]. Based on the safety population, dropout rates due to lack of efficacy were also much higher in the placebo group [21% (19/92) of venlafaxine ER patients and 43% (36/84) of placebo patients].

[43] Figures may not add up to 100% due to rounding.

Dosing Information
Dosing information is displayed in Table 10.1.10 below.

TABLE 10.1.10: MEAN DAILY DOSE OF VENLAFAXINE ER FOR PATIENTS BY TIME INTERVAL, SAFETY POPULATION, DOUBLE-BLIND PERIOD

Treatment Time on Therapy (days)	n	Mean Daily Dose, mg ± (SD)
Placebo		
1 - 14	84	69.6 (42.5)
15 - 28	70	0 (0.0)
29 - 42	59	0 (0.0)
43 - 70	53	0 (0.0)
71 - 98	44	0 (0.0)
99 - 126	38	0 (0.0)
127 - 154	34	0 (0.0)
155 - 182	32	0 (0.0)
> 182	13	0 (0.0)
Venlafaxine ER		
1 - 14	92	164.9 (56.9)
15 - 28	83	166.0 (56.4)
29 - 42	74	169.0 (55.4)
43 - 70	71	170.4 (55.3)
71 - 98	67	167.4 (55.4)
99 - 126	65	166.5 (55.4)
127 - 154	61	165.3 (55.1)
155 - 182	59	165.6 (54.2)
> 182	18	170.8 (56.4)

Data are from CDR 4-2 (30 Jun 2004)

Concomitant Medications
Up to 10 mg of zaleplon or zolpidem, ≤4 times per week, was permitted at bedtime through day 21 of open label treatment. Other psychopharmacologic drugs and ECT were prohibited. Nonpsychopharmacologic drugs with psychotropic effects were permitted only if the patient had been receiving a stable dose of the drug for at least 3 months before study day 1 and was expected to continue taking the drug without dose changes. Formal psychotherapy (other than cognitive behavioral therapy) was permitted if it was not introduced or changed in intensity within 60 days of study day 1. Hypnosis or relaxation therapy intended to treat anxiety was prohibited during the study.

With respect to the percentages of double blind safety population patients[44] using various concomitant medications during the study, there were no major differences between treatment groups (80% in placebo patients and 85% in ven ER patients), and the most frequently used were nonsteroidal anti-inflammatory/antirheumatic products, other analgesics and antipyretics, and hormonal contraceptives for systemic use. Based on the safety population, there was 1/313 (<1%) patient in the placebo group and 2/313 (1%) patients in the venlafaxine ER group

44 This information was not provided for the ITT population.

identified as protocol violators because of prohibited medication use during the double-blind period.

Efficacy Results
Efficacy data displays may be found in the following figures and tables.

FIGURE 10.1.1: SURVIVAL FUNCTION ESTIMATES, ITT POPULATION

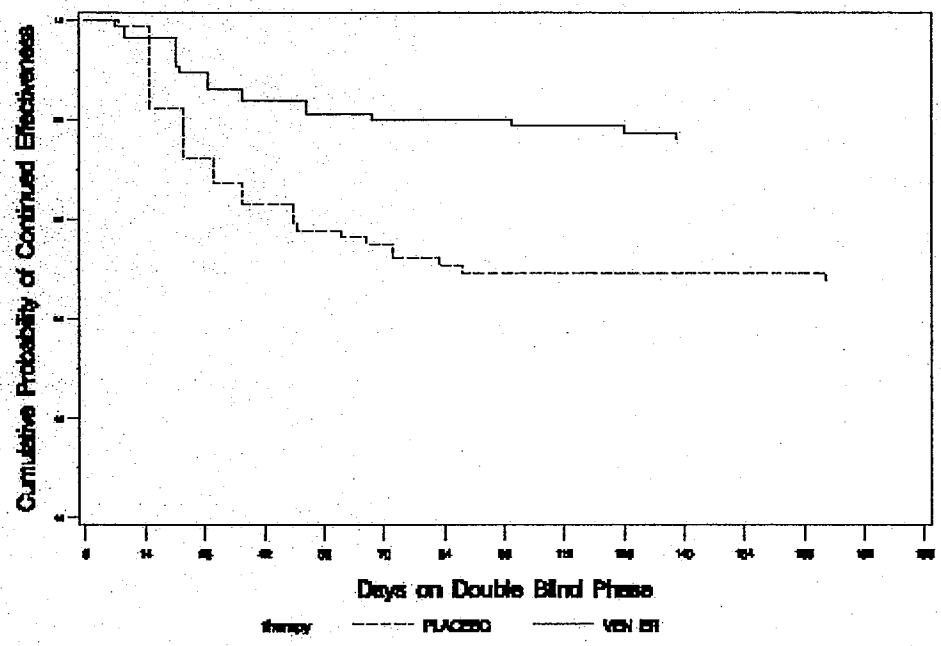


TABLE 10.1.11: SURVIVAL ANALYSIS FOR RELAPSE OF PANIC DISORDER, ITT POPULATION, DOUBLE-BLIND PERIOD

Therapy Group	n	Number of Relapses (%)	Cumulative Probability of Relapse	Chi-Square Statistics	p-Values[a]
Placebo	80	40 (50.0)	0.523		
Venlafaxine ER	89	20 (22.5)	0.239	14.314	< 0.001

a: p-Values obtained from log-rank statistics of Kaplan-Meier survival model.
Data from statistical report ITT/pa_surv.html (16 Jun 2004)

TABLE 10.1.12: LIFE-TABLE SUMMARY FOR CUMULATIVE PROBABILITY OF CONTINUED RESPONSE, ITT POPULATION, DOUBLE-BLIND PERIOD

	Placebo			Venlafaxine ER		
Time Period Month	Failed[a]	Censored[b]	Cumulative Probability	Failed[a]	Censored[b]	Cumulative Probability
1	26	3	0.67	12	5	0.86
2	8	2	0.56	4	4	0.81
3	5	2	0.49	1	0	0.80
4	0	1	0.49	1	3	0.79
5	0	3	0.49	2	0	0.76
6	1	8	0.47	0	16	0.76

a: Number of patients with relapses.
b: Number of withdrawals without relapses.
Data from biostatistics report ITT/pa_surv_lt.html (08 Jun 2004)

The primary efficacy analysis was a Kaplan-Meier survival analysis and the result was significant. The cumulative probability of relapse for placebo-treated patients was 0.523, compared with 0.239 for venlafaxine ER-treated patients. The relapse rate for the placebo-treated patients was 50% (40/80), compared with a 22.5% (20/89) relapse rate for venlafaxine ER-treated patients.

There was no evidence of a center-by-therapy interaction in this trial according to a May 25, 2005 email from the statistician, Ohidul Siddiqui.

Conclusions
176 patients with panic disorder who responded to venlafaxine ER 75 mg to 225 mg/day were randomized to either continuation of venlafaxine ER at their same dose (n=92) or to placebo (n=84), for observation of relapse. Response during the open-label phase was defined by having at most one full-symptom panic attack per week during the last two weeks of open label treatment and a CGI-I score of 1 or 2 compared to the assessment of open-label baseline. Relapse was defined as having a full symptom (defined as ≥ 4 symptoms) panic attack frequency of ≥ 2 panic attacks per week for 2 consecutive weeks or, to have been discontinued from the double-blind phase due to loss of effectiveness as determined by the investigators during the study. In the randomized phase, patients receiving continued venlafaxine ER experienced a significantly longer time to relapse.

10.2 Line-by-Line Labeling Review

See section 9.4 for a discussion of the clinical changes to labeling based on this supplement.

10.3 Appendix to Individual Study Reports

APPENDIX 10.3.1: LIST OF INVESTIGATORS for STUDY 398

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a: This site was closed on 29 Apr 2002 because of poor compliance with Good Clinical Practices; the 3 patients randomly assigned to treatment were withdrawn. These patients were included in the intent-to-treat, per-protocol, and safety analyses.
b: Each of these 6 sites had 1 patient who was a screen failure. No patients received double-blind study medication at these sites.
Data from clinical data report (CDR) 1-1SF (18 Sep 2002).

APPENDIX 10.3.2: RESULTS OF PRIMARY VARIABLE PAAS: % PATIENTS FREE OF FULL-SYMPTOM PANIC ATTACKS, ALL TIME POINTS, LOCF AND OBSERVED-CASES ANALYSES, ITT POPULATION

Analysis Days on Therapy	Therapy Group (mg)	n	Number (%) Panic-Free	Adjusted Odds Ratio to Placebo	95% Confidence Limits[a]	p-Value vs Placebo[b]
LOCF						
Days 1-14	Placebo	156	15 (9.6)			
	Venlafaxine ER 75	158	14 (8.9)	0.926	0.42, 2.03	0.848
	Venlafaxine ER 150	159	14 (8.8)	0.928	0.43, 2.02	0.851
	Paroxetine	161	9 (5.6)	0.570	0.24, 1.36	0.206
Days 15-28	Placebo	156	26 (16.7)			
	Venlafaxine ER 75	158	40 (25.3)	1.752	1.00, 3.08	0.052
	Venlafaxine ER 150	159	48 (30.2)	2.245	1.30, 3.89	0.004
	Paroxetine	161	41 (25.5)	1.763	1.01, 3.08	0.046
Days 29-42	Placebo	156	40 (25.6)			
	Venlafaxine ER 75	158	59 (37.3)	1.774	1.09, 2.90	0.022
	Venlafaxine ER 150	159	67 (42.1)	2.158	1.33, 3.49	0.002
	Paroxetine	161	64 (39.8)	1.967	1.21, 3.19	0.006
Days 43-56	Placebo	156	46 (29.5)			
	Venlafaxine ER 75	158	70 (44.3)	1.959	1.22, 3.15	0.005
	Venlafaxine ER 150	159	78 (49.1)	2.338	1.47, 3.73	<0.001
	Paroxetine	161	86 (53.4)	2.866	1.79, 4.59	<0.001
Days 57-70	Placebo	156	51 (32.7)			
	Venlafaxine ER 75	158	71 (44.9)	1.698	1.07, 2.69	0.024
	Venlafaxine ER 150	159	86 (54.1)	2.444	1.54, 3.87	<0.001
	Paroxetine	161	94 (58.4)	2.942	1.85, 4.67	<0.001
Days 71-84	Placebo	156	55 (35.3)			
	Venlafaxine ER 75	158	86 (54.4)	2.230	1.41, 3.52	<0.001
	Venlafaxine ER 150	159	95 (59.7)	2.737	1.73, 4.32	<0.001
	Paroxetine	161	98 (60.9)	2.939	1.85, 4.66	<0.001
Observed cases						
Days 1-14	Placebo	156	15 (9.6)			
	Venlafaxine ER 75	158	14 (8.9)	0.926	0.42, 2.03	0.848
	Venlafaxine ER 150	159	14 (8.8)	0.928	0.43, 2.02	0.851
	Paroxetine	161	9 (5.6)	0.570	0.24, 1.36	0.206
Days 15-28	Placebo	144	24 (16.7)			
	Venlafaxine ER 75	148	39 (26.4)	1.940	1.08, 3.49	0.027
	Venlafaxine ER 150	148	47 (31.8)	2.460	1.39, 4.35	0.002
	Paroxetine	152	40 (26.3)	1.824	1.03, 3.23	0.040
Days 29-42	Placebo	137	38 (27.7)			
	Venlafaxine ER 75	143	57 (39.9)	1.883	1.12, 3.16	0.016
	Venlafaxine ER 150	140	65 (46.4)	2.351	1.42, 3.90	<0.001
	Paroxetine	146	62 (42.5)	1.972	1.19, 3.26	0.008
Days 43-56	Placebo	131	44 (33.6)			
	Venlafaxine ER 75	138	67 (48.6)	2.070	1.24, 3.45	0.005
	Venlafaxine ER 150	134	75 (56.0)	2.642	1.59, 4.38	<0.001
	Paroxetine	141	82 (58.2)	2.919	1.76, 4.83	<0.001

Analysis Days on Therapy	Therapy Group (mg)	n	Number (%) Panic-Free	Adjusted Odds Ratio to Placebo	95% Confidence Limits[a]	p-Value vs Placebo[b]
Days 57-70	Placebo	125	49 (39.2)			
	Venlafaxine ER 75	136	68 (50.0)	1.635	0.99, 2.70	0.054
	Venlafaxine ER 150	135	84 (62.2)	2.631	1.59, 4.36	<0.001
	Paroxetine	138	88 (63.8)	2.811	1.70, 4.65	<0.001
Days 71-84	Placebo	120	52 (43.3)			
	Venlafaxine ER 75	134	82 (61.2)	2.242	1.34, 3.75	0.002
	Venlafaxine ER 150	133	92 (69.2)	3.009	1.79, 5.06	<0.001
	Paroxetine	136	90 (66.2)	2.671	1.60, 4.46	<0.001

Abbreviations: PAAS=Panic and Anticipatory Anxiety Scale; LOCF=last observation carried forward; ITT=intent-to-treat.
a: 95% Confidence limits for adjusted odds ratio.
b: Chi-square p-values obtained from logistic regression model logit (response)=treatment+center.
Data from statistical report ITT\pa_logit_a.html (21 Sep 2002).

APPENDIX 10.3.3: MEAN CHANGE FROM BASELINE IN PDSS TOTAL SCORE, LOCF AND OBSERVED-CASES ANALYSES, VENLAFAXINE ER 75 mg VS PLACEBO, ITT POPULATION

Analysis	Weeks On-Therapy	Therapy Group	n	Adjusted Mean Change from Baseline	Standard Error	95% Confidence Limits Adj Mean, Placebo-Therapy	p-Value vs Placebo[a]
LOCF							
	Baseline	Placebo	156				
		Ven ER	158				
	Week 2	Placebo	151	-2.66	0.29		
		Ven ER	152	-3.12	0.29	0.46 (-0.30, 1.22)	0.232
	Week 4	Placebo	151	-4.42	0.36		
		Ven ER	154	-5.64	0.36	1.22 (0.28, 2.16)	0.011
	Week 6	Placebo	152	-5.23	0.38		
		Ven ER	154	-7.10	0.38	1.87 (0.87, 2.87)	<0.001
	Week 8	Placebo	152	-5.93	0.41		
		Ven ER	154	-7.93	0.41	2.00 (0.92, 3.08)	<0.001
	Week 10	Placebo	152	-6.32	0.44		
		Ven ER	154	-8.85	0.44	2.53 (1.38, 3.68)	<0.001
	Week 12	Placebo	152	-6.89	0.46		
		Ven ER	154	-9.38	0.46	2.49 (1.29, 3.69)	<0.001
Observed cases							
	Baseline	Placebo	156				
		Ven ER	158				
	Week 2	Placebo	151	-2.66	0.29		
		Ven ER	152	-3.12	0.29	0.46 (-0.30, 1.22)	0.232
	Week 4	Placebo	138	-4.69	0.37		
		Ven ER	142	-6.09	0.38	1.40 (0.43, 2.37)	0.005
	Week 6	Placebo	135	-5.73	0.39		
		Ven ER	142	-7.50	0.40	1.77 (0.75, 2.79)	<0.001
	Week 8	Placebo	128	-6.69	0.43		
		Ven ER	139	-8.41	0.43	1.72 (0.62, 2.82)	0.002
	Week 10	Placebo	123	-7.47	0.46		
		Ven ER	136	-9.52	0.45	2.05 (0.89, 3.21)	<0.001
	Week 12	Placebo	122	-8.16	0.46		
		Ven ER	132	-10.21	0.47	2.05 (0.87, 3.23)	<0.001
Final on-therapy							
		Placebo	154	-6.80	0.46		
		Ven ER	155	-9.31	0.46	2.51 (1.31, 3.72)	<0.001

Abbreviations: PDSS=Panic Disorder Severity Scale; ITT=intent-to-treat; Adj=adjusted; LOCF=last observation carried forward; Ven ER=venlafaxine ER 75 mg.
a: p-Values obtained from ANCOVA model: change from baseline=baseline+treatment+center.
Data from statistical report ITT\a2_eff_pdss_2.html (21 Sep 2002).

APPENDIX 10.3.4: MEAN CHANGE IN PDSS TOTAL SCORE, LOCF AND OBSERVED-CASES ANALYSES, VENLAFAXINE ER 150 mg VS PLACEBO, ITT POPULATION

Analysis	Weeks On-Therapy	Therapy Group	n	Adjusted Mean Change from Baseline	Standard Error	95% Confidence Limits Adj Mean, Placebo-Therapy	p-Value vs Placebo[a]
LOCF							
	Baseline	Placebo	156				
		Ven ER	159				
	Week 2	Placebo	151	-2.63	0.29		
		Ven ER	153	-3.07	0.29	0.44 (-0.31, 1.19)	0.245
	Week 4	Placebo	151	-4.36	0.36		
		Ven ER	154	-5.38	0.37	1.03 (0.08, 1.98)	0.033
	Week 6	Placebo	152	-5.24	0.39		
		Ven ER	155	-7.02	0.40	1.78 (0.75, 2.80)	<0.001
	Week 8	Placebo	152	-5.93	0.42		
		Ven ER	155	-8.28	0.42	2.35 (1.26, 3.44)	<0.001
	Week 10	Placebo	152	-6.28	0.44		
		Ven ER	155	-8.99	0.44	2.70 (1.55, 3.85)	<0.001
	Week 12	Placebo	152	-6.91	0.47		
		Ven ER	155	-9.75	0.47	2.84 (1.63, 4.05)	<0.001
Observed cases							
	Baseline	Placebo	156				
		Ven ER	159				
	Week 2	Placebo	151	-2.63	0.29		
		Ven ER	153	-3.07	0.29	0.44 (-0.31, 1.19)	0.245
	Week 4	Placebo	138	-4.53	0.37		
		Ven ER	144	-5.71	0.37	1.18 (0.21, 2.15)	0.018
	Week 6	Placebo	135	-5.73	0.39		
		Ven ER	139	-7.85	0.39	2.12 (1.11, 3.13)	<0.001
	Week 8	Placebo	128	-6.72	0.40		
		Ven ER	135	-9.44	0.40	2.72 (1.69, 3.75)	<0.001
	Week 10	Placebo	123	-7.51	0.42		
		Ven ER	134	-10.30	0.41	2.79 (1.73, 3.84)	<0.001
	Week 12	Placebo	122	-8.24	0.42		
		Ven ER	132	-11.17	0.42	2.93 (1.85, 4.01)	<0.001
Final on-therapy							
		Placebo	154	-6.76	0.46		
		Ven ER	156	-9.63	0.47	2.87 (1.67, 4.08)	<0.001

Abbreviations: PDSS=Panic Disorder Severity Scale; ITT=intent-to-treat; Adj=adjusted; LOCF=last observation carried forward; Ven ER=venlafaxine ER 150 mg.
a: p-Values obtained from ANCOVA model: change from baseline=baseline+treatment+center.
Data from statistical report ITT\a2_eff_pdss_3.html (21 Sep 2002).

APPENDIX 10.3.5: CGI-I RESPONDERS IN ITT POPULATION, NO. RESPONDERS/NO. EVALUATED (%) LOCF AND OBSERVED-CASES ANALYSES

Analysis						p-Values vs Placebo (Fisher's Exact Test)		
Weeks On-Therapy	Placebo (n=156)	Ven ER 75 mg (n=158)	Ven ER 150 mg (n=159)	Paroxetine (n=161)	Ven ER 75 mg	Ven ER 150 mg	Paroxetine
LOCF							
Week 1	12/156 (7.7)	14/158 (8.9)	10/158 (6.3)	7/160 (4.4)	0.838	0.665	0.244
Week 2	29/156 (18.6)	37/158 (23.4)	37/159 (23.3)	36/160 (22.5)	0.333	0.334	0.407
Week 3	42/156 (26.9)	60/158 (38.0)	59/159 (37.1)	70/160 (43.8)	0.041	0.055	0.002
Week 4	61/156 (39.1)	76/158 (48.1)	84/159 (52.8)	90/160 (56.3)	0.113	0.018	0.002
Week 6	64/156 (41.0)	97/158 (61.4)	100/159 (62.9)	108/160 (67.5)	<0.001	<0.001	<0.001
Week 8	79/156 (50.6)	112/158 (70.9)	114/159 (71.7)	118/160 (73.8)	<0.001	<0.001	<0.001
Week 10	87/156 (55.8)	122/158 (77.2)	121/159 (76.1)	124/160 (77.5)	<0.001	<0.001	<0.001
Week 12	87/156 (55.8)	121/158 (76.6)	126/159 (79.2)	129/160 (80.6)	<0.001	<0.001	<0.001
Observed cases							
Week 1	12/156 (7.7)	14/158 (8.9)	10/158 (6.3)	7/160 (4.4)	0.838	0.665	0.244
Week 2	29/152 (19.1)	36/153 (23.5)	36/153 (23.5)	36/157 (22.9)	0.402	0.402	0.485
Week 3	42/146 (28.8)	57/145 (39.3)	58/147 (39.5)	69/152 (45.4)	0.064	0.065	0.004
Week 4	59/139 (42.4)	74/143 (51.7)	81/144 (56.3)	88/149 (59.1)	0.123	0.024	0.007
Week 6	63/135 (46.7)	94/142 (66.2)	97/139 (69.8)	107/144 (74.3)	0.001	<0.001	<0.001
Week 8	76/129 (58.9)	108/139 (77.7)	110/135 (81.5)	118/142 (83.1)	0.001	<0.001	<0.001
Week 10	84/123 (68.3)	116/136 (85.3)	116/134 (86.6)	120/137 (87.6)	0.002	<0.001	<0.001
Week 12	83/122 (68.0)	113/132 (85.6)	120/132 (90.9)	124/136 (91.2)	<0.001	<0.001	<0.001
Final on-therapy							
	87/156 (55.8)	121/158 (76.6)	126/159 (79.2)	129/160 (80.6)	<0.001	<0.001	<0.001

Abbreviations: CGI-I=Clinical Global Impression-improvement; ITT=intent-to-treat; LOCF=last observation carried forward; Ven ER=venlafaxine extended release.
Data from statistical report ITT\resp_g2_a.html (21 Sep 2002).

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a: Data from this site are excluded from the per-protocol population because of poor compliance with Good Clinical Practices discovered during monitoring visits and site quality evaluations. These data, however, were included in the intent-to-treat and safety analyses.

Data from clinical data report CDR 1-1SF (19 Feb 2004).

APPENDIX 10.3.7: RESULTS OF PRIMARY VARIABLE PAAS: % PATIENTS FREE OF FULL-SYMPTOM PANIC ATTACKS, ALL TIME POINTS, LOCF AND OBSERVED-CASES ANALYSES, ITT POPULATION

Analysis Days on Therapy	Therapy Group (mg)	n	Number (%) of Responders	Adjusted Odds Ratio to Placebo	95% Confidence Limit for Adjusted Odds Ratio[a]	p-Values[b]
LOCF						
Days 1-14	Placebo	157	10 (6.4)			
	Venlafaxine 75	156	9 (5.8)	1.140	(0.43, 3.00)	0.791
	Venlafaxine 225	160	16 (10.0)	1.890	(0.80, 4.44)	0.145
	Paroxetine	151	12 (7.9)	1.435	(0.59, 3.52)	0.430
Days 15-28	Placebo	157	32 (20.4)			
	Venlafaxine 75	156	46 (29.5)	1.766	(1.04, 3.00)	0.035
	Venlafaxine 225	160	48 (30.0)	1.834	(1.08, 3.12)	0.025
	Paroxetine	151	51 (33.8)	2.279	(1.33, 3.89)	0.003
Days 29-42	Placebo	157	49 (31.2)			
	Venlafaxine 75	156	67 (42.9)	1.799	(1.12, 2.90)	0.015
	Venlafaxine 225	160	78 (48.8)	2.318	(1.44, 3.74)	<0.001
	Paroxetine	151	64 (42.4)	1.793	(1.11, 2.91)	0.018
Days 43-56	Placebo	157	58 (36.9)			
	Venlafaxine 75	156	81 (51.9)	2.153	(1.33, 3.48)	0.002
	Venlafaxine 225	160	91 (56.9)	2.491	(1.56, 3.98)	<0.001
	Paroxetine	151	67 (44.4)	1.510	(0.94, 2.42)	0.087
Days 57-70	Placebo	157	64 (40.8)			
	Venlafaxine 75	156	91 (58.3)	2.279	(1.43, 3.64)	<0.001
	Venlafaxine 225	160	103 (64.4)	2.877	(1.80, 4.61)	<0.001
	Paroxetine	151	88 (58.3)	2.271	(1.41, 3.66)	<0.001
Days 71-84	Placebo	157	75 (47.8)			
	Venlafaxine 75	156	101 (64.7)	2.300	(1.43, 3.70)	<0.001
	Venlafaxine 225	160	112 (70.0)	2.773	(1.72, 4.46)	<0.001
	Paroxetine	151	88 (58.3)	1.769	(1.10, 2.86)	0.020
Observed-cases						
Days 1-14	Placebo	157	10 (6.4)			
	Venlafaxine 75	156	9 (5.8)	1.140	(0.43, 3.00)	0.791
	Venlafaxine 225	160	16 (10.0)	1.890	(0.80, 4.44)	0.145
	Paroxetine	151	12 (7.9)	1.435	(0.59, 3.52)	0.430
Days 15-28	Placebo	149	32 (21.5)			
	Venlafaxine 75	151	45 (29.8)	1.672	(0.98, 2.85)	0.060
	Venlafaxine 225	155	47 (30.3)	1.747	(1.02, 2.99)	0.042
	Paroxetine	137	49 (35.8)	2.312	(1.34, 3.99)	0.003
Days 29-42	Placebo	138	49 (35.5)			
	Venlafaxine 75	149	65 (43.6)	1.509	(0.93, 2.46)	0.098
	Venlafaxine 225	149	77 (51.7)	2.180	(1.33, 3.58)	0.002
	Paroxetine	134	62 (46.3)	1.717	(1.04, 2.84)	0.035
Days 43-56	Placebo	128	56 (43.8)			
	Venlafaxine 75	145	77 (53.1)	1.695	(1.02, 2.82)	0.042
	Venlafaxine 225	145	87 (60.0)	2.153	(1.30, 3.56)	0.003
	Paroxetine	130	64 (49.2)	1.369	(0.83, 2.27)	0.222

Analysis Days on Therapy	Therapy Group (mg)	n	Number (%) of Responders	Adjusted Odds Ratio to Placebo	95% Confidence Limit for Adjusted Odds Ratio[a]	p-Values[b]
Days 57-70	Placebo	123	62 (50.4)			
	Venlafaxine 75	138	86 (62.3)	1.804	(1.08, 3.01)	0.024
	Venlafaxine 225	139	97 (69.8)	2.543	(1.50, 4.30)	<0.001
	Paroxetine	127	84 (66.1)	2.158	(1.27, 3.67)	0.005
Days 71-84	Placebo	119	73 (61.3)			
	Venlafaxine 75	135	94 (69.6)	1.654	(0.96, 2.86)	0.071
	Venlafaxine 225	139	106 (76.3)	2.241	(1.28, 3.91)	0.005
	Paroxetine	124	82 (66.1)	1.400	(0.80, 2.44)	0.236

Abbreviations: PAAS = Panic and Anticipatory Anxiety Scale; LOCF = last observation carried forward; ITT = intent-to-treat.

a: 95% Confidence limits for adjusted odds ratio.

b: Chi-square p-values obtained from logistic regression model logit (response) = baseline severity + treatment + center.

Data from statistical report ITT\pa_logit_medb.a.html (12 Feb 2004).

APPENDIX 10.3.8: MEAN CHANGE FROM BASELINE IN PDSS TOTAL SCORE, LOCF AND OBSERVED-CASES ANALYSES, VENLAFAXINE ER 75 mg VS PLACEBO, ITT POPULATION

Analysis Weeks on Therapy	Therapy Group	n	Adjusted Mean Change From Baseline	Standard Error	95% Confidence Limits Adj Mean Placebo-Therapy	p-Value vs Placebo[a]
LOCF						
Baseline	Placebo	157				
	Ven ER	156				
Week 2	Placebo	148	-3.18	0.39		
	Ven ER	151	-3.82	0.39	0.64 (-0.27, 1.54)	0.166
Week 4	Placebo	149	-5.18	0.47		
	Ven ER	153	-6.67	0.46	1.49 (0.41, 2.56)	0.007
Week 6	Placebo	154	-6.41	0.49		
	Ven ER	155	-8.24	0.48	1.83 (0.71, 2.94)	0.001
Week 8	Placebo	154	-7.16	0.50		
	Ven ER	155	-9.71	0.50	2.56 (1.40, 3.71)	<0.001
Week 10	Placebo	154	-7.53	0.53		
	Ven ER	155	-10.19	0.53	2.65 (1.43, 3.87)	<0.001
Week 12	Placebo	154	-8.34	0.57		
	Ven ER	155	-11.15	0.56	2.81 (1.51, 4.11)	<0.001
Observed-cases						
Baseline	Placebo	157				
	Ven ER	156				
Week 2	Placebo	148	-3.18	0.39		
	Ven ER	151	-3.82	0.39	0.64 (-0.27, 1.54)	0.166
Week 4	Placebo	139	-5.59	0.48		
	Ven ER	147	-6.81	0.47	1.22 (0.12, 2.31)	0.030
Week 6	Placebo	137	-7.03	0.49		
	Ven ER	147	-8.12	0.48	1.09 (-0.04, 2.22)	0.059
Week 8	Placebo	128	-8.61	0.48		
	Ven ER	143	-10.06	0.46	1.44 (0.35, 2.54)	0.010
Week 10	Placebo	123	-9.27	0.50		
	Ven ER	137	-10.67	0.46	1.40 (0.28, 2.52)	0.015
Week 12	Placebo	119	-10.33	0.53		
	Ven ER	130	-11.72	0.50	1.39 (0.18, 2.60)	0.025
Final on-therapy	Placebo	155	-8.31	0.56		
	Ven ER	155	-11.24	0.56	2.92 (1.63, 4.21)	<0.001

Abbreviations: PDSS = Panic Disorder Severity Scale; ITT = intent-to-treat; Adj = adjusted; LOCF = last observation carried forward; Ven ER = venlafaxine ER 75 mg.
a: p-Values obtained from ANCOVA model: change from baseline = baseline + treatment + center.
Data from statistical report ITT\a2_eff_pdss_2.html (11 Feb 2004).

APPENDIX 10.3.9: MEAN CHANGE IN PDSS TOTAL SCORE, LOCF AND OBSERVED-CASES ANALYSES, VENLAFAXINE ER 225 mg VS PLACEBO, ITT POPULATION

Analysis Weeks on Therapy	Therapy Group	n	Adjusted Mean Change From Baseline	Standard Error	95% Confidence Limits Adj Mean Placebo-Therapy	p-Value vs Placebo[a]
LOCF						
Baseline	Placebo	157				
	Ven ER	160				
Week 2	Placebo	148	-3.71	0.41		
	Ven ER	155	-5.01	0.40	1.30 (0.36, 2.24)	0.007
Week 4	Placebo	149	-5.56	0.46		
	Ven ER	158	-8.23	0.45	2.67 (1.62, 3.72)	<0.001
Week 6	Placebo	154	-6.43	0.48		
	Ven ER	158	-9.42	0.47	2.99 (1.90, 4.08)	<0.001
Week 8	Placebo	154	-7.12	0.49		
	Ven ER	158	-10.58	0.49	3.46 (2.33, 4.59)	<0.001
Week 10	Placebo	154	-7.61	0.52		
	Ven ER	158	-11.50	0.51	3.89 (2.71, 5.08)	<0.001
Week 12	Placebo	154	-8.41	0.55		
	Ven ER	158	-12.76	0.54	4.35 (3.09, 5.61)	<0.001
Observed-cases						
Baseline	Placebo	157				
	Ven ER	160				
Week 2	Placebo	148	-3.71	0.41		
	Ven ER	155	-5.01	0.40	1.30 (0.36, 2.24)	0.007
Week 4	Placebo	139	-6.00	0.46		
	Ven ER	152	-8.38	0.45	2.38 (1.34, 3.43)	<0.001
Week 6	Placebo	137	-6.99	0.46		
	Ven ER	147	-9.60	0.45	2.61 (1.55, 3.67)	<0.001
Week 8	Placebo	128	-8.52	0.46		
	Ven ER	142	-11.00	0.44	2.48 (1.44, 3.52)	<0.001
Week 10	Placebo	123	-9.38	0.47		
	Ven ER	138	-12.17	0.45	2.79 (1.73, 3.86)	<0.001
Week 12	Placebo	119	-10.49	0.49		
	Ven ER	136	-13.66	0.47	3.18 (2.06, 4.29)	<0.001
Final on-therapy	Placebo	155	-8.39	0.55		
	Ven ER	160	-12.72	0.54	4.34 (3.08, 5.60)	<0.001

Abbreviations: PDSS = Panic Disorder Severity Scale; ITT = intent-to-treat; Adj = adjusted; LOCF = last observation carried forward; Ven ER = venlafaxine ER 225 mg.
a: p-Values obtained from ANCOVA model: change from baseline = baseline + treatment + center.
Data from statistical report ITT\a2_eff_pdss_3.html (11 Feb 2004).

APPENDIX 10.3.10: CGI-I RESPONDERS IN ITT POPULATION, NO. RESPONDERS/NO. EVALUATED (%) LOCF AND OBSERVED-CASES ANALYSES

Analysis						p-Values vs Placebo (Fishers Exact Test)		
	Weeks on Therapy	Placebo (n = 157)	Ven ER 75 mg (n = 156)	Ven ER 225 mg (n = 160)	Paroxetine (n = 151)	Ven ER 75 mg	Ven ER 225 mg	Paroxetine
LOCF								
	Week 1	19/ 155 (12.3)	21/ 155 (13.5)	18/ 156 (11.5)	23/ 150 (15.3)	0.866	0.863	0.507
	Week 2	36/ 157 (22.9)	51/ 156 (32.7)	55/ 160 (34.4)	44/ 150 (29.3)	0.059	0.026	0.242
	Week 3	52/ 157 (33.1)	74/ 156 (47.4)	74/ 160 (46.3)	69/ 150 (46.0)	0.011	0.022	0.026
	Week 4	64/ 157 (40.8)	85/ 156 (54.5)	105/ 160 (65.6)	85/ 150 (56.7)	0.018	<0.001	0.006
	Week 6	83/ 157 (52.9)	99/ 156 (63.5)	114/ 160 (71.3)	105/ 150 (70.0)	0.067	<0.001	0.002
	Week 8	87/ 157 (55.4)	121/ 156 (77.6)	121/ 160 (75.6)	111/ 150 (74.0)	<0.001	<0.001	<0.001
	Week 10	88/ 157 (56.1)	122/ 156 (78.2)	135/ 160 (84.4)	122/ 150 (81.3)	<0.001	<0.001	<0.001
	Week 12	94/ 157 (59.9)	127/ 156 (81.4)	136/ 160 (85.0)	125/ 150 (83.3)	<0.001	<0.001	<0.001
Observed-cases								
	Week 1	19/ 155 (12.3)	21/ 155 (13.5)	18/ 156 (11.5)	23/ 150 (15.3)	0.866	0.863	0.507
	Week 2	35/ 151 (23.2)	50/ 154 (32.5)	55/ 156 (35.3)	42/ 144 (29.2)	0.075	0.024	0.289
	Week 3	52/ 152 (34.2)	67/ 144 (46.5)	71/ 151 (47.0)	65/ 136 (47.8)	0.033	0.026	0.022
	Week 4	58/ 139 (41.7)	81/ 148 (54.7)	103/ 154 (66.9)	81/ 134 (60.4)	0.033	<0.001	0.002
	Week 6	78/ 137 (56.9)	93/ 147 (63.3)	109/ 147 (74.1)	101/ 131 (77.1)	0.332	0.003	<0.001
	Week 8	81/ 128 (63.3)	114/ 143 (79.7)	113/ 142 (79.6)	106/ 129 (82.2)	0.003	0.004	<0.001
	Week 10	81/ 123 (65.9)	112/ 137 (81.8)	127/ 138 (92.0)	116/ 127 (91.3)	0.004	<0.001	<0.001
	Week 12	85/ 119 (71.4)	111/ 130 (85.4)	126/ 136 (92.6)	115/ 123 (93.5)	0.008	<0.001	<0.001
Final on-therapy		94/ 157 (59.9)	128/ 156 (82.1)	137/ 160 (85.6)	125/ 150 (83.3)	<0.001	<0.001	<0.001

Abbreviations: CGI-I = Clinical Global Impressions-improvement; ITT = intent-to-treat; LOCF = last observation carried forward; Ven ER = venlafaxine extended release.
Data from statistical report ITT\resp_g2_a.html (12 Feb 2004).

APPENDIX 10.3.11: LIST OF INVESTIGATORS STUDY 353

Investigator (number)	Address	Number of Patients Randomly Assigned
Gregory M. Asnis, MD (35305)	Anxiety and Depression Clinic Montefiore Medical Center 111 East 210th Street Bronx, NY 10467 USA	25
Gregory M. Asnis, MD (35375)	Depression and Anxiety Institute 344 Main Street, Suite 003 Mount Kisco, NY 10549 USA	4
Charles E. Bailey, MD (35367)	Clinical Neuroscience Solutions, Inc. 77 West Underwood Street, 3rd Floor Orlando, FL 32806 USA	5
Scott E. Balogh, MD (35309)	SouthEastern NeuroScience, Inc. (SENSe) 1210 Roy Road Augusta, GA 30909 USA	9
Bijan Bastani, MD (35312)	NorthCoast Clinical Trials 3733 Park East Drive, Suite 100 Beachwood, OH 44122 USA	10
Louise Beckett, MD (35343)	IPS Research Company 1211 North Shartel Suite 407 Oklahoma City, OK 73103 USA	8
Rudradeo Bowen, MD *(replaced Vernon L. Bennett, MD, who is listed on CDRs)* (35338)	Royal University Hospital 103 Hospital Drive Saskatoon, Saskatchewan S7N 0W8 Canada	3

Investigator (number)	Address	Number of Patients Randomly Assigned
Maria Regina Cenzon, MD (35345)	Dominion Psychiatric Associates 2580 Potters Road Virginia Beach, VA 23454 USA	7
Alice A. Chenault, MD (35346)	Huntsville Research Associates 608 Davis Circle Huntsville, AL 35801 USA	2
Herman R. Clements II, MD (35347)	Pharmacotherapy Research Associates, Inc. 750 Princeton Avenue, Suite 2 Zanesville, OH 43701 USA	9
Howard S. Cummins, PhD (35326)	The Clinical Trial Center, LLC 100 Old York Road, Suite L-136 Jenkintown, PA 19046 USA	11
Lynn Cunningham, MD (35348)	1121 University Dr., Suite 4 Edwardsville, IL 62025 USA	4
Joseph J. David, MD (35308)	Charlottesville Medical Research 1139 East High Street, Suite 105 Charlottesville, VA 22902 USA	4
Michael DePriest, MD (35327)	Protocare Trials Las Vegas Center for Clinical Research 2940 South Jones, Suite C Las Vegas, NV 89146 USA	3
Larry Eisner, MD *(replaced Dr. Umbert)* (35323)	Baumel-Eisner Neuromedical Institute 7301 N. University Drive, #300 Ft. Lauderdale, FL 33321 USA	1
Gary Gerard, MD (35307)	Neurology Center of Ohio 1000 Regency Court, Suite 208 Toledo, OH 43623 USA	10

Investigator (number)	Address	Number of Patients Randomly Assigned
Michael S. Greenbaum, MD (35350)	Ingenium Clinical Research 1117 South Milwaukee Avenue, #B-6 Libertyville, IL 60048 USA	1
James T. Hartford, MD (35351)	Hartford Research Group 51 Cavalier Blvd, Suite 220 Florence, KY 41042 USA	4
Howard A. Hassman, DO (35301)	CNS Research Institute, P.C. 130 White Horse Pike Clementon, NJ 08021 USA	5
Alan F. Jacobson, MD (35353)	Medical Care Center 12995 NE 7th Avenue North Miami, FL 33161 USA	5
Georgia Jones, MD (35318)	MEDEX Healthcare Research 100 North Euclid Ave., Suite 201 St. Louis, MO 63108 USA	5
Jasbir Kang, MD (35356)	Crossroads Counseling and Consulting Associates 1000 Commerce Drive, Suite 1002 Moon Township, PA 15108 USA	3
Ethan B. Kass, DO (35354)	ICSL Clinical Studies Center for Medical Arts at Coral Springs 8100 Royal Palm Blvd., Suite 103 Coral Springs, FL 33065 USA	5
Arifulla Khan, MD (35355)	Northwest Clinical Research Center 1900 116th Avenue Bellevue, WA 98004 USA	9
Ari Kiev, MD (35328)	Social Psychiatry Research Institute 150 East 69th Street, Suite 2H New York, NY 10021 USA	4

Investigator (number)	Address	Number of Patients Randomly Assigned
Paul R. Latimer, MD (35374)	Okanagan Clinical Trials Suite 304 - 3001 Tutt Street Kelowna, British Columbia VIY 2H4 Canada	2
Elly R. Lee, MD (35317)	Irvine Center for Clinical Research 16259 Laguna Canyon Road Irvine, CA 92618 USA	3
Michael R. Liebowitz, MD (35357)	The Medical Research Network, LLC 123 West 79th St, Ste. 106 New York, NY 10024 USA	11
Peter D. Londborg, MD (35358)	Summit Research Network, LLC Cabrini Medical Tower 901 Boren, Suite 1800 Seattle, WA 80212 USA	5
Julio C. Machado, MD (35315)	Miami Research Associates, Inc. 7500 SW 87th Avenue, Suite 202 Miami, FL 33173 USA	5
Raymond Matte, MD (35332)	Q&T Recherche Inc. 95, rue Camirand Bureau 130 Sherbrooke, Québec J1H 4J6 Canada	11
Jeffrey A. Mattes, MD (35360)	Psychopharmacology Research Association of Princeton Princeton Professional Park 601 Ewing Street, Suite A-12 Princeton, NJ 08540 USA	4
Craig M. McCarthy, MD (35341)	Pivotal Research Centers 1220 South Alma School Road Suite 206 Mesa, AZ 85210 USA	1

Investigator (number)	Address	Number of Patients Randomly Assigned
Janice Miller, MD (35361)	Clinical Neuroscience Solutions, Inc. 5601 Corporate Way Suite 210 Bldg. 2 West Palm Beach, FL 33407 USA	3
Dennis J. Munjack, MD (35306)	Southwestern Research, Inc. 2031 West Alameda Ave., Suite 300 Burbank, CA 91506 USA	10
John J. Murphy, MD (35342)	Southwestern Research, Inc. 435 North Bedford Drive Suite 216 Beverly Hills, CA 90210 USA	9
Philip Ninan, MD *(replaced Dr. Kelsey)* (35313)	Emory University Department of Psychiatry & Behavioral Sciences Mood & Anxiety Disorders Clinical Trials Program 1841 Clifton Road, NE, 4th Floor, Rm 402 Atlanta, GA 30329 USA	3
Margarita Nunez, MD (35362)	Comprehensive Neuroscience, Inc. 780-94th Avenue North, Suite 102 St. Petersburg, FL 33702 USA	1
Margaret A. Oakander, MD *(replaced Dr. Johnston)* (35337)	Psychiatric Outpatient Service Peter Lougheed Centre 3500 - 26th Avenue NE Room 1932 Calgary, Alberta T1Y 6J4 Canada	5
Jorg J. Pahl, MD, FCP (SA) (35363)	Pahl Brain Associates, Inc. 3939 N. Classen Oklahoma City, OK 73118 USA	3
Anil S. Patel, MD (35364)	Psychiatric Centers at San Diego 120 Craven Road, Suite 205 San Marcos, CA 92078 USA	4

Investigator (number)	Address	Number of Patients Randomly Assigned
William Patterson, MD (35365)	Birmingham Research Group, Inc. 2120 Lynngate Drive Birmingham, AL 35216 USA	12
Jacques Plamondon, MD (35373)	Centre Hospitalier Universitaire de Québec - Pavillon C.H.U.L. R.C. 157 2705, boul. Laurier Sainte-Foy, Québec G1V 4G2 Canada	8
Mark H. Pollack, MD (35320)	Massachusetts General Hospital WACC 815 15 Parkman Street Boston, MA 02114 USA	2
Raj P. Rajani, MD (35303)	Behavioral & Medical Research, LLC 1000 S. Anaheim Blvd. Suite 204 Anaheim, CA 92805 USA	6
Robert A. Riesenberg, MD (35370)	Atlanta Center for Medical Research 811 Juniper Street, NE Atlanta, GA 30308 USA	8
Angelo Sambunaris, MD (35314)	5901-A-Peachtree-Dunwoody Road Suite 525 Atlanta, GA 30328 USA	14
Anantha Shekhar, MD, PhD (35366)	Indiana University IU Adult Psychiatry, Methodist Campus 1701 North Capital Avenue C2 Indianapolis, IN 46202 USA	2
Ram K. Shrivastava, MD (35321)	Eastside Comprehensive Medical Services 133 East 73rd Street, Suite 209 New York, NY 10021 USA	8

Investigator (number)	Address	Number of Patients Randomly Assigned
Jeffrey Simon, MD (35304)	Northbrooke Research Center 9275 N 49th, Suite 200 Brown Deer, WI 53223 USA	9
Leslie van Houten Taylor, MD (35372)	Dean Foundation 2711 Allen Blvd. #300 Middleton, WI 53562 USA	3
Peter G. Turner, MD (35334)	Mood & Anxiety Disorders Clinic 3155 Harvester Road, Suite 205 Burlington, Ontario L7N 3V2 Canada	1
Michael Van Ameringen, MD (35335)	Anxiety Disorders Clinic Outpatient Psychiatry - 3G McMaster University Medical Centre Hamilton Health Sciences 1200 Main Street West Hamilton, Ontario L8N 3Z5 Canada	2
Thomas R. Weiss, MD (35316)	San Antonio Center for Clinical Research 8122 Datapoint Drive, Suite 1010 San Antonio, TX 78229 USA	23
Dan L. Zimbroff, MD (35311)	Pacific Clinical Research 100 S. Vincent, #405 West Covina, CA 91790 USA	8
Ben Zimmer, MD (35369)	Clinical Trials Research Services, LLC 5750 Centre Avenue, Suite 360 Pittsburgh, PA 15206 USA	1

APPENDIX 10.3.12: RESULTS OF PRIMARY VARIABLE PAAS: PATIENTS FREE OF FULL-SYMPTOM PANIC ATTACKS, ALL TIME POINTS, ITT POPULATION

Analysis Days on Therapy	Therapy Group	n	Number (%) of Responders	Adjusted Odds Ratio to Placebo	95% Confidence Limits[a]	p-Values Venlafaxine ER vs Placebo[b]
LOCF						
1-14	Placebo	155	13 (8.4)			
	Venlafaxine ER	155	15 (9.7)	1.161	0.53, 2.52	0.706
15-28	Placebo	155	36 (23.2)			
	Venlafaxine ER	155	37 (23.9)	1.048	0.61, 1.79	0.864
29-42	Placebo	155	50 (32.3)			
	Venlafaxine ER	155	57 (36.8)	1.216	0.74, 1.98	0.435
43-56	Placebo	155	58 (37.4)			
	Venlafaxine ER	155	71 (45.8)	1.424	0.90, 2.26	0.135
57-70	Placebo	155	67 (43.2)			
	Venlafaxine ER	155	80 (51.6)	1.464	0.92, 2.33	0.108

Analysis Days on Therapy	Therapy Group	n	Number (%) of Responders	Adjusted Odds Ratio to Placebo	95% Confidence Limits[a]	p-Values Venlafaxine ER vs Placebo[b]
Observed						
1-14	Placebo	155	13 (8.4)			
	Venlafaxine ER	155	15 (9.7)	1.161	0.53, 2.52	0.706
15-28	Placebo	143	34 (23.8)			
	Venlafaxine ER	135	37 (27.4)	1.217	0.70, 2.11	0.485
29-42	Placebo	140	48 (34.3)			
	Venlafaxine ER	123	54 (43.9)	1.519	0.90, 2.57	0.120
43-56	Placebo	124	51 (41.1)			
	Venlafaxine ER	114	63 (55.3)	1.781	1.05, 3.03	0.033
57-70	Placebo	115	57 (49.6)			
	Venlafaxine ER	110	70 (63.6)	2.025	1.14, 3.60	0.016

Abbreviations: PAAS=Panic and Anticipatory Anxiety Scale; ITT=intent-to-treat; LOCF=last observation carried forward.

a: 95% Confidence limits for adjusted odds ratio.

b: Chi-square p-values obtained from logistic regression model logit (response)=treatment+center.

Data from statistical report ITT\pa_logit.htm (21 Feb 2003).

APPENDIX 10.3.13: COMPARISON BETWEEN TREATMENT GROUPS FOR PDSS TOTAL SCORE: ITT PATIENTS

Analysis	Week of Therapy	Therapy Group	n	Adjusted Mean Change from Baseline	Standard Error	Adjusted Mean Placebo-Therapy (95% Confidence Limits)	p-Values[a] vs Placebo
LOCF							
	Baseline	Placebo	155				
		Venlafaxine ER	155				
	2	Placebo	143	-3.27	0.35		
		Venlafaxine ER	134	-3.72	0.36	0.46 (-0.53, 1.44)	0.361
	4	Placebo	149	-5.04	0.36		
		Venlafaxine ER	139	-6.27	0.37	1.23 (0.23, 2.23)	0.016
	6	Placebo	150	-6.42	0.38		
		Venlafaxine ER	140	-7.51	0.39	1.09 (0.03, 2.16)	0.044
	8	Placebo	150	-6.88	0.42		
		Venlafaxine ER	140	-8.38	0.43	1.49 (0.33, 2.66)	0.012
	10	Placebo	150	-7.50	0.45		
		Venlafaxine ER	140	-9.28	0.46	1.78 (0.53, 3.03)	0.006

Analysis	Week of Therapy	Therapy Group	n	Adjusted Mean Change from Baseline	Standard Error	Adjusted Mean Placebo-Therapy (95% Confidence Limits)	p-Values[a] vs Placebo
Observed							
	Baseline	Placebo	155				
		Venlafaxine ER	155				
	2	Placebo	143	-3.27	0.35		
		Venlafaxine ER	134	-3.72	0.36	0.46 (-0.53, 1.44)	0.361
	4	Placebo	137	-5.10	0.37		
		Venlafaxine ER	123	-6.48	0.39	1.38 (0.32, 2.44)	0.011
	6	Placebo	134	-6.83	0.39		
		Venlafaxine ER	117	-8.03	0.41	1.20 (0.09, 2.31)	0.034
	8	Placebo	123	-7.36	0.43		
		Venlafaxine ER	109	-9.15	0.46	1.78 (0.54, 3.03)	0.005
	10	Placebo	107	-8.20	0.50		
		Venlafaxine ER	106	-10.37	0.50	2.17 (0.77, 3.56)	0.003
Final on-Therapy							
		Placebo	152	-7.36	0.47		
		Venlafaxine ER	148	-8.90	0.47	1.53 (0.25, 2.82)	0.020

Abbreviations: ITT=intent-to-treat; LOCF=last observation carried forward.
a: p-Values obtained from ANCOVA model: change from baseline=baseline + treatment + center.

APPENDIX 10.3.14: CGI-I RESPONDERS IN ITT POPULATION: NUMBER OF RESPONDERS/NUMBER EVALUATED (%)

	Weeks On Therapy	Placebo[a] (n=155)	Venlafaxine ER[a] (n=155)	p-Values (Fisher)
LOCF data	1	10/150 (6.7)	10/150 (6.7)	1.000
	2	37/153 (24.2)	44/152 (28.9)	0.366
	3	54/153 (35.3)	60/152 (39.5)	0.479
	4	63/153 (41.2)	84/152 (55.3)	0.016
	6	83/153 (54.2)	98/152 (64.5)	0.081
	8	92/153 (60.1)	102/152 (67.1)	0.234
	10	90/153 (58.8)	108/152 (71.1)	0.031
Observed data	1	10/150 (6.7)	10/150 (6.7)	1.000
	2	37/145 (25.5)	43/136 (31.6)	0.291
	3	50/135 (37.0)	53/126 (42.1)	0.448
	4	61/139 (43.9)	77/127 (60.6)	0.007
	6	80/134 (59.7)	84/117 (71.8)	0.047
	8	83/123 (67.5)	83/109 (76.1)	0.149
	10	70/107 (65.4)	88/106 (83.0)	0.005
Final on-therapy		90/153 (58.8)	108/152 (71.1)	0.031

Abbreviations: ITT=intent-to-treat; LOCF=last observation carried forward; CGI-I= Clinical Global Impressions-Improvement

a: Responder was defined as a patient with a CGI-I score of 1 or 2.

Data from statistical report ITT/resp_g2.htm (21 Feb 2003).

APPENDIX 10.3.15: LIST OF INVESTIGATORS STUDY 391

Investigator (Number)	Address	n
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Horst Berzewski, MD (39117)	Universitätsklinikum Benjamin Franklin Suizid- und Forschungsambulanz der Psychiatrischen Intensiv- und Krisenintervention sstation Hindenburgdamm 30 12200 Berlin Germany	33
Jiří Bilík, MD (39138)	Military Hospital Department of Psychiatry Susilovo námestí 5 771 11 Olomouc Czech Republic	3
Mark Blagden, MD (39122)	Avondale Surgery 3/5 Avondale Road Chesterfield, S40 4TF United Kingdom	9
Bhavesh Bodalia, MD (39123)	268 Holbrook Lane Coventry, CV6 4DD United Kingdom	1

Investigator (Number)	Address	n
Jacques Bradwejn, MD (39146)	Royal Ottawa Hospital, Stress & Anxiety Clinical Research Unit-Perley 2 West 1145 Carling Avenue Ottawa, Ontario K1Z 7K4 Canada	4
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Christer Engström, MD (39156)	Sundsvalls sjukhus Dept. of Psychiatry Öppenvårdmott.4 SE - 851 86 Sundsvall Sweden	3
Peter Franz, MD (39115)	Praxis für Psychiatrie und Psychotherapie Orankestraße 84 13053 Berlin Germany	10
Joël Gailledreau, MD (39113)	3, avenue Mont Cassel 78990 Elancourt France	12
Lennart Gelius, MD (39154)	Ludvikakälsan ABLG Psykiatrikonsult Skogsrudan 4 SE - 771 51 Ludvika Sweden	14
Francis Gheysen, MD (39143)	1 avenue du 6 Juin 14000 Caen France	4

Investigator (Number)	Address	n
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Jonathan Hamling, MD (39125)	Clinical Research Unit, Oldfield Surgery 45 Upper Oldfield Park Bath, BA2 3HT United Kingdom	6
Bryan Hopwood, MD (39126)	The Burngreave Surgery 5 Burngreave Road, Sheffield, South Yorkshire, S3 9DA United Kingdom	11
Rolf Horn, MD (39133)	Giradetallee 7 53604 Bad Honnef Germany	3
Frank Hoyles, MD (39166)	Bron AB Hagagatan 28 SE-791 33 Falun Sweden	3
Jaroslav Hronek, MD (39139)	NZZ Psychiatric Department Jagellonská 7 301 36 Plzen Czech Republic	12

Investigator (Number)	Address	n
Bart Jacobs, MD (39120)	Richterslaan 56 3431 AK Nieuwegein The Netherlands	2
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Hans Martin Kolbinger, MD (39116)	Praxis für Neurologie und Psychiatrie Buchholzstraße 2 53127 Bonn Germany	4
Hannu Koponen, MD (39152)	Mikkelin Neurologipalvelu Oy Maaherrankatu 19A 50100 Mikkeli Finland	5
Joel Langeard, MD (39165)	1 avenue du 6 Juin 14000 Caen France	1
Paul Latimer, PhD, MD (39150)	Kelowna General Hospital 2268 Pandosy street Kelowna, British Columbia V1Y 1T2 Canada	7
Joseph Lejeune, MD (39103)	Centre Hospitalier Régional de la Citadelle Service de Psychiatrie Boulevard du 12ème de Ligne, 1 4000 Liège Belgium	11

Investigator (Number)	Address	n
Jean-Michel LeMellédo, MD (39148)	University of Alberta Psychopharmacology Research Unit 1800 College Plaza 8215 - 112th Street Edmonton, Alberta T6G 2C8 Canada	1
Ulla Marjatta Lepola, MD (39104)	Psychiatric Research Clinic of Kuopio Asemakatu 46 B 23 FIN-70110 Kuopio Finland	13
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Investigator (Number)	Address	n
Jacques Plamondon, MD (39149)	Centre Hospitalier Universitaire de Québec – Pavillon CHUL, Département de Psychiatrie 2705 boul. Laurier Québec, Québec G1V 4G2 Canada	16
Ján Praško, MD (39141)	Psychiatric Center Prague Ústavní 91 181 03 Prague 8 Czech Republic	6
Christine Reynaert, MD (39102)	Cliniques Universitaires de Mont-Godinne (UCL) Service de Psychopathologie et de Médecine Psychosomatique Avenue G. Therasse, 1 5530 Mont-Godinne (Yvoir) Belgium	10
Hilda Russouw, MD (39159)	Vergelegen MediClinic Block 2 Sir Lowrey's Pass Road Somerset West 7130 Republic of South Africa	11
Pierre Savard, MD (39151)	Clinique des Troubles Anxieux 1575, boul.Henri-Bourrassa Ouest Bureau # 505 Montreal, Quebec H3M 3A9 Canada	3
Ingemar Sjödin, MD (39153)	University Hospital Dept. of Psychiatry SE - 581 85 Linköping Sweden	8

Investigator (Number)	Address	n
Zdenska Stankova, MD (39142)	Masaryk's Hospital, Department of Psychiatry Sociální péče 3136/5 401 13 Ústí nad Labem Czech Republic	2
Dan Stein, MD (39158)	University of Stellenbosch Department of Psychiatry Francie van Zyl Road Tygerberg 1505 Republic of South Africa	3
John Tilley, MD (39130)	Pulteney Street Surgery 35 Great Pulteney Street Bath, Avon, BA2 4BY United Kingdom	7
Anneli Timonen, MD (39107)	Rautakiskonkuja 5D 02600 Espoo Finland	16
Laetitia van der Walt, MD (39160)	93 12th Street Menlo Park Pretoria 0081 Republic of South Africa	6
Kurt Wahlstedt, MD (39167)	Läkarhuset i Uppsala Kungsgatan 43 SE – 75 321 Uppsala Sweden	3
Hermanus Arnoldus Wessels, MD (39161)	42 Monument Road Kempton Park Johannesburg 1620 Republic of South Africa	4
Dora Wynchank, MD (39162)	29 Jellicoe Avenue Rosebank Johannesburg 2193 Republic of South Africa	11

APPENDIX 10.3.16: RESULTS OF PRIMARY VARIABLE PAAS: PATIENTS FREE OF FULL-SYMPTOM PANIC ATTACKS, ALL TIME POINTS, ITT POPULATION, LOCF DATA

Days of On Therapy	Therapy Group	Number of Patient	Number of Responder	Adjusted Odds Ratio To Placebo	Wald 95% Confidence Limit For Adjusted Odds Ratio	P-Values* (Chisq)
Days 1-14	Placebo	176	27 (15.3%)			
	Venlafaxine ER	167	27 (16.2%)	1.065	(0.60, 1.89)	0.830
Days 15-28	Placebo	176	56 (31.8%)			
	Venlafaxine ER	167	75 (44.9%)	1.752	(1.11, 2.77)	0.016
Days 29-42	Placebo	176	74 (42.0%)			
	Venlafaxine ER	167	80 (47.9%)	1.275	(0.81, 2.01)	0.295
Days 43-56	Placebo	176	76 (43.2%)			
	Venlafaxine ER	167	96 (57.5%)	1.905	(1.21, 3.01)	0.006
Days 57-70	Placebo	176	94 (53.4%)			
	Venlafaxine ER	167	96 (57.5%)	1.193	(0.76, 1.86)	0.438

* P-Values obtained from logistic regression model logit(response)=treatment + center.

APPENDIX 10.3.17: RESULTS OF PRIMARY VARIABLE PAAS: PATIENTS FREE OF FULL-SYMPTOM PANIC ATTACKS, ALL TIME POINTS, ITT POPULATION, OC DATA

Days of On Therapy	Therapy Group	Number of Patient	Number of Responder	Adjusted Odds Ratio To Placebo	Wald 95% Confidence Limit For Adjusted Odds Ratio	P-Values* (Chisq)
Days 1-14	Placebo	176	27 (15.3%)			
	Venlafaxine ER	167	27 (16.2%)	1.065	(0.60, 1.89)	0.830
Days 15-28	Placebo	166	54 (32.5%)			
	Venlafaxine ER	153	74 (48.4%)	1.965	(1.23, 3.15)	0.005
Days 29-42	Placebo	159	71 (44.7%)			
	Venlafaxine ER	146	75 (51.4%)	1.282	(0.79, 2.09)	0.317
Days 43-56	Placebo	149	70 (47.0%)			
	Venlafaxine ER	142	91 (64.1%)	2.181	(1.30, 3.67)	0.003
Days 57-70	Placebo	141	85 (60.3%)			
	Venlafaxine ER	137	89 (65.0%)	1.257	(0.75, 2.11)	0.385
Final	Placebo	176	92 (52.3%)			
	Venlafaxine ER	167	94 (56.3%)	1.196	(0.77, 1.87)	0.432

* P-Values obtained from logistic regression model logit(response)=treatment + center.

APPENDIX 10.3.18: LIST OF INVESTIGATORS STUDY 354

Investigator (No.)	Address	Number of Patients Enrolled: Open-Label Phase	Number of Patients Enrolled: Double-Blind Phase
Mocrane Abbar, MD (35448)	Chu De Nimes Hopital Caremeau, Psychiatrie A Rue Du Pr Robert Debre 30900 Nimes France	4	2
Bjarne Bahr, MD (35443)	Osterbrogade 142.1 DK2100 Kobenhavn O Denmark	10	7
James Barbee, MD (35401)	LSU HSC Anxiety and Mood Disorders Clinic 1401 Fouscher Street Room 312, Gumbel Building New Orleans, LA 70115 USA	2	1
Benny Barnhart, MD (35402)	Grayline Clinical Drug Trials 3300 Seymour Hwy Wichita Falls, TX 76309 USA	9	5
Kirsten Behnke, MD (35444)	Falkoner Allee 112.1 DK2000 Frediksberg Denmark	14	0
Graham Burrows, MD (35416)	Department of Psychiatry Austin Campus Austin & Repatriation Medical Centre Studley Road Heidelberg, Victoria 3084 Australia	6	5
Alexander Bystritsky, MD (35403)	Pacific Institute For Medical Research 10921 Wilshire Boulevard Suite 701 Los Angeles, CA 90024 USA	11	3

Investigator (No.)	Address	Number of Patients Enrolled: Open-Label Phase	Number of Patients Enrolled: Double-Blind Phase
John Carman, MD (35404)	Carman Research 4015 South Cobb Drive Suite 245 Smyrna, GA 30080 USA	5	2
Włodzimierz Chrzanowski, MD (35464)	Wojewodzka Poradnia Zdrowia Psychicznego Samodzielny Publiczny Zaklad Psychiatricznej Opieki Zdrowotnej w Choroszczy Plac Brodowicza 1 16-070 Choroszcz Poland	16	8
Maciej Czerwinski, MD (35482)	Prywatny Gabinet Lekarski Ul. Matejki 8/1 87-100 Torun Poland	2	1
G. Michael Dempsey, MD (35476)	Albuquerque Neuroscience, Inc. 715 Dr. Martin Luther King Jr. Ave NE Suite 203 Albuquerque, NM 87102 USA	10	5
Caroline Dupont, MD (35477)	Dupont Clinical Research, Inc. 6191 Executive Boulevard Rockville, MD 20852 USA	2	1
Nizar El-Khalili, MD (35406)	Alpine Clinic 3660 Rome Dr. Lafayette, IN 47905 USA	9	3
James Ferguson, MD (35407)	Radiant Research Clinic Salt Lake City-64th South 448 East 6400 South Suite 200 Salt Lake City, UT 84107 USA	8	3

Investigator (No.)	Address	Number of Patients Enrolled: Open-Label Phase	Number of Patients Enrolled: Double-Blind Phase
Thomas George, MD (35418)	Suite 6, North West Specialist Centre 137a Flockton Street Everton Park Brisbane, QLD 4053 Australia	6	5
Francis Gheysen, MD (35471)	1 avenue du 6 Juin 14000 Caen France	2	2
Robert Gibson, MD (35408)	Piedmont Medical Research Associates 1901 S. Hawthorne Road Suite 306 Winston-Salem, NC 27103 USA	4	2
Lawrence Ginsberg, MD (35409)	Red Oak Psychiatry Associates 17115 Red Oak Drive, Suite 109 Houston, TX 77090 USA	1	0
James Grimm, MD (35410)	Oregon Ctr for Clinical Investigations, Inc. 572 West 11th Avenue Eugene, OR 97401 USA	9	2
Antonio Guerrini, MD (35460)	Dipartimento di Salute Mentale Padiglione Grossoni, Psichiatria I Azienda Ospedaliera Ospedale Niguarda Ca'Granda Piazza Ospedale Maggiore, 3 20 162 Milan Italy	2	1
Leckraj Gujadhur, MD (35450)	Centre Hospitalier De Saint-Egreve 3 Rue De La Gare 38521 Saint Egrève Cedex France	2	2
Saul Helfing, MD (35478)	Oregon Center for Clinical Investigations, Inc. 2230 NW Pettygrove Street Suite 120 Portland, OR 97210 USA	2	1

Investigator (No.)	Address	Number of Patients Enrolled: Open-Label Phase	Number of Patients Enrolled: Double-Blind Phase
Peter Holland, MD (35479)	Summit Research Network (Florida), Inc. Boca Raton Medical Research 7284 Palmetto Park Road Suite 205 Boca Raton, FL 33433 USA	0[a]	0[a]
Jozsef Horvath, MD (35453)	Dr. Albert Kenessey Hospital II Department of Psychiatry RAKOCZI 125-127 2660 Balassagyarmat Hungary	13	10
Rakesh Jain, MD, MPH (35411)	R/D Clinical Research Inc. 461 This Way, P.O. Drawer B Lake Jackson, TX 77566 USA	5	1
Sandor Jancsovics, MD (35454)	Jasz Nagykun-Szolnok Megyei Hetenyi Geza Hospital I Department of Psychiatry Toszegi Ut. 21 5400 Szolnok Hungary	14	12
Mieczyslaw Janiszewski, MD (35465)	Wojewódzki Osrodek Lecznictwa, Psychiatrycznego, Ul. M. Sklodowskiej Curie 27/29, 87-100 Torun Poland	13	10
Nicholas Keks, MD (35419)	Box Hill Hospital 131 Thames Street Box Hill, VIC 3128 Australia	1	0
Kevin Kjernisted, MD (35436)	Anxiety Disorders Clinic St Boniface General Hospital M5-409 Taché Avenue Winnipeg, Manitoba R2H 2A6 Canada	7	5

Investigator (No.)	Address	Number of Patients Enrolled: Open-Label Phase	Number of Patients Enrolled: Double-Blind Phase
Zoltan Lajos, MD (35455)	Markhot Ferenc Megyei Hospital 2nd Department of Psychiatry Szechenyi u. 28 3300 Eger Hungary	7	6
Paul Latimer, MD (35474)	Okanagan Clinical Trials Suite 304-3001 Tutt Street Kelowna, British Colombia V1Y 2H4 Canada	6	6
Jean-Michel LeMellédo, MD (35437)	Psychopharmacology Research Unit 1800 College Plaza 8215 112th Street Edmonton, Alberta T6G 2C8 Canada	0[a]	0[a]
Carlo Maggini, MD (35461)	Instituto di Clinica Psichiatrica Universita degli Study di Parma Piazzale Matteotti 43100 Parma Italy	1	0
Kevin McKenna, MD (35438)	Grey Nuns Community Hospital Room 1801 1100 Youville Drive West Edmonton, Alberta T6L 5X8 Canada	1	1
Saibal Nandy, MD (35439)	631 Prospect Drive S.W. Medicine Hat, Alberta T1A 4C2 Canada	8	5
Gyorgy Ostorharics-Horvath, MD (35456)	Petz Aladar Megyei Hospital 2nd Department of Psychiatry Zrinyi U.13 9024 Gyor Hungary	5	1
Olivier Phan, MD[b] (35451)	Hopital De Meaux 6-8 Rue Saint-Fiacre 77104 Meaux France	4	1

Investigator (No.)	Address	Number of Patients Enrolled: Open-Label Phase	Number of Patients Enrolled: Double-Blind Phase
Anna Potoczek, MD (35466)	Klinika Psychiatrii Doroslych, Oddzia D Katedra Psychiatrii Collegium Medicum Uniwersytetu Jagiellonskiego Ul. Kopernika 21 A 31-501 Krakow Poland	7	6
Stig Rasmussen, MD (35446)	Slotsgade 65C DK3400 Hillerod Denmark	7	6
Carlo Robotti, MD (35462)	Servizio Psichiatrico Diagnosi e Cura Ospedale Civile Maggiore Piazzale Stefani 1 37121 Verona Italy	2	2
Steven Rudolph, DO (35412)	Medical Center for Clinical Research 9040 Friars Road Suite 540 San Diego, CA 92108 USA	4	0
Isaac Schweitzer, MD (35421)	The Melbourne Clinic 130 Church Street Richmond, Victoria 3121 Australia	2	2
David Sheehan, MD (35413)	University of South Florida College of Medicine Psychiatry Center 3515 East Fletcher Tampa, FL 33613 USA	12	6
Richard Singer, MD (35414)	Neurological Clinical Research, Inc. 350 NW 84th Ave. Suite 206 Plantation, FL 33324 USA	2	1
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Investigator (No.)	Address	Number of Patients Enrolled: Open-Label Phase	Number of Patients Enrolled: Double-Blind Phase
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John Tiller, MD (35423)	Suite A, First Floor Albert Road Clinic 31-33 Albert Road Melbourne 3004 Australia	2	2
Martin Tremblay, MD[b] (35440)	Expertise Neurosciences 1030, rue Cherrier Bureau 208 Montréal, Québec H2L 1H9 Canada	8	2
Louis Van Zyl, MD (35442)	Kingston General Hospital Consultation, Liaison Psychiatry 76 Stuart Street Kingston, Ontario K7L 2V7 Canada	0[c]	0
Gabor Vincze, MD (35457)	Pandy Kalman Hospital 3rd Department of Psychiatry Semmelweis U. 1 5701 Gyula Hungary	9	3
Karen Weihs, MD (35415)	George Washington University Medical Center 2300 K Street, NW Warwick Building, Room 205 Washington, DC 20037 USA	7	1
Evan Zimmer, MD (35481)	Bioquan Research Group, Inc. 12995 NE 7th Avenue North Miami, FL 33161 USA	25	16

a: One (1) patient was a screen failure; no study medication was dispensed.
b: The investigator's address changed after study close-out; the current address is shown.
c: Two (2) patients were screen failures; no study medication was dispensed.

APPENDIX 10.3.19: LOGISTIC REGRESSION FOR PATIENTS FREE OF PAAS FULL-SYMPTOM PANIC ATTACKS, OBSERVED DATA: ITT PATIENTS (DOUBLE-BLIND PERIOD)

Days of On Therapy	Therapy Group	Number of Patient	Number of Responder	Adjusted Odds Ratio To Placebo	Wald 95% Confidence Limit For Adjusted Odds Ratio	P-Values* (Chisq)
DB DAYS 1-14	Placebo	80	46 (57.5%)			
	Venlafaxine ER	89	68 (76.4%)	2.454	(1.25, 4.81)	0.009
DB DAYS 15-28	Placebo	62	42 (67.7%)			
	Venlafaxine ER	79	58 (73.4%)	1.348	(0.64, 2.84)	0.431
DB DAYS 29-42	Placebo	55	36 (65.5%)			
	Venlafaxine ER	74	57 (77.0%)	1.944	(0.87, 4.33)	0.104
DB DAYS 43-56	Placebo	49	33 (67.3%)			
	Venlafaxine ER	70	59 (84.3%)	2.746	(1.13, 6.69)	0.026
DB DAYS 57-70	Placebo	48	30 (62.5%)			
	Venlafaxine ER	69	56 (81.2%)	2.633	(1.13, 6.16)	0.026
DB DAYS 71-84	Placebo	41	31 (75.6%)			
	Venlafaxine ER	65	57 (87.7%)	2.336	(0.83, 6.58)	0.108
DB DAYS 85-98	Placebo	38	29 (76.3%)			
	Venlafaxine ER	64	55 (85.9%)	1.888	(0.67, 5.33)	0.230
DB DAYS 99-112	Placebo	37	30 (81.1%)			
	Venlafaxine ER	62	57 (91.9%)	2.889	(0.83, 10.10)	0.097
DB DAYS 113-126	Placebo	35	30 (85.7%)			
	Venlafaxine ER	62	56 (90.3%)	1.648	(0.48, 5.66)	0.427
DB DAYS 127-140	Placebo	33	26 (78.8%)			
	Venlafaxine ER	60	59 (98.3%)	11.534	(1.85, 71.75)	0.009
DB DAYS 141-154	Placebo	33	29 (87.9%)			
	Venlafaxine ER	60	57 (95.0%)	2.568	(0.59, 11.21)	0.210
DB DAYS 155-168	Placebo	31	25 (80.6%)			
	Venlafaxine ER	57	50 (87.7%)	1.775	(0.52, 6.02)	0.357
DB DAYS 169-182	Placebo	28	23 (82.1%)			
	Venlafaxine ER	54	51 (94.4%)	3.883	(0.83, 18.05)	0.084
FINAL	Placebo	80	25 (31.3%)			
	Venlafaxine ER	89	47 (52.8%)	2.475	(1.31, 4.66)	0.005

* P-Values obtained from logistic regression model logit(response)=treatment+center.

10.4 Appendix to Integrated Review of Efficacy (Section 6)

APPENDIX 10.4.1: PRIMARY EFFICACY VARIABLE PAAS BY AGE GROUP; PERCENT OF PATIENTS FREE OF FULL-SYMPTOM PANIC ATTACKS, ITT POPULATION, POOLED DATA FOR STUDIES 398, 399, 353, AND 391

	< 50 years		≥ 50 years		p-Value		
Variable	Pbo	Ven ER	Pbo	Ven ER	Age	Therapy	Interaction[a]
PAAS, % patients free of full-symptom panic attacks	231/537 (43%)	459/804 (57%)	46/97 (47%)	102/142 (72%)	0.0054	<0.0001	0.1128

Abbreviations: ITT = intent-to-treat; Pbo=placebo; Ven ER = venlafaxine ER; PAAS = Panic and Anticipatory Anxiety Scale.
a: Interaction is age-therapy interaction in the statistical model.
Data from Summary of Drug-demo, drug-disease interaction for 353, 391, 398 and 399 (03 May 2004).

APPENDIX 10.4.2: PRIMARY EFFICACY VARIABLE PAAS BY GENDER; PERCENT OF PATIENTS FREE OF FULL-SYMPTOM PANIC ATTACKS, ITT POPULATION, POOLED DATA FOR STUDIES 398, 399, 353, AND 391

	Male		Female		p-Value		
Variable	Pbo	Ven ER	Pbo	Ven ER	Sex	Therapy	Interaction[a]
PAAS, % patients free of full-symptom panic attacks	114/227 (50%)	202/312 (65%)	163/407 (40%)	359/634 (57%)	0.0006	< 0.0001	0.7466

Abbreviations: ITT = intent-to-treat; Pbo=placebo; Ven ER = venlafaxine ER; PAAS = Panic and Anticipatory Anxiety Scale.
a: Interaction is sex-therapy interaction in the statistical model.
Data from Summary of Drug-demo, drug-disease interaction for 353, 391, 398 and 399 (03 May 2004).

APPENDIX 10.4.3: PRIMARY EFFICACY VARIABLE PAAS BY ETHNIC ORIGIN; PERCENT OF PATIENTS FREE OF FULL-SYMPTOM PANIC ATTACKS, ITT POPULATION, POOLED DATA FOR STUDIES 398, 399, 353, AND 391

	White		Non-White		p-Value		
Variable	Pbo	Ven ER	Pbo	Ven ER	Race	Therapy	Interaction[a]
PAAS, % patients free of full-symptom panic attacks	215/502 (43%)	426/727 (59%)	62/132 (47%)	135/219 (62%)	0.2425	< 0.0001	0.8728

Abbreviations: ITT = intent-to-treat; Pbo=placebo; Ven ER = venlafaxine ER; PAAS = Panic and Anticipatory Anxiety Scale.
a: Interaction is race-therapy interaction in the statistical model.
Data from Summary of Drug-demo, drug-disease interaction for 353, 391, 398 and 399 (03 May 2004).

APPENDIX 10.4.4: PRIMARY EFFICACY VARIABLE PAAS BY BASELINE SEVERITY OF PANIC ATTACKS; PERCENT OF PATIENTS FREE OF FULL-SYMPTOM PANIC ATTACKS ITT POPULATION, POOLED DATA FOR STUDIES 398, 399, 353, AND 391

	≤ Median[a]		> Median[a]		p-Value		
Variable	Pbo	Ven ER	Pbo	Ven ER	Severity	Therapy	Interaction[b]
PAAS, % patients free of full-symptom panic attacks	188/357 (53%)	307/446 (69%)	88/276 (32%)	253/499 (51%)	< 0.0001	< 0.0001	0.6378

Abbreviations: ITT = intent-to-treat; Pbo=placebo; Ven ER = venlafaxine ER; PAAS = Panic and Anticipatory Anxiety Scale.
a: Median number of episodes at baseline.
b: Interaction is baseline severity-therapy interaction in the statistical model.
Data from Summary of Drug-demo, drug-disease interaction for 353, 391, 398 and 399 (03 May 2004).

APPENDIX 10.4.5: PRIMARY EFFICACY VARIABLE PAAS BY PRESENCE OR ABSENCE OF AGORAPHOBIA AT FINAL ON-THERAPY; PERCENT OF PATIENTS FREE OF FULL-SYMPTOM PANIC ATTACKS, ITT POPULATION, POOLED DATA FOR STUDIES 398, 399, 353, AND 391

	---Agoraphobia Present---		---Agoraphobia Absent---		----------p-Value----------		
Variable	Pbo	Ven ER	Pbo	Ven ER	Agoraphobia	Therapy	Interaction[a]
PAAS, % patients free of full-symptom panic attacks	191/452 (42%)	366/662 (55%)	87/187 (47%)	198/289 (69%)	< 0.0013	< 0.0001	0.0878

Abbreviations: ITT = intent-to-treat; Pbo=placebo; Ven ER = venlafaxine ER; PAAS = Panic and Anticipatory Anxiety Scale.
a: Interaction is agoraphobia presence-therapy interaction in the statistical model.
Data from interact_agoraphobia (15 Jun 2004).

10.5 Appendix to Integrated Review of Safety (Section 7)

APPENDIX 10.5.1: NUMBER (%) OF PATIENTS REPORTING ADVERSE EVENTS THAT CAUSED WITHDRAWAL FROM STUDY SAFETY POPULATION ON-THERAPY (STUDIES 353, 391, 398, 399)

VENLAFAXINE ER IN ADULT OUTPATIENTS WITH PANIC DISORDER IN POOLED STUDIES 353 391 398 399
NUMBER (%) OF PATIENTS REPORTING ADVERSE EVENTS THAT CAUSED WITHDRAWAL FROM STUDY SAFETY POPULATION (ON THERAPY)

BODY SYSTEM (1) ADVERSE EVENT	Placebo (N = 662)	Venlafaxine ER (N = 1001)	Paroxetine (N = 327)
ANY ADVERSE EVENT	41 (6)	74 (7)	30 (9)
BODY AS A WHOLE	7 (1)	22 (2)	4 (1)
ABDOMINAL PAIN	0	3 (<1)	2 (<1)
ALLERGIC REACTION	1 (<1)	0	0
ASTHENIA	0	11 (1)	0
CHEST PAIN	0	1 (<1)	1 (<1)
FACE EDEMA	0	1 (<1)	0
HEADACHE	5 (<1)	8 (<1)	1 (<1)
LAB TEST ABNORMAL	1 (<1)	0	0
SUICIDE ATTEMPT	0	1 (<1)	0
CARDIOVASCULAR SYSTEM	6 (<1)	8 (<1)	3 (<1)
HYPERTENSION	2 (<1)	5 (<1)	2 (<1)
MYOCARDIAL INFARCT	1 (<1)	0	0
PALPITATION	3 (<1)	0	2 (<1)
SYNCOPE	0	1 (<1)	0
TACHYCARDIA	1 (<1)	1 (<1)	1 (<1)
VASODILATATION	0	1 (<1)	0
DIGESTIVE SYSTEM	4 (<1)	24 (2)	4 (1)
ANOREXIA	1 (<1)	4 (<1)	0
DIARRHEA	1 (<1)	2 (<1)	2 (<1)
DRY MOUTH	0	3 (<1)	0
GASTRITIS	1 (<1)	0	0
NAUSEA	3 (<1)	20 (2)	1 (<1)
VOMITING	1 (<1)	6 (<1)	2 (<1)
METABOLIC AND NUTRITIONAL	1 (<1)	1 (<1)	0
PERIPHERAL EDEMA	0	1 (<1)	0
WEIGHT LOSS	1 (<1)	0	0

NERVOUS SYSTEM	27 (4)	42 (4)	15 (5)
ABNORMAL DREAMS	1 (<1)	0	0
AGITATION	7 (1)	2 (<1)	3 (<1)
ANXIETY	6 (<1)	11 (1)	3 (<1)
APATHY	0	1 (<1)	0
CIRCUMORAL PARESTHESIA	0	1 (<1)	0
CONVULSION	0	1 (<1)	0
DEPERSONALIZATION	1 (<1)	2 (<1)	1 (<1)
DEPRESSION	5 (<1)	3 (<1)	3 (<1)
DIZZINESS	3 (<1)	8 (<1)	0
EMOTIONAL LABILITY	1 (<1)	0	0
HALLUCINATIONS	0	1 (<1)	0
HOSTILITY	0	0	1 (<1)
HYPERKINESIA	0	1 (<1)	0
HYPERTONIA	0	1 (<1)	0
HYPESTHESIA	0	2 (<1)	0
INCOORDINATION	0	1 (<1)	0
INSOMNIA	4 (<1)	13 (1)	2 (<1)
LIBIDO DECREASED	0	1 (<1)	1 (<1)
NERVOUSNESS	4 (<1)	1 (<1)	0
OBSESSIVE-COMPULSIVE SYMPTOMS	1 (<1)	0	0
PARESTHESIA	1 (<1)	0	0
SOMNOLENCE	0	1 (<1)	1 (<1)
SUICIDAL IDEATION	1 (<1)	1 (<1)	0
THINKING ABNORMAL	1 (<1)	1 (<1)	0
TREMOR	2 (<1)	5 (<1)	1 (<1)
VERTIGO	1 (<1)	2 (<1)	2 (<1)
RESPIRATORY SYSTEM	1 (<1)	1 (<1)	0
DYSPNEA	1 (<1)	1 (<1)	0
SKIN AND APPENDAGES	3 (<1)	14 (1)	2 (<1)
ECZEMA	1 (<1)	0	0
PRURITUS	0	1 (<1)	0
RASH	1 (<1)	4 (<1)	2 (<1)
SWEATING	1 (<1)	8 (<1)	0
URTICARIA	0	1 (<1)	0
SPECIAL SENSES	1 (<1)	4 (<1)	3 (<1)
ABNORMALITY OF ACCOMMODATION	0	1 (<1)	0
MYDRIASIS	0	1 (<1)	1 (<1)
TINNITUS	1 (<1)	2 (<1)	2 (<1)
UROGENITAL SYSTEM	3 (<1)	7 (<1)	3 (<1)
ABNORMAL EJACULATION/ORGASM	0	0	2 (<1)
AMENORRHEA	0	1 (<1)	0
ANORGASMIA	0	1 (<1)	0
OLIGURIA	0	1 (<1)	0
OVARIAN CYST	0	1 (<1)	0
SEXUAL FUNCTION ABNORMAL	0	1 (<1)	0
UNINTENDED PREGNANCY	3 (<1)	1 (<1)	1 (<1)
URINARY FREQUENCY	0	1 (<1)	0

NOTE (1)- BODY SYSTEM TOTALS ARE NOT NECESSARILY THE SUM OF THE INDIVIDUAL ADVERSE EVENTS SINCE A PATIENT MAY REPORT TWO OR MORE DIFFERENT ADVERSE EVENTS IN THE SAME BODY SYSTEM.

APPENDIX 10.5.2: CRITERIA FOR DETERMINING POTENTIALLY CLINICALLY IMPORTANT LABORATORY TEST RESULTS

Test[a]	Criteria
Hematology	
Hemoglobin	<95 g/L or >165 g/L (women) or <115 g/L or >185 g/L (men)
Hematocrit	<0.32 or >0.50 (women) or <0.37 or >0.55 (men)
WBC count	$<2.8 \times 10^9$/L or $>16 \times 10^9$/L
Platelet count	$<75 \times 10^9$/L or $>700 \times 10^9$/L
Blood Chemistry	
Sodium	<126 mmol/L or >156 mmol/L
Potassium	<2.5 mmol/L or >6.5 mmol/L
Calcium	<2.046 mmol/L or >2.994 mmol/L
Chloride	<90 mmol/L or >118 mmol/L
Triglycerides, fasting/not fasting/unknown	≥2.258 mmol/L
Glucose, fasting/not fasting/unknown	<2.22 mmol/L or ≥11.10 mmol/L
Uric acid	>0.4758 mmol/L (women) or >0.5948 mmol/L (men)
Total protein	<45 g/L or ≥100 g/L
Albumin	<25 g/L
Total bilirubin	*≥1.5 x ULN*
ALT	*≥3 x ULN*
AST	*≥3 x ULN*
Alkaline phosphatase	*≥3 x ULN*
BUN	*≥1.5 x ULN*
Creatinine	*≥1.5 x ULN*
Bicarbonate	*Increase or decrease from baseline of ≥4 mmol/L and ONR*
Cholesterol, fasting/not fasting/unknown	≥7.758 mmol/L
Total cholesterol, fasting	*Increase ≥1.29 mmol/L and value ≥6.75 mmol/L*
Total cholesterol, not fasting/unknown	*Increase ≥1.29 mmol/L and value ≥6.75 mmol/L*
HDL cholesterol, fasting	*Decrease >0.21 mmol/L and value <0.91 mmol/L*
HDL cholesterol, not fasting/unknown	*Decrease >0.21 mmol/L and value <0.91 mmol/L*
LDL cholesterol, fasting	*Increase ≥1.29 mmol/L and value ≥4.91 mmol/L*
Urinalysis	
Specific gravity	<1.001 or >1.035
pH	≤4 or ≥9
Protein/albumin	Positive value
Glucose/sugar	Positive value
Hemoglobin/blood	Positive value
Ketones	Positive value

Abbreviations: ULN=upper limit of normal range; ALT=alanine aminotransferase; AST=aspartate transaminase; BUN=blood urea nitrogen; ONR=outside normal range; HDL=high-density lipoprotein; LDL=low-density lipoprotein; PD=panic disorder, WBC=white blood cell.

a: Criteria defined by FDA. If FDA did not provide criteria for a test, Wyeth criteria (shown in *italics*) were used.

APPENDIX 10.5.3: NUMBER OF PATIENTS WITH POTENTIALLY CLINICALLY IMPORTANT VITAL SIGN RESULTS/NUMBER TESTED (%), DOUBLE BLIND PERIOD IN STUDIES 398, 399, 353, AND 391

Vital Signs **Position** Test (units) *Criterion*	Placebo[a,b] (n=650)	Venlafaxine ER[b,c] (n=973)	Paroxetine[d,e] (n=319)
Total	107 (16)	187 (19)	62 (19)
Standing			
Diastolic BP (mm Hg)			
Increase of ≥15 mm Hg and pressure ≥105 mm Hg	20 (3)	23 (2)	7 (2)
Decrease of ≥15 mm Hg and pressure ≤50 mm Hg	7 (1)	14 (1)	4 (1)
Systolic BP (mm Hg)			
Increase of ≥20 mm Hg and pressure ≥180 mm Hg	3 (< 1)	1 (< 1)	0
Decrease of ≥20 mm Hg and pressure of ≤90 mm Hg	15 (2)	37 (4)	14 (4)

Vital Signs **Position** Test (units) *Criterion*	Placebo[a,b] (n=650)	Venlafaxine ER[b,c] (n=973)	Paroxetine[d,e] (n=319)
Supine			
Diastolic BP (mm Hg)			
Increase of ≥15 mm Hg and pressure ≥105 mm Hg	11 (2)	11 (1)	6 (2)
Decrease of ≥15 mm Hg and pressure ≤50 mm Hg	11 (2)	14 (1)	5 (2)
Systolic BP (mm Hg)			
Increase of ≥20 mm Hg and pressure ≥180 mm Hg	3 (< 1)	7 (< 1)	0
Decrease of ≥20 mm Hg and pressure of ≤90 mm Hg	17 (3)	29 (3)	6 (2)
Pulse (beats/min)			
High (≥120 beats/min)	4 (< 1)	5 (< 1)	0
Postural BP change[f]			
Diastolic BP (mm Hg)			
Decrease of ≥15 mm Hg	26 (4)	40 (4)	26 (8)
Systolic BP (mm Hg)			
Decrease of ≥30 mm Hg	3 (< 1)	17 (2)	2 (< 1)
Weight (kg) change from baseline			
Increase of ≥7%	12/ 569 (2)	22/ 855 (3)	6/ 291 (2)
Decrease of ≥7%	9/ 569 (2)	29/ 855 (3)	9/ 291 (3)

Abbreviations: BP=blood pressure; SDBP=supine diastolic blood pressure.
a. For placebo, n=650 except where indicated.
b. For venlafaxine ER and placebo, used pooled data from studies 398, 399, 353, and 391.
c. For venlafaxine ER, n=973 except where indicated.
d. For paroxetine, n =319 except where indicated.
e. Paroxetine data are from studies 398 and 399.
f. Systolic and diastolic delta variables are derived as change from last supine to first standing, respectively.
Data are from CDR Group 1, 6-5VPCI (06 May 2004)

APPENDIX 10.5.4: CRITERIA FOR DETERMINING POTENTIALLY CLINICALLY IMPORTANT VALUES IN ECG RESULTS

Test[a]	Criteria
Heart rate	≤40 beats/min or ≥120 beats/min
PR interval	≥200 ms
QT interval	≥480 ms
QRS interval	≥120 ms
QTc	≥500 ms
Rhythm	*Change from normal to abnormal*[b]

Abbreviation: ECG=electrocardiogram.
a: Wyeth criteria in *italics*.
b: Normal rhythm is defined as sinus rhythm; abnormal is any other rhythm.

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

/s/

Michelle Chuen
6/10/05 11:24:48 AM
MEDICAL OFFICER

Thomas Laughren
7/5/05 08:25:07 AM
MEDICAL OFFICER
I agree that these supplements are approvable; see memo to file for more detailed comments.--TPL

Review and Evaluation of Clinical Data
NDA #20-699

Sponsor:	Wyeth Pharmaceuticals, Inc.
Drug:	Venlafaxine HCl Extended Release Capsules
Indication:	Panic Disorder
Material Submitted:	Response to 7/15/05 Approvable Letter
Correspondence Date:	September 23, 2005
Date Received:	September 26, 2005

I. Background

On 9/29/04, the sponsor submitted this NDA for the approval of venlafaxine ER in the treatment of panic disorder.

The Office issued an approvable letter on 7/15/05. In summary, this letter indicated that, prior to approval, the sponsor would need to address several points, to include the following clinical issues:

1) clarification of ITT population definition used in study analyses and warrant that ITT population definition changes were not made after unblinding
2) enumeration and line listing of patients with greater than 3 days of missing PAAS data who were included in the efficacy analyses (further efficacy analyses may have been required if this number was large)
3) recomputation of incidence of suicidal ideation and behavior for all patients in the pool of short-term studies
4) explanation of line entries in adverse event case report tabulations missing both verbatim and preferred terms, explanation of verbatim adverse events that were not coded to preferred terms, and explanation of preferred term missing an associated verbatim adverse event
5) clarification of discrepancy in number of patients completing the open label period in Study 354
6) clarification of patient dataset used in Tables 2.7.4.3.2.1C and 2.7.4.3.2.2B of the Summary of Clinical Safety
7) enumeration of mean daily dose and total duration of exposure for all 5 studies combined

8) clarification of tables in which mean daily dose for a 225 mg fixed dose group was 100-200 mg.
9) mean daily dose at the end of the open-label phase of study 354
10) mean time in continuous responder status during the open-label phase of study 354
11) QT data using the Fredericia correction formula
12) incorporation of adverse events that occurred in patients randomized to placebo during the double-blind period of study 354.
13) world literature update
14) foreign regulatory update/foreign labeling
15) proposed promotional materials

This submission contains their response to the above.

II. Clinical Data

A. ITT Population Definition

The sponsor states that, though there are discrepancies in their ITT population as defined in clinical study reports and protocols, the ITT population definition under which the analyses were conducted is the same. The intent-to-treat (ITT) patients were those who:

- had a baseline evaluation
- had at least one on-therapy double-blind evaluation (defined as a period ≥7 days of double-blind PAAS data) of the primary efficacy variable within 3 days of stopping nontaper test article

In addition, the sponsor states that for studies 398 and 354, the ITT population was defined before study unblinding.

B. PAAS Data

The sponsor provided a tabulation showing that in the venlafaxine ER- and placebo-treatment groups, there were 2 patients in study 398, 4 patients in study 399, and 2 patients in study 354 who were included in the ITT efficacy analyses population but who were missing ≥ 3 days of PAAS data in any 14-day analysis interval. Given the small number of such patients, further efficacy analyses are not necessary.

C. Suicidality

The sponsor updated the adverse event record for patient 35370-1066 to include the verbatim COSTART terms "suicidal ideation" and "homicidal ideation". They also corrected incidences for suicidal ideation and homicidal ideation taking into account this updated adverse event record.

D. SAS Transport Files

To account for the line entries that were missing both verbatim and preferred terms, the sponsor states that some sites involving a few cases in studies 354 and 398 sent in blank pages of an AE form, although no AEs actually occurred. However, I noted that in the SAS transport files, many (12,475) line entries from all 5 studies were missing both verbatim and preferred terms. I requested clarification in a 10/27/05 email to the sponsor. The sponsor responded in an 11/1/05 email stating that the dataset was designed to capture the entire patient case report form including all visits regardless of adverse event reporting status, and that some patients who were screen failures were also included.

To account for the case in which a preferred term was not associated with a verbatim term, the sponsor states that one patient was found to have an adverse event, but subsequent correspondence requested that the adverse event be deleted from the database. The preferred term was inadvertently retained. They state that the preferred term will be removed from the database. However, they state the patient was 3530017-0653 when, according to the SAS transport files, the patient is 3910017-0653.

To account for verbatim terms not coded to preferred terms, the sponsor states that these are patients who enrolled into the screening period but were never randomized to a treatment, and that the COSTART coding dictionary was never applied in these cases.

E. Discontinuations during the Open-Label Treatment Period in Study 354

The sponsor satisfactorily explained the patient disposition for the open-label period of study 354.

F. Mean Laboratory Results Tables

The sponsor states that the Table 2.7.4.3.2.1C is based on the safety population (defined as patients who took at least 1 dose of study medication) from the pooled short-term double-blind studies. However, I noted that the numbers of patients in the table at final on-therapy did not correlate with the safety population numbers. In addition, a table footnote stated that final is week 10 in studies 353 and 391, and week 12 in study 398, contradicting the definition of final on-therapy given in the text of their response to the approvable letter.

I requested clarification in a 10/27/05 email to the sponsor. The sponsor responded in an 11/1/05 email stating that only patients with both baseline and on-therapy laboratory measurements were included in the on-therapy analysis. Patients were not included if they discontinued early without having on-therapy laboratory measurements, or if they missed more than 3 days of study medication before the on-therapy visit. In addition, the sponsor stated that reference to study 399 was omitted in error from the table.

The sponsor states that Table 2.7.4.3.2.2B is based on patients who entered the double-blind period. The final on-therapy visit was defined as the day of the last full dose of study medication, or when a patient withdrew from a study prematurely. However, I noted that the numbers of patients at final on-therapy did not correlate with the numbers of patients who entered the double-blind period.

I requested clarification in a 10/27/05 email to the sponsor. The sponsor responded in an 11/1/05 email and stated that only patients with both baseline and on-therapy laboratory measurements were included in the on-therapy analysis. Patients were not included if they discontinued early without having on-therapy laboratory measurements, or if they missed more than 3 days of study medication before the on-therapy visit.

G. Total Duration of Exposure for All 5 Studies

The sponsor provided a table presenting the overall exposure for all 5 studies. This table (Table 7.0-1) is extracted from the sponsor's submission and included in Appendix 1. Patients who took at least 1 dose of venlafaxine ER during the on-therapy period are categorized

by their total mean daily dose for the entire on-therapy period and by each time interval in which they were exposed. Patients are included in only 1 column (mean daily dose) but are included in multiple rows (exposure days) depending on the duration of treatment.

A total of 65 patients (5% of all 1314 patients) had an exposure to venlafaxine ER of over 182 days. Twenty-five of these 65 patients received a mean daily dose over 200 mg/day. Twenty-seven patients (2%) of all 1314 patients received a mean dose over 200 mg/day.

H. Overall Extent of Exposure

The sponsor states the mean daily dose in the mentioned tables includes the titration period at start of study, resulting in mean daily doses less than 200 mg/day.

I. Mean Daily Dose at End of Open-Label Treatment for ITT Population Qualified for Randomization into Double-Blind Period of Study 354

Table 9.0-1 is extracted from the sponsor's submission and included in Appendix 1. The overall mean daily dose was 141.8 mg.

J. Mean Time in Continuous Responder Status during Open-Label Period for Patients Qualified for Randomization into Double-Blind Period of Study 354

Table 10.0-1 is extracted from the sponsor's submission and included in Appendix 1. The responder status was determined by checking the CGI-I score at each visit date and the weekly number of full-symptom panic attacks between that visit date and the previous visit date. When both criteria were met (i.e., no more than one full-symptom panic attack per week and a CGI-I score of 1 or 2), the patient was considered a responder at that visit date. The time in continuous responder status was calculated as the time between the first and last visit date as a responder.

They state that 34 of the 169 patients had "0 days" for continuous responder status. Twenty-nine (29) of these were patients who were responders at the last visit (week 12) only (did not meet responder criteria at week 10). Five (5) of these patients did not meet responder criteria at the last visit (week 12) but were responders at the

previous visits. According to protocol, these 5 patients should not have entered the double-blind period of the study. However, since the number of such patients is small, and evenly distributed between placebo and venlafaxine ER treatment groups (2 in placebo and 3 in venlafaxine ER) it is unlikely this would significantly influence study efficacy results.

K. QTc Interval by Fredericia Correction Formula

The sponsor submitted QT data using the Fredericia formula.

Mean Change from Baseline in ECG parameters
For the pool of the 3 short-term studies and for study 391, mean changes from baseline to final on-therapy assessment were not statistically significantly different between venlafaxine ER and placebo for QTc interval using the Fredericia Correction Formula. Data are presented in Tables 11.1 and 11.2 below.

TABLE 11.1: MEAN CHANGES FROM BASELINE FOR FREDERICIA CORRECTION QTC (SHORT-TERM STUDIES 398, 399, AND 353): DOUBLE-BLIND PERIOD

	Placebo		Venlafaxine ER	
	N	Mean Δ^a	N	Mean Δ^a
QTc interval (ms)	395	-0.26	661	-2.06

a. No significant ($p \leq 0.05$) differences between groups for comparison based on adjusted means using ANCOVA with baseline as covariate.

TABLE 11.2: MEAN CHANGES FROM BASELINE FOR FREDERICIA CORRECTION QTC (SHORT-TERM STUDY 391): DOUBLE-BLIND PERIOD

	Placebo		Venlafaxine ER	
	N	Mean Δ^a	N	Mean Δ^a
QTc interval (ms)	143	-2.90	129	0.53

a. No significant ($p \leq 0.05$) differences between groups for comparison based on adjusted means using ANCOVA with baseline as covariate.

Potentially Clinically Significant ECG Changes
Using the Fredericia correction formula, there were no patients with Potentially Clinically Important QTc results.

L. Pooled Treatment-Emergent Adverse Events

Under ADVERSE REACTIONS in the subsection of labeling entitled "Other Adverse Events Observed during the Premarketing Evaluation of Effexor and Effexor XR," the sponsor has satisfactorily incorporated a revision to include the 84 patients in study 354 who were randomized to placebo. In addition, "homicidal ideation" was added as a new term based on additional information on patient 35370-1066 (see section C).

M. World Literature Update

The world's literature was updated by Helen Kellar-Wood, Ph.D., Senior Information Scientist II in Research Information Management. The databases searched with the appropriate search items included MEDLINE, BIOSIS, Current Contents, Derwent Drug File, and EMBASE. The search interval was from March 4, 2004 through July 26, 2005. Eighteen articles were reviewed.

Karen Tourian, M.D., Effexor XR Medical Monitor for Panic Disorder, provided a warrant attesting that she reviewed the worldwide literature review and that no relevant papers or issues that would adversely affect the conclusions about the safety profile of Effexor XR were found.

N. Foreign Regulatory Update/Foreign Labeling

As of 9/1/05, Effexor XR has been approved in Canada, Germany, New Zealand, Norway, Netherlands, and Portugal for the short-term and long-term treatment of panic disorder. Marketing authorization applications for the short-term and long-term treatment of panic disorder have been submitted in 26 countries, and there are no jurisdictions that have specifically not approved an application for the panic disorder indication. It has not been withdrawn in any country for any reason.

A review of the approved labeling from Canada, Germany, New Zealand, Norway, and Portugal revealed no important clinical information that should be added to the U.S. labeling currently under consideration. An English

translation of labeling from Netherlands is not currently available.

D. Product Labeling

The following comments are provided regarding the clinical sections of the sponsor's proposed labeling:

CLINICAL PHARMACOLOGY/Clinical Trials/Panic Disorder
The sponsor's proposed changes are acceptable, with the following exception:

I object to the sponsor's proposal that the sentence, "[redacted]." be deleted. The robustness ($p<0.001$) and magnitude of effect size (54.4% and 59.7% for 75 mg and 150mg, and 64.7% and 70.0% for 75 mg and 225 mg) for all three doses were similar. Therefore, there appears to be no substantial advantage of the higher doses (150 and 225 mg) over the lower dose (75mg). b(4)

ADVERSE REACTIONS/Other Adverse Events Observed During the Premarketing Evaluation of Effexor and Effexor XR
The sponsor's proposed changes are acceptable, with the following exception:

According to the undersigned reviewer's calculations, there were 1314 patients in Phase 3 panic disorder studies, not [redacted] as written in the sponsor's proposed labeling. The sponsor should explain this discrepancy. b(4)

DOSAGE AND ADMINISTRATION/Maintenance Treatment
I object to the sponsor's proposal to delete the term [redacted], claiming that the protocol for study 354 did not specify the time of day the daily dose was to be given. Review of the protocol for study 354 revealed the following sentence: "The test article will consist of capsules that will be administered orally, once per day, in the morning with food." In addition, the following paragraph describing the double-blind portion of the study is extracted from the protocol: "On study completion or early withdrawal, patients who have taken 2 or more capsules for more than 1 week will have their dose tapered in the following manner. Patients receiving 3 capsules in the morning will take 2 capsules in the morning during the first week of taper and 1 capsule in the morning during the b(4)

second week of taper. Patients receiving 2 capsules in the morning will take 1 capsule in the morning during the first week of taper. Patients receiving 1 capsule in the morning do not need to have their dose tapered. The taper period may be omitted or prolonged if medically indicated."

III. Conclusions and Recommendations

This submission is a full and adequate response to the clinical issues raised in our approvable letter. There is no clinical information in this submission that would change our previous conclusions about the approvability of venlafaxine ER for treatment of panic disorder.

From a clinical perspective, this application may be approved when agreement is reached on product labeling.

Michelle M. Chuen, M.D.
November 8, 2005

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

APPENDIX 1

Table 7.0–1: Summary Tabulation of Overall Exposure to Study Medication by Therapy According to Mean Daily Dose and Duration of Therapy Including Days of Missed Dose: Safety Population in Pooled Short-term Double-blind Studies 353, 398, 399 and 391 and Relapse Prevention Study 354 – Venlafaxine ER Treatment Group

Duration of Exposure (days)[a]	Mean Daily Dose (mg)[b] >0 – 50	>50 – 100	>100 – 200	>200 – 300	Total
> 0	89	477[c]	721	27	1314
> 7	23	473	721	27	1244
> 14	1	442	721	27	1191
> 21	0	413	721	27	1161
> 28	0	386	709	27	1122
> 42	0	373	688	27	1088
> 56	0	356	660	27	1043
> 70	0	332	528	27	887
> 84	0	109	189	27	325
> 98	0	17	40	27	84
> 112	0	13	34	27	74
> 126	0	12	32	27	71
> 154	0	12	29	26	67
> 182	0	12	28	25	65
> 210	0	11	27	23	61
> 238	0	10	27	22	59
> 266	0	3	7	8	18

a. For the short-term double-blind studies (353, 391, 398, and 399), the duration of exposure (on-therapy period) is the double-blind period, excluding taper doses. For patients in relapse prevention study 354 who did not enter the double-blind period or who were randomized to receive placebo during the double-blind period, the on-therapy period is the open-label period, excluding taper doses. For patients in relapse prevention study 354 who were randomized to receive venlafaxine ER during the double-blind period, the on-therapy period is the open-label period plus the double-blind period, excluding taper doses.

b. Mean daily dose does not include zero doses at the end of the dose records. This is similar to the pooled short-term double-blind studies in the Summary of Clinical Safety. However, for study 354 in the Summary of Clinical Safety, zero doses at the end of the dose records were included in the mean daily dose; thus, mean daily doses in this table (and the number of patients in the dose ranges) may differ slightly from those in the Summary of Clinical Safety.

c. Includes patient 398-4301 with duplicate dose records due to recording the same dose (37.5 mg) on 2 case report forms (first and last dose); the mean daily dose should have been in the >0 – 50 mg range.

Table 9.0-1: Study 354: Overall Exposure (Mean Daily Dose, Including Days of Missed Dose) to Venlafaxine ER at the End of the Open-Label Period for ITT Patients Who Were Randomized Into the Double-Blind Period

Double-Blind Treatment Assignment	Mean Daily Dose (mg) >0 – 50	>50 – 100	>100 – 200	>200 – 300	>300	Total	Daily Dose Mean (SD) mg
Placebo[a]	0	9	71	0	0	80	144.4 (37.6)
Venlafaxine ER[b]	0	18	71	0	0	89	139.4 (41.5)
Overall	0	27	142	0	0	169	141.8 (39.7)

a. These patients had received venlafaxine ER during the open-label period, but were randomized to receive placebo during the double-blind period.

b. These patients had received venlafaxine ER during the open-label period, and were randomized to continue receiving venlafaxine during the double-blind period.

Abbreviation: ITT = intent-to-treat.

Table 10.0-1: Study 354: Mean Time in Continuous Responder Status During the Open-Label Period For ITT Patients Who Qualified for Randomization Into the Double-Blind Period

Treatment Group	Number of Patients [a]	Total Time (Days)	Mean Time (Days) [b]
Total	169	5815	34.41
Placebo	80	2481	31.01
Venlafaxine ER	89	3334	37.46

Abbreviation: ITT=intent-to-treat

a. Of the 169 total patients, 80 were randomized to receive placebo during the double blind period and 89 were randomized to receive venlafaxine ER during the double-blind period.

b. Thirty-four (34) of the 169 patients had a time of "0 days" for continuous responder status because they did not meet the 2 criteria (ie, no more than 1 full-symptom panic attack per week and a CGI-I score of 1 or 2) at either the week 10 or week 12 evaluation. See Tables 10.0-2 and 10.0-3 for the double-blind period randomization assignments for these patients. .

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/s/

Michelle Chuen
11/8/2005 02:28:17 PM
MEDICAL OFFICER

Paul Andreason
11/10/2005 03:55:37 PM
MEDICAL OFFICER
I believe that the Division may approve supplements 54 and 57. Please see my memo to the file dated November 10, 2005.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-699/S-054, 057

CHEMISTRY REVIEW(S)

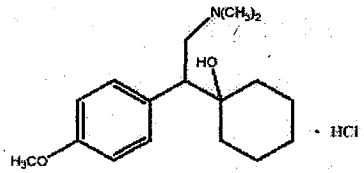
CHEMIST'S REVIEW OF SUPPLEMENT

ORGANIZATION:	**HFD-120**
NDA NUMBER:	**20-699**
SUPPLEMENT NUMBER:	**SE1-054 and SE1-057**
LETTER DATE	29-SEP-04
STAMP DATE	29-SEP-04
	SE5-059
LETTER DATE	01-DEC-04
STAMP DATE	01-DEC-04
AMENDMENTS/REPORTS:	N/A

APPLICANT NAME AND ADDRESS: Wyeth Pharmaceuticals Inc.
P.O. Box 8299
Philadelphia, PA 19101-8299

NAME OF DRUG: Effexor® XR
NONPROPRIETARY NAME: Venlafaxine hydrochloride

CHEMICAL NAME / STRUCTURE: (*R,S*)-1-[2-(dimethylamino)-1-(4-methoxyphenyl)ethyl] cyclohexanol hydrochloride



DOSAGE FORM(S): Extended Release Capsules
POTENCY(IES): 37.5 mg; 75 mg, 100 mg, 150 mg
PHARMACOLOGICAL CATEGORY: Social Anxiety Disorder (Pediatric) [S-059]
Panic Disorder [S-054, S-057]

SPECIAL PRODUCTS: (YES) XX (NO)
HOW DISPENSED: XX (Rx) (OTC)
RECORDS / REPORTS CURRENT: XX (YES) (NO)
RELATED IND / NDA / DMF(S): N/A

SUPPLEMENT PROVIDES FOR: Supplements S-054 and S-057 provide for the obtaining of a new indication of Effexor® XR, i.e. for the treatment of panic disorder. Supplement S-059 provides the results from one completed clinical study as required under the Pediatric Research Equity Act (PREA) of 2003.

COMMENTS: Supplements **SE1-054 and SE1-057** are to obtain a new indication of Effexor® XR, i.e. for the treatment of panic disorder. The five double-blind, placebo-controlled studies were included in the SE1-054 application to support the new indication. **SE5-059** is to provide the results from one completed clinical study. This 16-week, multicenter, double-blind, flexible-dose study evaluated the anxiolytic efficacy, safety and tolerability of flexible dosing of Effexor® XR(37.5 mg to 225 mg/day) versus placebo in children and adolescent outpatients with Social Anxiety Disorder. The applicant did not identify any changes to the drug substance and drug product in these supplements. The package insert information for DESCRIPTION and HOW SUPPLIED sections remains unchanged in these supplements. The environmental assessment consult was requested for SE1-054 supplement; a finding of no significant impact (FONSI) was recommended. A categorical exclusion to the environmental analysis requirements is granted in accordance with 21 CFR 25.31 (a) for the supplement SE5-059.

CONCLUSIONS AND RECOMMENDATIONS. Recommend **Approval.**

Lyudmila N. Soldatova, Ph.D., Review Chemist

cc: Orig. NDA 20-699
HFD-120/RTaylor
HFD-120/TOliver
HFD-120/LSoldatova
Filename: N20699s054s057s059
Review Completed: 08-JUL-2005

CHEMIST'S REVIEW NOTES

1. DRUG SUBSTANCE

The sponsor did not identify any changes to the drug substance.

Evaluation: Acceptable.

2. DRUG PRODUCT

The sponsor did not identify any changes to the drug product.

Evaluation: Acceptable.

3. PACKAGE INSERT AND LABELING

The package inserts for SE1-054/SE1-057 and for SE5-059 were reviewed and there were no changes to the Description and to the How Supplied sections of the package inserts.

Evaluation: Acceptable since no changes were made to the Description and to the How Supplied sections of the package inserts.

4. ENVIRONMENTAL ASSESSMENT

Wyeth completed the environmental assessment for new indication of the Effexor® XR capsules (SE1-054), and indicated that the expected introduction concentration (EIC) from use is expected to increase to [redacted] kg/year of venlafaxine hydrochloride) in 2007. Use of venlafaxine hydrochloride is expected to be [redacted] g/year in 2008 and [redacted] kg/year in 2009. The environmental assessment consult was requested for this supplement (SE1-054) on October 6, 2004. The review of the environmental assessment (dated February 1, 2005) indicated that previously submitted environmental effects test data revealed the EC_{50} = 34 ppm and NOEC (no observed effect concentration) = 4.2 ppm for venlafaxine (free base). A FONSI was recommended for NDA 20-699 / S-054 because EC_{50} is more than 1000 greater than EIC and the NOEC is greater than the EIC.

b(4)

Wyeth stated that preparation of an Environmental Assessment for the proposed action in the supplement SE5-059 is categorically excluded according to 21 CFR 25.31 (a). The proposed action (no new indication) does not change the use of active moiety. To the best knowledge of Wyeth, no "extraordinary circumstances" exist associated with the proposed action.

Evaluation: Acceptable based on the information provided in the environmental assessment consult, i.e. the action proposed in the supplement SE1-054 has no potential adverse environmental effects. For SE5-059, a categorical exclusion is granted based on 21 CFR 25.31 (a).

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/s/

Lyudmila Soldatova
7/8/05 06:16:48 PM
CHEMIST

Thomas Oliver
7/11/05 07:26:38 AM
CHEMIST

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-699/S-054, 057

ENVIRONMENTAL ASSESSMENT

FINDING OF NO SIGNIFICANT IMPACT

AND

ENVIRONMENTAL ASSESSMENT

FOR

EFFEXOR XR (venlafaxine hydrochloride)
Extended Release Capsules
(37.5, 75, 100 and 150 mg)

NDA 20-699 / S-054
(Treatment of Panic Disorder)

Food and Drug Administration
Center for Drug Evaluation and Research

Division of Neuropharmacological Drug Products
(HFD-120)

January 27, 2005

FINDING OF NO SIGNIFICANT IMPACT
NDA 20-699 / SE1-054

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 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 [redacted] drug that is currently approved for use in treating certain types of depression and anxiety disorders. b(4)

The supplemental application provides for use of venlafaxine HCl for treatment of panic disorder.

Venlafaxine HCl 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 HCl to environmental organisms was characterized. The results indicate that the compound is not expected to be toxic to 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
Environmental Officer, Center for Drug Evaluation and Research

CONCURRED BY
Jon E. Clark
Associate Director for Policy Development, Center for Drug Evaluation and Research

CONCURRED BY
Moheb M. Nasr
Acting Office Director, Office of New Drug Chemistry, Center for Drug Evaluation and Research

Attachment: Environmental Assessment
Appended Electronic Signature Page

TABLE OF CONTENTS

SUMMARY

Wyeth Pharmaceuticals, Inc. is seeking approval for a new indication of Effexor XR (venlafaxine HCl) Extended-Release Capsules (37.5, 75, 100 and 150 mg) for the treatment of panic 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. The proposed action is expected to increase the use of the drug product. Approval of the proposed action is not reasonably expected to result in any adverse impact to the environment.

ENVIRONMENTAL ASSESSMENT

Effexor® XR

Supplement to NDA No. 20-699

DATE

April 7, 2004

NAME OF APPLICANT

Wyeth Pharmaceuticals, Inc.

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 Pharmaceuticals, Inc. (Wyeth) is seeking approval for a new indication of Effexor XR (venlafaxine HCl) for the treatment of panic disorder. 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 for Effexor XR for the treatment of panic disorder. Wyeth expects the action will increase the use of the drug product.

This environmental assessment will update the information provided in previously submitted environmental assessments to assist the FDA in its review. 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)
- 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)

1.0 ENVIRONMENTAL ISSUES

1.1 Expected Introduction Concentration (EIC) From Use

Confidential Appendix I contains a five-year forecast of the bulk requirement for venlafaxine HCl that includes the anticipated production increase associated with the proposed action.

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 the 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 will have a negligible vapor pressure.

1.2 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.

1.3 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.

1.4 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.

1.5 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 show no net oxygen uptake.

Aerobic Biodegradation: This test was conducted using C^{14} - venlafaxine HCl 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 indicate that venlafaxine HCl 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 HCl.

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 HCl to determine the partitioning of the compound between soil/activated carbon and water.

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

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

1.6 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 were 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.

2.0 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 Wyeth. 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.

3.0 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.

4.0 LIST OF PREPARERS

Harry Yekel
Principal Project Engineer
Wyeth Pharmaceuticals, Inc.

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.

Richard A. Constable
Director, Environmental, Health and Safety
Wyeth Pharmaceuticals, Inc.

Over 30 years' experience in environmental, health and safety related fields. Mr. Constable is responsible for Wyeth's global environmental program. Mr. Constable has BS and MS degrees in Chemical Engineering.

5.0 CERTIFICATION

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

Date April 19, 2004

Signature Richard A. Constable

Richard A. Constable
Director, Environmental, Health and Safety
Wyeth Pharmaceuticals, Inc.

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)

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/s/

Florian Zielinski
1/27/05 04:24:06 PM

Jon E. Clark
2/1/05 08:56:05 AM

Moheb Nasr
2/1/05 11:57:01 AM

REVIEW

OF

ENVIRONMENTAL ASSESSMENT

FOR

EFFEXOR XR (venlafaxine hydrochloride)
Extended Release Capsules
(37.5, 75, 100 and 150 mg)

NDA 20-699 / S-054
(Treatment of Panic Disorder)

Food and Drug Administration
Center for Drug Evaluation and Research

Division of Neuropharmacological Drug Products
(HFD-120)

January 27, 2005

Environmental Assessment Review #1, NDA 20-699 / SE1-054

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
NDA 20669 / S-022	Apr 24, 2001	Dec 13, 2002	Social Anxiety Disorder (SAD)
NDA 20699 / S-030	Nov 5, 2001	Dec 5, 2002	Pediatric depression and GAD
NDA 20699 —			
NDA 20699 / S-047	Mar 4, 2003	Dec 7, 2003	Long Term Treatment of SAD

b(4)

This supplement (NDA 20-699 / S-054) dated April 7, 2004 provides for treatment panic disorder. It contains new information about the quantity of venlafaxine hydrochloride required for use in all products manufactured by Wyeth Pharmaceuticals. All other information is identical to that submitted previously.

The maximum amount of venlafaxine hydrochloride used for all products and all indications is expected to increase to —— g/year in 2007. This corresponds to — ppb EIC. Use of venlafaxine hydrochloride is expected to be ——— g/year in 2008 and —— g/year in 2009..

b(4)

Previously submitted environmental effects test data for *Daphnia Magna* revealed EC_{50} = 34 ppm and NOEC = 4.2 ppm for venlafaxine (free base).

A FONSI is recommended for NDA 20-699 / S-054 because EC_{50} is more than 1000 greater than EIC and the NOEC is greater than the EIC.

REVIEW OF EA FOR NDA 20-699/SE1-054

Treatment of Panic Disorder

I. DATE: March 4, 200

II APPLICANT: Wyeth Pharmaceuticals, Inc

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

IV PROPOSED ACTION:

Supplemental application (20-699/S-054) is requesting approval of venlafaxine hydrochloride for treatment of panic disorder.

The total amount of drug substance manufactured for all indications in any of the next 5 years is expected to be NMT [redacted] (ref: Current EA, Confidential Appendix I dated April 7, 2004) b(4)

ADEQUATE

V IDENTIFICATION OF CHEMICALS

NDA 20-699 / S-047 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). Fate data are summarized on pages 5 and 6 of this EA; effects data are summarized on page 7.

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.

The amount of venlafaxine hydrochloride used for all products and all indications is expected to increase to [redacted] ear in 2007. This corresponds tc [redacted] EIC. b(4)

Previously submitted environmental effects test data for *Daphnia Magna* revealed EC_{50} = 34 ppm and NOEC = 4.2 ppm for venlafaxine (free base).

A FONSI is recommended for NDA 20-699 / S-054 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 PREPARERS

Names, job titles and qualifications are provided.

ADEQUATE

X CERTIFICATION

Provided.

ADEQUATE

XI APPENDICES

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

ADEQUATE

Review by: Florian Zielinski, CDER Environmental Officer on January 27, 2005

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/s/

Florian Zielinski
1/27/05 02:28:27 PM
ENV ASSESSMENT

Jon E. Clark
2/1/05 08:48:38 AM
CHEMIST

Moheb Nasr
2/1/05 11:55:11 AM
CHEMIST

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-699/S-054, 057

STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmacoepidemiology and Statistical Science
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number:	NDA 20699 /Supp 054/057
Drug Name:	Venlafaxine Extended-Release Capsules
Indication(s):	Panic Disorder
Applicant:	WYETH RESEARCH
Date(s):	September 29, 2004 (date of Document)
Review Priority:	Standard
Biometrics Division:	Division 1 (HFD-710)
Statistical Reviewer:	Ohidul Siddiqui, Ph.D
Concurring Reviewers:	Kun Jin, Ph.D; James Hung, Ph.D
Medical Division:	HFD-120
Clinical Team:	Michelle Chuen, MD
Project Manager:	Richardae Taylor, Pharm D

Keywords: NDA review, endpoint analysis/LOCF, multi-center, Kaplan-Meier product limit, logrank test

Table of Contents

1. EXECUTIVE SUMMARY

The sponsor has submitted the efficacy findings of four short-term trials, and one long-term relapse prevention trial to demonstrate the efficacy of venlafaxine extended-release (ER) in the short-term and long-term treatment of panic disorder (PD) in adult outpatients. The studies were conducted in the United States, Canada, Europe, South Africa, Latin America, and Australia.

Among the four short-term randomized studies, two studies demonstrated the efficacy of venlafaxine extended-release (ER) in the short-term treatment of panic disorder (PD) in adult outpatients. Another short-term study approached to demonstrate the efficacy of venlafaxine extended-release (ER). The long-term relapse prevention study also demonstrated the efficacy of Venlafaxine ER in preventing or delaying the relapse of PD.

1.1 Conclusions and Recommendations

Venlafaxine ER in doses of 75 to 225 mg/day was effective in the treatment of PD in adult outpatients. Venlafaxine ER in dose range 75 to 225 mg/day was also effective in preventing or delaying the relapse of PD.

1.2 Brief Overview of Clinical Studies

The short-term studies were randomized, double-blind, placebo-controlled and parallel-group studies in adults. The design and statistical analysis methods were similar across the studies.

Patients were required to have at least 8 full-symptom panic attacks during the 4 weeks before the screening visit and at least 4 full-symptom panic attacks during the 14 ± 3 days placebo lead-in period between the screening and baseline visits. Eligible patients were then randomly assigned to receive venlafaxine ER, paroxetine hydrochloride, or placebo for up to 12 / 10 weeks followed by a taper period of up to 14 days. Doses of venlafaxine ER started at 37.5 mg and were titrated upwards, but patients had to be able to tolerate at least 75 mg to continue in the studies.

The primary efficacy variable was the full-symptom panic attack frequency from the Panic and Anticipatory Anxiety Scale (PAAS). The primary outcome measure was the percentage of patients who were free of full-symptom panic attacks (defined as panic attacks with 4 or more symptoms) at the final on-therapy observation.

The relapse prevention study was a double-blind, placebo-controlled and parallel-group study. The study was designed to evaluate the long-term efficacy of venlafaxine ER in adult outpatients with PD who responded to open-label venlafaxine ER.

Patients who completed the 12-week open-label treatment phase of the study and became responders, were randomly assigned to receive either venlafaxine ER or placebo in a double-blind manner for up to an additional 6 months; dose adjustments were not permitted after week 8 of the open-label period. Responders were defined as the patients who had no more than 1 full-symptom panic attack per week during the last 2 weeks of open-label treatment and a CGI-I score of 1 or 2 based on improvement from the open-label baseline.

Relapse of PD was defined as having 2 or more full-symptom panic attacks per week for 2 consecutive weeks or as having been discontinued from the double-blind phase due to loss of effectiveness as determined by the investigator during the study.

1.3 Statistical Issues and Findings

In two short-term studies, the primary efficacy measure- the full-symptom panic attack frequency from the PAAS demonstrated statistically significant efficacy of venlafaxine ER for the treatment of PD in adult outpatients. Another short-term study approached to demonstrate the efficacy of venlafaxine ER for the treatment of PD. In each of the three studies, the key secondary measures PDSS and CGI-I also showed significant efficacy of venlafaxine ER for the treatment of PD.

In the relapse prevention study, venlafaxine ER demonstrated significant treatment efficacy for the long-term treatment of PD and the prevention of relapse. In addition to preventing relapse of PD, the overall efficacy of venlafaxine ER was maintained during the double-blind period relative to placebo as evidenced by the suppression of panic attacks. No statistical issues were found in any of the short-term and long-term studies.

2. INTRODUCTION

2.1 Overview

The sponsor has submitted the efficacy findings of four short-term, and one long-term relapse prevention trials to demonstrate the efficacy of venlafaxine extended-release (ER) in the short-term and long-term treatment of panic disorder (PD) in adult outpatients. The studies were conducted in the United States, Canada, Europe, South Africa, Latin America, and Australia. Table 1 lists an overview of the studies.

Table 1: Overview of the randomized studies-ITT Population

Study	Treatment Duration	Venlafaxine ER Dose (mg/day)	Comparator(s)
398-EU	12 weeks	Fixed 75 and 150	Paroxetine/placebo
399-AC	12 weeks	Fixed 75 and 225	Paroxetine/placebo
353-US/CA	10 weeks	Flexible 75 to 225	Placebo
391-CA /EU	10 weeks	Flexible 75 to 225	Placebo
354-AU/CA/EU/US	12 weeks OL, 6 months DB	OL flexible 75 to 225; DB fixed 75, 150, or 225 (based on OL dose)	Placebo

Abbreviations: EU=Europe (includes South Africa in study 391); AC=countries in Latin America; US=United States; CA=Canada; AU=Australia; OL=open-label; DB=double-blind.

2.2 Data Sources

SAS data sets of the studies are available at \\Cdsesub1\N20699\S_054\2004-09-29\crt\datasets. The study reports are available at \\Cdsesub1\N20699\S_054\2004-09-29\clinstat.

3. STATISTICAL EVALUATION

3.1 Study reviewed

Among the four short-term studies, the primary efficacy findings of two short-term studies (# 398 and #399) were positive. In another short-term study#353, the primary efficacy finding approached to positive ($p = 0.056$). Study#391 (short-term study) was a failed study. In this review, the efficacy findings of three short-term studies #398, #399 and #353 will be reviewed. In addition, the efficacy findings of the relapsed prevention study #354 (a positive study) will also be reviewed here. The efficacy findings of the study #391 (a failed short-term study) will be reported in the appendix.

3.1.2 Study Design

Short-term Studies: Studies #398, #399 and #353

Studies #398, #399 and #353 were randomized, double-blind, placebo-controlled and parallel-group studies in adults. The study design and statistical analysis methods were similar across the three studies.

Patients in studies #398, #399 and #353 were required to have at least 8 full-symptom panic attacks during the 4 weeks before the screening visit and at least 4 full-symptom panic attacks during the 14± 3 days placebo lead-in period between the screening and baseline visits. Eligible patients were then randomly assigned to receive venlafaxine ER, paroxetine hydrochloride, or placebo for up to 12 weeks in studies #398 and #399 and up to 10 weeks in study#353 followed by a taper period of up to 14 days. In all of the studies, doses of venlafaxine ER started at 37.5 mg and were titrated upwards, but patients had to be able to tolerate at least 75 mg to continue in the studies.

Long-Study #354

Study#354 was a relapse prevention study. It was a double-blind, placebo-controlled and parallel-group study. The study was designed to evaluate the long-term efficacy of venlafaxine ER in adult outpatients with PD who responded to open-label venlafaxine ER. There were 4 phases in this study: (a) a 14±3-day baseline period, (b) a 12-week open-label safety and efficacy evaluation, followed by (c) a randomized, double-blind, placebo-controlled 6-month period of venlafaxine ER, and (d) a taper period. Among the eligible patients for the study, the patients who had 3 or more panic attacks per week during the baseline period were enrolled in the open-label phase.

Patients who completed the 12-week open-label treatment phase of the study, and met the criteria for "responder" during the last 2 weeks of the open-label phase, were randomly assigned to receive either venlafaxine ER or placebo in a double-blind manner for up to an additional 6 months; dose adjustments were not permitted after week 8 of the open-label period. Responders were defined as patients who had no more than 1 full-symptom panic attack per week during the last 2 weeks of open-label treatment and a CGI-I score of 1 or 2 based on improvement from the open-label baseline.

Relapse of PD was defined as having 2 or more full-symptom panic attacks per week for 2 consecutive weeks or as having been discontinued from the double-blind phase due to loss of effectiveness as determined by the investigator during the study.

During the double-blind phase, responders assigned to venlafaxine ER continued to receive the same dose of venlafaxine ER that they had taken at the end of the open-label phase (75, 150, or 225 mg). Patients randomly assigned to placebo, who were receiving 150 or 225 mg of venlafaxine ER at the end of the open-label period, received a tapered dose over the first 7 or 14 days, respectively, of the 6-month double-blind period. Patients who were non-responders during the open-label phase, and patients that discontinued from the study,

received a taper dose of venlafaxine ER if they were receiving a dose higher than 75 mg.

3.1.3 Patient Population

Studies #398, #399 and #353

The randomized patients were outpatients, from both gender and aged 18 years or older. The patients met the *Diagnostic and Statistical Manual of Mental Disorders*, *Fourth Edition* (DSM-IV) criteria for PD (with or without agoraphobia) for at least 3 months before study day 1. They had to have a score ≥4 on the Clinical Global Impressions-Severity (CGI-S) subscale, at least 8 full-symptom panic attacks during the 4 weeks before the screening visit, and at least 4 full-symptom panic attacks during the 14 ± 3-day placebo lead-in period between the screening and baseline (study day -1) visits. They also had to have a Covi Anxiety Scale total score greater than their Raskin Depression Scale total score.

Study #354

The patients were outpatients, from both gender and aged 18 years or older. The patients met the *Diagnostic and Statistical Manual of Mental Disorders*, *Fourth Edition* (DSM-IV) criteria for PD (with or without agoraphobia) for at least 3 months before study day 1. Patients had to have a score ≥ 4 on the Clinical Global Impressions-Severity (CGI-S) subscale, at least 6 full-symptom panic attacks during the 2 weeks before the screening visit, and at least 3 full-symptom panic attacks per week during the 2 weeks before baseline. Patients also had to have a Covi Anxiety Scale total score greater than the Raskin Depression Scale total score.

3.1.4 Efficacy Measures

Studies #398, #399 and #353

The primary efficacy variable was the full-symptom panic attack frequency from the Panic and Anticipatory Anxiety Scale (PAAS). The primary outcome measure was the percentage of patients who were free of full-symptom panic attacks (defined as panic attacks with 4 or more symptoms) at the final on-therapy observation. The double-blind period for efficacy was defined as starting from study day 1, the day after the baseline evaluations, until up to 3 days after the last full dose of study medication (excluding the placebo lead-in period and the taper period). The on-therapy full-symptom panic attack frequency from the PAAS was evaluated in 2-week periods. The final on-therapy evaluation was defined as the last 14 days of PAAS data collected during the on-therapy period.

Two key secondary efficacy variables were defined in each of the three studies- the total score on the Panic Disorder Severity Scale (PDSS) and the response rate based on the CGI-I subscale. A CGI-I responder was defined as a patient who had a score of 1 (very much improved) or 2 (much improved) on the CGI-I.

As agreed to by the FDA at the pre-phase 3 meeting discussing the clinical development plan

for PD, secondary efficacy variables declared as "key" in the protocols could be analyzed, and positive results would be included in the labeling, if the results of the primary efficacy variable were positive.

Handling Missing Data on Efficacy Scales

For the primary efficacy measure PAAS, in each 2-week (14 days) analysis period, if more than 50% of the PAAS data (8 days or more) were missing, the evaluation was considered missing for that 2-week period. For the key secondary measure PDSS, if more than 50% of the items were missing, then the total score was missing. If less than or equal to 50% of the items were missing, then the average of the available items was multiplied by the total number of items to impute the total score.

Study #354

The primary efficacy endpoint was the time until relapse for patients who had entered the double-blind maintenance phase of the study. Relapse of PD was defined as having a full-symptom panic attack frequency of ≥ 2 panic attacks per week for 2 consecutive weeks or, to have been discontinued from the double-blind phase due to loss of effectiveness as determined by the investigators during the study. Time to relapse was measured from the beginning of the randomization phase (study day 85) until the first occurrence of relapse.

3.1.5 Statistical Analyses – Studies #398, #399 and #353

The primary analysis population was the intent-to-treat (ITT) patients. A patient was considered part of the ITT population if he/she had a baseline evaluation, and had at least one double-blind on-therapy evaluation on the primary efficacy measure.

In study #353, small sites were pooled to form centers with a minimum of 8 patients per center. This was accomplished by combining sites with smallest number of patients with those having the largest numbers until every center consisted of at least eight patients. This pooling method was performed prior the unblinding of the studies.

In study #398, the term "center" referred to geographic location, with countries of eastern Europe grouped together as one center, and countries of western Europe grouped together as the other center.

In two studies (Studies#398 and #353), the primary outcome measure the percentage of patients who were free of full-symptom panic attacks (defined as panic attacks with 4 or more symptoms) at the end of the study period (final on-therapy observation) was analyzed with categorical methods using logistic regression model with treatment group and center as factors.

In study#399, the primary efficacy variable the percentage of patients who were free of full-symptom panic attacks (defined as panic attacks with 4 or more symptoms) at the end of the study period (final on-therapy observation) was analyzed with categorical methods using logistic

regression model with treatment group and country site as factors and baseline severity as covariate. Severity was determined by a dichotomization of the median number of full symptom panic attacks at baseline from all patients in the analysis. Patients with a baseline full symptom panic attack frequency that was greater than or equal to the median number of full symptom panic attacks for all patients in the analysis was considered as more severe group relative to those patients who had below the median.

In fixed-dose studies 398 and 399, each venlafaxine ER dose group was compared with the placebo group. The Hochberg setup method was used to control the overall error rate at 0.05.

The key secondary variable PDSS was analyzed using ANCOVA model: change from baseline = baseline + treatment +center/country. The other key secondary CGI-I responder was analyzed using Fisher's Exact Test. Sequential testing was applied to these 2 variables if the results of the primary variable were positive; the PDSS was tested first and the CGI-I was tested second.

Study #354

The primary efficacy endpoint the time until relapse was analyzed using survival (Kaplan-Meier) analysis.

Interim Analysis

No interim analysis was planned and carried out in any of the short term and relapse prevention studies.

3.1.6 Sponsor's Results

3.1.6.1. Patient Characteristics

In each of the short-term and long-term studies, the demographic and baseline characteristics of the randomized patients did not reveal any differences or trends across the treatment groups.

Table 1 lists the disposition of the patients. Within each study, patient discontinuation rates due to adverse event were similar across the treatment groups.

Table 1: Summary of Patient Disposition

For Study # 398				
Patient Disposition	Placebo	Venlafaxine ER 75 mg	Venlafaxine ER 150 mg	Paroxetine
Randomized	163	166	168	167
Safety Population [a]	163	166	168	166
ITT Population	156	158	159	161
Completed Treatment	120	134	133	136
Withdrawn Prior to End of Treatment	41 (25%)	32 (19%)	35 (21%)	30 (18%)
Withdrawn Due to:				
Adverse Event	14 (9%)	13 (8%)	20 (12%)	17 (10%)
Lack of efficacy	14 (9%)	7 (4%)	4 (2%)	6 (4%)
Other/Administrative	13 (7%)	12 (7%)	11 (7%)	7 (4%)
For Study # 399				
Patient Disposition	Placebo	Venlafaxine ER 75 mg	Venlafaxine ER 150 mg	Paroxetine
Randomized	162	163	167	161
Safety Population [a]	162	160	166	161
ITT Population	157	156	160	151
Completed Treatment	119	135	139	124
Withdrawn Prior to End of Treatment	43 (27%)	24 (15%)	29 (17%)	35 (22%)
Withdrawn Due to:				
Adverse Event	3 (2%)	3 (2%)	1 (1%)	8 (5%)
Lack of efficacy	19 (12%)	8 (5%)	10 (6%)	12 (7%)
Other/Administrative	21 (13%)	13 (8%)	18 (10%)	15 (9%)
For Study # 353				
Patient Disposition	Placebo	Venlafaxine ER		
Randomized	168	175		
Safety Population [a]	159	164		
ITT Population	155	155		
Completed Treatment	115	110		
Withdrawn Prior to End of Treatment	43 (27%)	55 (34%)		
Withdrawn Due to:				
Adverse Event	6 (4%)	10 (6%)		
Lack of efficacy	9 (6%)	8 (5%)		
Other/Administrative	28 (18%)	37 (23%)		
For Study # 354	**(Double-Blind Phase)**			
Patient Disposition	Placebo	Venlafaxine ER		
Entered Double-Blind	84	92		
Safety Population [a]	84	92		
ITT Population	80	89		
Completed double-blind	30	56		
Withdrawn Total	54 (64%)	36 (39%)		
Withdrawn Due to:				
Adverse Event	2 (2%)	1 (1%)		
Lack of efficacy	36 (43%)	19 (21%)		
Other/Administrative	16 (20%)	16 (18%)		

a: Safety population included all randomly assigned patients who received at least 1 dose of study medication, excluding the patient with no data. The safety population total of each study is used to calculate the percentages.

Sources: Tables 8.1A & 8.1.1A of the individual study reports.

3.1.6.2. Primary Efficacy Analyses

Table 2 lists the primary efficacy results of the three short-term studies. In the two short-term studies (#398 and #399), the findings indicate that all of the venlafaxine ER treatment arms (75 mg, 150 mg, and 225 mg/day) were statistically significantly (p<.001) superior to placebo in reducing the full-Symptom Panic Attacks of the patients with PD. In the third study (study#353), venlafaxine ER treatment group (a flexible dose 75-225 mg/day) approached statistically significantly (p=0.056) superior to placebo in reducing the full-Symptom Panic Attacks of the patients with PD.

Table 2. Primary Efficacy Variable PAAS: Percent of Patients Free of Full-Symptom Panic Attacks, Final On-Therapy (12 Weeks in Studies#398 and #399, 10 Weeks in Study#353), ITT Population

Study Treatment	n	Number (%) Panic-Free	p-Value vs Placebo [a]
Study#398			
Placebo	154	53 (34.4)	
Venlafaxine ER 75 mg	157	85 (54.1)	< 0.001
Venlafaxine ER 150 mg	158	97 (61.4)	< 0.001
Paroxetine	160	96 (60.0)	< 0.001
Study#399			
Placebo	157	73 (46.5)	
Venlafaxine ER 75 mg	156	100 (64.1)	< 0.001
Venlafaxine ER 225 mg	160	112 (70.0)	< 0.001
Paroxetine	151	89 (58.9)	0.008
Study#353			
Placebo	155	63 (40.6)	
Venlafaxine ER 75-225 mg	155	79 (51.0)	0.056

a: p-values (in studies 398 and 353) obtained from logistic regression model logit (response) = treatment + center; and in study 399, logistic regression model logit (response) = baseline + treatment + country.
Sources: Table 9.1.1.1A. of the individual study reports.

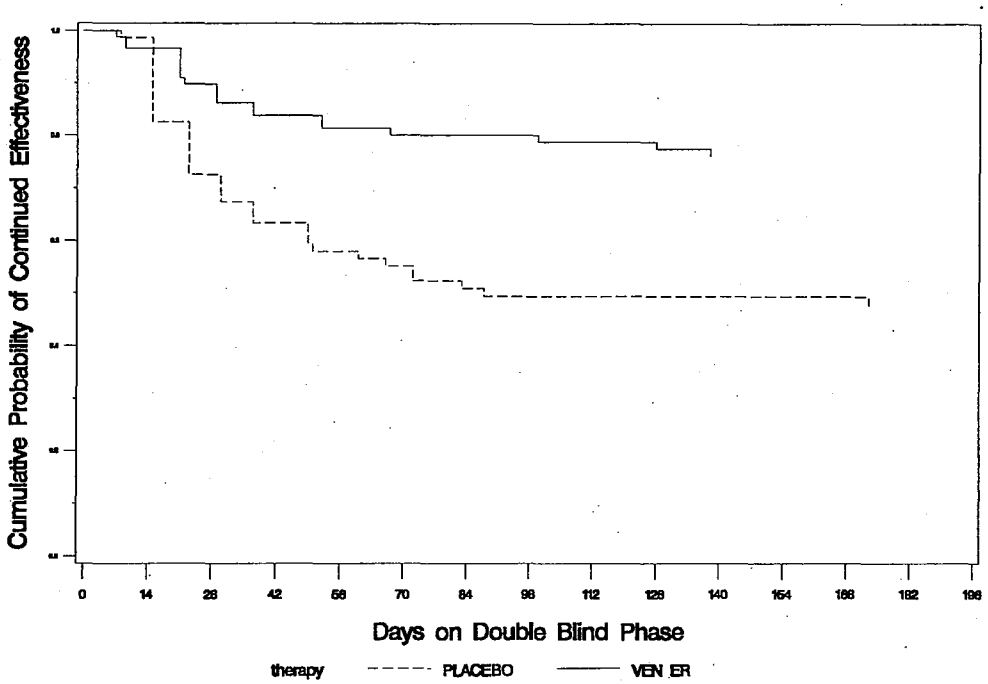
Table 2.1 and Figure 1 list the results of Kaplan-Meier survival analysis of the relapse prevention study#354. The survival analysis indicates that, in a double-blind evaluation, venlafaxine ER is significantly (p<.001) better than placebo in preventing relapse of PD in patients who responded to open-label treatment with venlafaxine ER.

Table 2.1. Survival Analysis for Relapse of Panic Disorder, ITT Population, Double-Blind Period – Study # 354

Study#354	N	Number of Relapses (%)	p-Value vs Placebo [a]
Placebo	80	40 (50.0)	
Venlafaxine ER	89	20 (22.5)	<0.001

a: p-Values obtained from log-rank statistics of Kaplan-Meier survival model.

Figure 1. Survival Function Estimates, ITT Population



3.1.6.3. Key Secondary Efficacy Analyses

Tables 3 and 3.1 list statistical significances of the key secondary efficacy measures PDSS and CGI-I responders. The mean changes from baseline in the PDSS total score were statistically significantly different from placebo at the endpoint for the venlafaxine ER 75 mg, venlafaxine ER 150 mg, venlafaxine ER 225 mg, and venlafaxine ER 75-225 mg groups. There were also significantly more CGI-I responders in the venlafaxine ER groups at the endpoint than in the placebo group.

The mean changes from baseline in the PDSS total score were also significantly different from placebo for all treatment groups at weeks 4, 6, 8, 10, and 12 (in LOCF and observed case analyses). There were also significantly more CGI-I responders for the venlafaxine ER groups at several time points (weeks 3, 6, 8, 10, and 12, LOCF; weeks 6, 8, 10, 12, observed-cases), compared with placebo .

Table 3. End point Comparison between treatment groups for Key secondary measure PDSS total score-ITT LOCF population,

Treatment Group	N	Least Square Mean Change from Baseline	P-Value vs. Placebo
Study#398			
Placebo	152	-6.89	
Venlafaxine ER 75 mg	154	-9.38	<.001
Venlafaxine ER 150 mg	155	-9.75	<.001
Paroxetine	159	-9.60	<.001
Study#399			
Placebo	154	-8.34	
Venlafaxine ER 75 mg	155	-11.15	<.001
Venlafaxine ER 225 mg	158	-12.76	<.001
Paroxetine	148	-11.59	<.001
Study#353			
Placebo	150	-7.50	
Venlafaxine ER 75-225 mg	140	-9.28	.006

p-Values obtained from ANCOVA model: change from baseline=baseline + treatment + center/country.

Table 3.1. End point Comparison between treatment groups for Key secondary measure CGI-I Responders-ITT LOCF population,

Treatment Group	N	Number of Responders	P-Value vs. Placebo (Fisher's Exact Test)
Study#398			
Placebo	156	87	
Venlafaxine ER 75 mg	158	121	<.001
Venlafaxine ER 150 mg	159	126	<.001
Paroxetine	161	129	<.001
Study#399			
Placebo	157	94	
Venlafaxine ER 75 mg	156	127	<.001
Venlafaxine ER 225 mg	160	136	<.001
Paroxetine	151	125	<.001
Study#353			
Placebo	153	90	
Venlafaxine ER 75-225 mg	152	108	.031

3.1.6.4. FDA Reviewer's Data Analyses and Comments

This reviewer re-analyzed the data sets of the four studies according to the protocol specified statistical analysis plans. The findings for the primary and key secondary efficacy measures matched with the findings submitted by the sponsor.

In studies 398 and 399, the primary efficacy measure PAAS and the key secondary efficacy measures PDSS and CGI-I demonstrated the efficacy of each dose group of venlafaxine ER (75, 150, and 225 mg) in the short-term treatment of PD. In these two studies, venlafaxine ER also demonstrated comparable efficacy on the primary endpoint to paroxetine, a marketed comparator for the treatment of PD.

In study 353, venlafaxine ER (75 to 225 mg) approached significance ($p = 0.056$) versus placebo for the primary efficacy variable PASS. For the key secondary measures PDSS and CGI-I, venlafaxine ER demonstrated significant treatment efficacy for the treatment of PD.

In study 354, venlafaxine ER (75 to 225 mg) demonstrated significant treatment efficacy for the long-term treatment of PD and the prevention of relapse. In addition to preventing relapse of PD, the overall efficacy of venlafaxine ER was maintained during the double-blind period relative to placebo as evidenced by the suppression of panic attacks.

In each of the three short term studies, the observed-cases data analyses also demonstrated the statistically significant efficacy of venlafaxine ER at the endpoints.

As a secondary analysis in study 354, this reviewer recoded the times-to-censor of the patients who were censored before the end of study period as times-to-event and reanalyzed the data set. Venlafaxine ER (75 to 225 mg) still remained statistically significantly superior as compared to placebo for the long-term treatment of PD and the prevention of relapse.

4. Subgroup Analyses

The sponsor reported subgroup analyses findings based on the pooled data of the three short-term studies. The FDA reviewer did the subgroup analyses on the individual study data sets. In each of the three short-term studies, subgroup analyses were performed on the primary efficacy measure to evaluate the uniformity of treatment effect within patient subgroups (age, sex, ethnic origin). Patients' ages were grouped into two groups (younger than 50 years, and 50 years and older) in the subgroup analyses.

Table 4. Percent of Patients Free of Full-Symptom Panic Attacks, Final On-Therapy (12 Weeks in Studies#398 and #399, 10 Weeks in Study#353) by Gender, Race, and Age Groups.

Study Treatment	% of Patients Panic-Free			
Study#398	Placebo	Venlafaxine ER 75 mg	Venlafaxine ER 150 mg	Paroxetine
Gender: Female	38.3%	50.9%	59.4%	57.8%
Male	25.5%	60.3%	65.9%	63.8%
Age: <50 years	35.4%	53.6%	60.4%	61.4%
>=50 years	29.2%	57.9%	66.6%	46.7%
Race: All patients (except 1 patient) are Whites.				
Study#399	Placebo	Venlafaxine ER 75 mg	Venlafaxine ER 225 mg	Paroxetine
Gender: Female	42.2%	57.4%	68.5%	60.8%
Male	56.2%	76.4%	73.1%	55.1%
Race: Hispanic	48.0%	61.0%	67.1%	48.6%
White	45.1%	67.6%	73.3%	67.9%
Age: <50 years	46.2%	62.8%	66.2%	56.6%
>=50 years	50.0%	75.0%	88.9%	72.7%
Study#353	Placebo		Venlafaxine ER 75-225 mg	
Gender: Female	33.7%		48.6%	
Male	50.8%		56.8%	
Race: Hispanic/Black	49.1%		57.1%	
White	36.3%		48.1%	
Age: <50 years	39.2%		47.3%	
>=50 years	46.7%		69.2%	

Table 4 lists the percentages of patients were free of Full-Symptom Panic Attacks at the final on-therapy period in each subgroup. In each of the three short term studies, the efficacy of venlafaxine ER was similar within each subgroup (Gender, Race, and age group).

In addition, an ANCOVA model that included the subgroup characteristic, treatment group, baseline PAAS total score, and a treatment-by-characteristic interaction term was used to test at $\alpha < 0.05$, for evidence of a difference in the treatment effect across levels of the subgroup characteristic. No significant interaction effect of treatment group by any of the subgroup characteristics was demonstrated. The lack of significant interaction indicates that the treatment effect is similar irrespective of the patients' characteristics.

In the relapse prevention study (#354), majority of the patients are females, whites, and younger than 50 years. So, no subgroup analysis was done on patients' gender, age, and ethnicity.

5. SUMMARY AND CONCLUSIONS

5.1 Collective Evidence of Efficacy

The results of two short-term studies (studies #398 and #399) demonstrated statistical efficacy of venlafaxine ER in reducing free of full-symptom panic attacks (defined as panic attacks with 4 or more symptoms). Analysis of the results of the two key secondary efficacy variables (PDSS and CGI-I) showed strong statistical separation of each venlafaxine ER dose from the placebo group.

In study #353, the percentage of patients who were panic free at the final on-therapy evaluation from the PAAS approached significance and demonstrated significance on the key two secondary efficacy variables.

The results of the long-term study #354 demonstrated that the efficacy of venlafaxine ER is maintained over time for the treatment of PD.

5.2 Conclusions and Recommendations

Among the four short-term studies, the results of two studies demonstrated the efficacy of venlafaxine ER in the short-term treatment of PD in adult outpatients. Venlafaxine ER in doses of 75 to 225 mg/day was effective in the short-term treatment of PD.

The long-term maintenance study also demonstrated the significant efficacy of Venlafaxine ER (dose range 75 to 225 mg) in preventing or delaying the relapse of PD.

APPENDIX I

No statistical review has been done on the submitted short-term study #391. According to the sponsor's finding, the study was a failed study.

The sponsor's efficacy findings of the study are copied (Cut and Paste) from the sponsor's documents (Ref: clinefficacy.pdf) in the appendix-1. Table Appendix-1 lists the efficacy findings of the study.

Stdy#391 was a multicenter, randomized, double-blind, placebo-controlled, parallel-group flexible-dose study of venlafaxine ER (75 to 225 mg/day) in adult outpatients who met the criteria for PD (with or without agoraphobia) according to *Diagnostic and Statistical Manual of Mental Disorders,* fourth edition (DSM-IV) criteria. After a 14±3-day single-blind placebo lead-in period, eligible patients were randomly assigned to receive venlafaxine ER or placebo for up to 10 weeks followed by a taper period of up to 14 days.

The planned enrollment was 330 patients; 361 patients were randomly assigned to receive double-blind medication, 355 were analyzed for safety; 328 were analyzed for efficacy (intent-to-treat [ITT] population excluding site 27), and 265 were considered efficacy completers.

The primary efficacy variable was the full-symptom (≥4 symptoms) panic attack frequency from the Panic and Anticipatory Anxiety Scale (PAAS); the primary outcome measure was the percentage of patients free of full-symptom panic attacks at the final on-therapy (FOT) evaluation.

The on-therapy full-symptom panic attack frequency from the PAAS was analyzed in 2-week periods and at FOT. The percentage of patients free of full symptom panic attacks from PAAS was analyzed using logistic regression with treatment group and sites as factors (sites with ≤5 patients were combined).

The percentage of patients who were panic free at the FOT evaluation from the PAAS did not differ significantly between treatment groups in the ITT (55.0% venlafaxine ER, 52.4% placebo) population.

Table 1: RESULTS OF PRIMARY VARIABLE PAAS: % PATIENTS FREE OF FULLSYMPTOM PANIC ATTACKS, FINAL ON-THERAPY, ITT POPULATION

Treatment Group	n	Number (%) of Responders	Adjusted Odds Ratio to Placebo	95% Confidence Limits[a]	p-Value Venlafaxine ER vs Placebo[b]
Placebo	168	88 (52.4)			
Venlafaxine ER[c]	160	88 (55.0)	1.122	(0.71, 1.77)	0.622

Source: Table is copied from the study report

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

/s/

Ohidul Siddiqui
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Kun Jin
6/8/05 08:00:46 AM
BIOMETRICS

James Hung
6/8/05 08:08:12 AM
BIOMETRICS

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-699/S-054, 057

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA # : 20-699 Supplement Type (e.g. SE5): SE1 Supplement Number: 054 &057

Stamp Date: 9/29/04 Action Date: 7/29/05

HFD 120 Trade and generic names/dosage form: Effexor XR (venlafaxine HCL) Extended-Release Capsules

Applicant: Wyeth Pharmaceuticals, Inc. Therapeutic Class: Antidepressant

Indication(s) previously approved: Major Depressive Disorder (MDD), Generalized Anxiety Disorder (GAD), Social Anxiety Disorder (SAD)

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): 2

Indication #1: Short-Term Panic Disorder

Is there a full waiver for this indication (check one)?

X Yes: Please proceed to Section A.

☐ No: Please check all that apply: ____Partial Waiver ____Deferred ____Completed
NOTE: More than one may apply
Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- ☐ Products in this class for this indication have been studied/labeled for pediatric population
- ☐ Disease/condition does not exist in children
- ☐ Too few children with disease to study
- ☐ There are safety concerns
- ☐ X Other: extremely difficult enrollment

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min____ kg____ mo.____ yr.____ Tanner Stage____
Max____ kg____ mo.____ yr.____ Tanner Stage____

Reason(s) for partial waiver:

- ☐ Products in this class for this indication have been studied/labeled for pediatric population
- ☐ Disease/condition does not exist in children
- ☐ Too few children with disease to study
- ☐ There are safety concerns
- ☐ Adult studies ready for approval
- ☐ Formulation needed
- ☐ Other:_____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min ____	**kg____**	**mo.____**	**yr.____**	**Tanner Stage____**
Max____	**kg____**	**mo.____**	**yr.____**	**Tanner Stage____**

Reason(s) for deferral:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**

Other:_____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min ____	**kg____**	**mo.____**	**yr.____**	**Tanner Stage____**
Max____	**kg____**	**mo.____**	**yr.____**	**Tanner Stage____**

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

_____

Regulatory Project Manager

cc: NDA 20-699/S-054, 057
HFD-960/ Grace Carmouze

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337.

(revised 12-22-03)

Attachment A
(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: Long-Term Panic Disorder

Is there a full waiver for this indication (check one)?

X Yes: Please proceed to Section A.

☐ **No: Please check all that apply: ____Partial Waiver ____Deferred ____Completed**
NOTE: More than one may apply
Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- **X Other: Extremely difficult enrollment**

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min ____	**kg____**	**mo.____**	**yr.____**	**Tanner Stage____**
Max____	**kg____**	**mo.____**	**yr.____**	**Tanner Stage____**

Reason(s) for partial waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**
- ☐ **Other:**

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Reason(s) for deferral:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**
- ☐ **Other:_____**

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Comments:

If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

cc: NDA 20-699/S-054, 057
HFD-960/ Grace Carmouze

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337.

(revised 10-14-03)

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/s/

Thomas Laughren
7/15/05 01:33:46 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-699
NDA 20-151

Wyeth Pharmaceuticals Inc.
Attention: Kenneth Bonk
Director II, Global Regulatory Affairs
P.O. Box 8299
Philadelphia, PA 19101-8299

Dear Mr. Bonk:

Please refer to your new drug applications submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Effexor (venlafaxine hydrochloride) Immediate Release (NDA 20-151) and Effexor XR (venlafaxine hydrochloride) Extended Release Capsules (NDA 20-699).

Please refer to your submissions dated December 3, 2004, December 9, 2004, December 22, 2004, April 24, 2006, and May 15, 2006 pertaining to the toxicity of venlafaxine in overdosage.

We have carefully evaluated the data contained in these submissions as well as additional analyses conducted by the FDA Office of Surveillance and Epidemiology (OSE) at our request. Based on a comprehensive examination of these data, it seems likely that venlafaxine is associated with greater toxicity in overdosage compared to selective serotonin reuptake inhibitors (SSRI's) in terms of mortality and the risk of certain serious adverse events, such as seizures and serotonin syndrome. We acknowledge that some data suggest that venlafaxine may be prescribed more commonly in patients at greater risk for suicidal ideation and behavior (e.g., analyses of data from the U.K. GPRD database contained in your December 3, 2004, submission) and such usage patterns may, in part, explain the findings of greater toxicity. However, we are not convinced that this factor entirely explains the observed increased toxicity.

If you feel that there is further information that would be critical in evaluating the toxicity of venlafaxine in overdosage, such as an analysis of venlafaxine prescribing patterns in the U.S. with respect to suicide risk (similar to the GPRD analysis in the U.K.), we would interested in examining such data.

In the absence of substantive new data, we request that the following language be added in the labeling so as to furnish adequate information for the safe and effective use of the drug:

OVERDOSAGE/ Human Experience:

"Published studies suggest that venlafaxine overdosage may be associated with an increased risk of fatal outcomes or other serious adverse events, such as seizures and serotonin syndrome, compared to that observed with SSRI antidepressant products. The extent to which these findings can be attributed to the toxicity of venlafaxine in overdosage as opposed to some characteristic(s) of venlafaxine-treated patients is not clear. Based on current experience with venlafaxine overdosage in humans, greater than approximately 2,100 mg of venlafaxine should not be dispensed at one time to outpatients judged to be at increased risk of suicide."

WARNINGS/Clinical Worsening and Suicide Risk: as well as under DOSAGE AND ADMINISTRATION:

"Greater than approximately 2,100 mg of venlafaxine should not be dispensed at one time to outpatients judged to be at increased risk of suicide (for example, not greater than a 14 day supply at a dose of 150 mg/day) (see OVERDOSAGE/ Human Experience)."

These labeling revisions should be submitted in the form of a "Supplement - Changes Being Effected" within 30 days from the date of this letter.

The Agency would like you to alert prescribers of the risks of overdose with venlafaxine. We are requesting that you issue a "Dear Healthcare Provider" letter explaining the change of labeling regarding venlafaxine and overdose toxicity.

Finally, we note that consideration has been given to [redacted] as a measure to minimize overdose ingestion and toxicity. Please inform us of the status of this proposal and an assessment of whether such a measure could be easily implemented in the U.S. b(4)

If you have any questions, call Renmeet Gujral, Pharm.D., Regulatory Project Manager, at 301-796-1080.

Sincerely,

{See appended electronic signature page}

Thomas Laughren, M.D.
Director
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

Thomas Laughren
8/10/2006 04:31:32 PM

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: November 10, 2005

FROM: Paul J. Andreason, M.D.
Acting Deputy Director,
Division of Psychiatry Products
HFD-130

SUBJECT: Recommendation for Approvable Action on Supplements 54 and 57: Effexor XR for the treatment of Panic Disorder

TO: File NDA 20-699
[Note: This memo should be filed with the original September 23, 2005 submission of this NDA.]

BACKGROUND

On 9/29/04, the sponsor submitted Supplements 54 and 57 for the approval of venlafaxine ER in the acute and extended treatment of panic disorder. The Division issued an approvable letter on 7/15/05. The sponsor submitted a complete response to the 7/15/05 Approvable Action letter on 9/23/05.

Michelle Chuen, MD was the medical officer who reviewed both the original supplement as well as this complete response. There were only clinical question in the 7/15/05 letter and there are no CMC, Pre-Clinical Pharmacology, Biopharmacology, or Safety Team issues outstanding with these supplements.

Dr. Chuen concluded that Wyeth had adequately responded to her questions except for three issues in the draft labeling.

1. Wyeth proposed deleting, "[redacted]." Dr Chuen argued that the robustness ($p<0.001$) and magnitude of effect size (54.4% and 59.7% for 75 mg and 150mg, and 64.7% and 70.0% for 75 mg and 225 mg) for all three doses were similar. Therefore, there appears to be no substantial advantage of the higher doses (150 and 225 mg) over the lower dose (75mg). The sponsor argued that pooling the two studies provided evidence of a dose response. Since the studies only have the 75-mg dose group in common, pooling only affects the 75-mg group outcome without changing the mean response percentages for either the 150-or 225 mg groups. Nonetheless, with pooling there is suggestion of dose response on visual examination though it is not clear that the slope is clinically significant. Therefore I think that it is reasonable to include a statement that a dose response relationship is not "clear" as opposed to there being [redacted] b(4)
2. Dr. Chuen stated that there were 1314 patients in Phase 3 panic disorder studies, not [redacted], as written in the sponsor's proposed labeling. Wyeth acknowledged that this was a typographical error and that 1314 patients is the correct number.

3. Wyeth proposed deleting the term "---" from the Dosage and Administration section. Dr. Chuen noted that the protocol stipulated morning dosing. Wyeth was able to show that giving the dose in either the morning or the evening was actually allowed in the clinical trial based on patient tolerance; though, starting with a morning dose as Dr Chuen pointed out, was the default choice. In the end, there is nothing to indicate that one time should be required over another for specific clinical reasons since individual patients might feel stimulated, somnolent, or unaffected by the drug. b(4)

Recommendations

I concur with Dr Chuen and believe that Wyeth has adequately addressed the outstanding clinical questions from the 7/15/05 Approvable Action letter. I also believe that I have addressed the outstanding labeling issues that remained in Dr. Chuen's review. I recommend that the Division approve supplements 54 and 57 using the draft labeling attached to this action package.

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/s/

Paul Andreason
11/10/2005 04:13:40 PM
MEDICAL OFFICER

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: July 7, 2005

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 extended release) capsules for panic disorder (both short-term and long-term efficacy and safety)

TO: File NDA 20-699/S-054 (ST) and S-057 (LT)
[**Note:** This overview should be filed with the 9-29-04 original submission of these supplements.]

1.0 BACKGROUND

Effexor XR is an extended release formulation of venlafaxine, a serotonin and norepinephrine reuptake inhibitor, that is approved for major depressive disorder, generalized anxiety disorder, and social anxiety disorder. Venlafaxine is also available in an immediate release form (Effexor) that is approved for major depressive disorder. These supplements provide data in support of claims for both short-term (S-054) and long-term (S-057) efficacy in the treatment of panic disorder in a dose range of 75 to 225 mg/day.

Other products currently approved for panic disorder include 2 benzodiazepines (alprazolam [IR and XR] and clonzaepam) and 3 SSRIs (sertraline, paroxetine, and fluoxetine).

We held an EOP2 meeting with the sponsor on 12-4-00 and reached agreement on most issues for this planned program, however, did not agree to a full pediatric waiver at that time (we did subsequently agree to such a waiver). In subsequent corresponce we reached agreement on remaining issues, including designation of 2 key secondary endpoints.

Since the proposal is to use the currently approved Effexor XR capsules, there was no need for chemistry (except for an environmental assessment), biopharmaceutics, or pharm/tox reviews of these supplements.

The primary review of the efficacy and safety data was done by Michelle Chuen, M.D., from the clinical group. Ohidul Siddiqui, Ph.D., from the biometrics group, also reviewed the efficacy data.

The studies supporting these supplements were conduced under IND 41,412, and these supplements were submitted on 9-29-04.

We decided not to take Effexor XR for panic disorder to the Psychopharmacological Drugs Advisory Committee (PDAC).

2.0 CHEMISTRY

Effexor XR is an approved product, and there were no CMC issues that required review as part of these supplements, except for an environmental assessment for which a FONSI was recommended.

3.0 PHARMACOLOGY

Effexor XR is an approved product, and there were no pharm/tox issues that required review as part of these supplements.

4.0 BIOPHARMACEUTICS

Effexor XR is an approved product, and there were no biiopharmaceutics issues that required review as part of these supplements.

5.0 CLINICAL DATA

5.1 Efficacy Data

5.1.1 Overview of Studies Pertinent to Efficacy

Our review of this application considered 4 short-term trials in patients with panic disorder (398, 399, 353, and 391) and 1 longer-term trial (354) in this population. The sponsor identified 2 of the short-term studies (398 and 399) and the longer-term study (354) as positive, and our review focuses on these 3 studies.

The 4 short-term trials were all randomized, double-blind, parallel group, placebo-controlled, 10 to 12 week studies in adults with panic disorder (DSM-IV). Patients were required to have at least 8 full-symptom panic attacks during the 4 weeks before screening and at least 4 such attacks during the 2-week placebo lead-in between screening and baseline.

Two of the short-term studies were fixed dose (398 and 399) and 2 were flexible dose (353 and 391). The longer-term trial was flexible dose. In all studies, patients receiving venlafaxine were started on 37.5 mg/day for the first week, then up to 75 mg/day for week 2. Patients getting higher doses were advanced to 150 mg/day for week 3 and 225 mg/day for week 4 (for those patients getting this higher dose).

All short-term studies used the Panic and Anticipatory Anxiety Scale (PAAS) as the primary assessment, and the primary outcome was the percentage of patients who were free of full-symptom attacks at the final on-therapy observation. The PAAS was extracted from panic diaries that patients kept. Mean change from baseline on the Panic Disorder Severity Scale (PDSS) was one key secondary endpoint and response rate on the CGI-I was a second key secondary (defined as a rating of very much [1] or much [2] improved).

The primary analyses were conducted on a modified ITT population, defined as all randomized patients who had a baseline and at least one followup efficacy assessment. The analyses of the primary endpoint in the short-term trials used a logistic regression model with treatment group and country site as factors and baseline severity as covariate. For the 2 fixed dose studies, each drug group was compared with placebo, and the Hochberg method was used to control the overall error rate at 0.05. PDSS change from baseline was analyzed using ANCOVA, with baseline as covariate, and treatment and center/country as factors. CGI-I responder rate was analyzed using Fisher's Exact Test. The sequence for testing the key secondaries was PDSS, and then CGI-I.

5.1.2 Summary of Studies Pertinent to Efficacy Claims

5.1.2.1 Study 398

This was a 12-week fixed dose study comparing venlafaxine XR (75 and 150 mg/day), paroxetine 40 mg/day, and placebo. It was conducted at 71 European sites. The demographics of patients in this trial were: mean age = 37; 66% female; virtually all white. The ITT populations and proportions completing were as follows:

Treatment Group	ITT Sample	Fraction (%) Completing
Effexor XR 75	158	134/158 (85%)
Effexor XR 150	159	133/159 (84%)
Paroxetine 40	161	136/161 (82%)
Placebo	156	120/156 (77%)

Efficacy Results on % Patients Panic Free for Study 398 (LOCF)

Treatment Group	**% Panic Free**	**[P-value(vs pbo)]**
Effexor XR 75	**54%**	**<0.001**
Effexor XR 150	**61%**	**<0.001**
Paroxetine 40	**60%**	**<0.001**
Placebo	**34%**	

While not described here, results on various secondary endpoints also favored Effexor XR over placebo as did the OC analyses.

Comment: Both Drs. Chuen and Siddiqui considered this a positive study, and I agree.

5.1.2.2 Study 399

This was a 12-week fixed dose study comparing venlafaxine XR (75 and 225 mg/day), paroxetine 40 mg/day, and placebo.

This was a 12-week fixed dose study comparing venlafaxine XR (75 and 225 mg/day), paroxetine 40 mg/day, and placebo. It was conducted at 39 Latin American sites. The demographics of patients in this trial were: mean age = 36; 68% female; about 50% white and 50% hispanic. The ITT populations and proportions completing were as follows:

Treatment Group	ITT Sample	Fraction (%) Completing
Effexor XR 75	156	135/158 (87%)
Effexor XR 150	160	139/159 (87%)
Paroxetine 40	151	124/161 (78%)
Placebo	157	119/156 (76%)

Efficacy Results on % Patients Panic Free for Study 399 (LOCF)

Treatment Group	**% Panic Free**	**[P-value(vs pbo)]**
Effexor XR 75	**64%**	**<0.001**
Effexor XR 150	**70%**	**<0.001**
Paroxetine 40	**59%**	**0.008**
Placebo	**47%**	

While not described here, results on various secondary endpoints also favored Effexor XR over placebo as did the OC analyses.

Comment: Both Drs. Chuen and Siddiqui considered this a positive study, and I agree.

5.1.2.3 Study 353

This was a 10-week flexible dose study comparing venlafaxine XR (75 to 225 mg/day) and placebo. It was conducted at 56 US and Canadian sites. The demographics of patients in this trial were: mean age = 36; 66% female; about 2/3 white. The mean venlafaxine XR dose at week 12 was 194 mg/day. The ITT populations and proportions completing were as follows:

Treatment Group	ITT Sample	Fraction (%) Completing
Effexor XR 75-225	155	115/155 (71%)
Placebo	155	110/155 (74%)

Efficacy Results on % Patients Panic Free for Study 353 (LOCF)

Treatment Group	% Panic Free	[P-value(vs pbo)]
Effexor XR 75-225	51%	0.056
Placebo	41%	

While not described here, results on two key secondary endpoints statistically significantly favored Effexor XR over placebo, as did the OC analyses for both the primary endpoint and the 2 key secondaries.

Comment: Dr. Chuen considered this a negative study, as did Dr. Siddiqui. I agree this must be considered a negative study, given that it failed on the primary endpoint, however, it must be acknowledged that it is a close call.

5.1.2.4 Study 391

This was similar in design to study 353, but failed to show a difference between venlafaxine XR and placebo on the primary endpoint (p=0.622). I will not provide any of the details for this study.

5.1.2.5 Study 354

This was a 52 center double-blind, placebo-controlled, parallel group study (US, Australia, Canada, and Europe) sites), having the usual design for long-term efficacy, i.e., patients "responding" to open treatment with Effexor XR for panic disorder were randomized to continuation on drug or placebo and observed for time to relapse. This trial recruited adult outpatients ($\geq$ 18) who met DSM-IV criteria for panic disorder. There was a 14 day baseline period, followed by a 12-week open label phase during which all patients received Effexor XR (75-225 mg/day). Response was defined as (1) at most 1 full symptom panic attack per week during the last 2 weeks, and (2) a CGI-I score of 1 or 2 (compared to baseline). The PAAS was used to count panic attacks. Responders were randomized to continuation on Effexor XR (at their optimal dose during the open period) or were switched to placebo (1:1). Patients switched to placebo had a tapering period. There was a 26 week period of observation for relapse. Patients were considered to have relapsed if they met the following criteria at 2 consecutive visits, 2 weeks apart:
-Having a full symptom panic attack frequency of $\geq$ 2 panic attacks per week for 2 consecutive weeks, or
-Having been discontinued due to loss of effectiveness in the judgement of the investigator.

The mean age of patients in this study was 38, patients were predominantly white (about 90%), and patients were about 2/3 female.

The sample used was a modified ITT sample, i.e., all randomized patients who were assessed at baseline and at least 1 followup time. The primary outcome was time to relapse. Survival curves were estimated using Kaplan-Meier methodology, and the log-rank test was used to compare

survival distributions.

A total of n=321 patients were treated during the open label phase, and of these, n=176 met responder criteria and were randomized into the double-blind phase (n=92 to Effexor XR and n=84 to placebo). Of these, n=169 comprised the ITT population for analysis (n=89 to Effexor XR and n=80 to placebo).

The overall rates of discontinuation prior to reaching the 26 week endpoint were as follows:

Effexor XR: 35/89 (39%)
Placebo: 52/80 (65%)

Proportions relapsed by 26 weeks favored EffexorXR over placebo:

Effexor XR: 20/89 (23%)
Placebo: 40/80 (50%)

The log-rank analysis of survival curves favored Effexor XR over placebo: $p<0.001$.

As a sensitivity analysis, Dr. Siddiqui considered all censored patients as having an event and the analysis continued to favor Effexor XR over placebo.

Comment: Both Drs. Chuen and Siddiqui considered this a positive study in support of a claim of longer-term efficacy for Effexor XR in panic disorer, and I agree. Since the run-in period for this study was quite brief, the study contributes relatively little information on duration of effect.

5.1.3 Comment on Other Important Clinical Issues Regarding Effexor XR for Panic Disorder

Evidence Bearing on the Question of Dose/Response for Efficacy

The 2 positive trials (398 and 399) were both fixed dose, and neither suggested any benefit of the higher doses explored in those trials. Thus, labeling will recommend [redacted] b(4)

Clinical Predictors of Response

Exploratory analyses were done to detect subgroup interactions on the basis primarily of gender, because there were not sufficient data to explore differences based on age or race. There was no indication of any difference in effectiveness based on gender.

Size of Treatment Effect

The effect sizes as measured by the difference between drug and placebo in the proportion of patients free of panic attacks at endpoint observed in the 2 positive short-term studies (398 and 399) were modest (about 20%), but not unlike those seen in other positive panic disorder trials.

Duration of Treatment

Study 354 provides some information of maintenance effectiveness. Unfortunately, the run-in period for this study was so brief that the study contributes relatively little information on duration of effect, and this limitation will be noted in labeling.

5.1.4 Conclusions Regarding Efficacy Data

The sponsor has, in my view, provided sufficient evidence to support the claim of short-term and limited longer-term efficacy for Effexor XR in the treatment of panic disorder

5.2 Safety Data

5.2.1 Clinical Data Sources for Safety Review

The safety data for these supplements included safety data from a total of n=1314 patients exposed to venlafaxine XR across these 5 trials (n=1001) in the 4 short-term trials and n=313 in the longer-term trial.

5.2.2 Adverse Event Profile for Effexor XR in Panic disorder

There were no deaths in the short-term trials, but a patient in the longer-term trial died of lung cancer. There were a total of 29 SAEs in venlafaxine patients and 12 in placebo patients in these 5 trials. Several of these may have been drug-related (e.g., metrorrhagia, manic reaction, vertigo), but none represented adverse events not already mentioned in labeling. Adverse dropouts overall occurred at about the same rate for drug and placebo in the short-term trials. Adverse dropouts deemed common and drug-related (1% and > placebo) included asthenia, nausea, anxiety, and insomnia (a similar profile to that seen with other Effexor XR indications. The profile of common and drug-related adverse events included: anorexia, constipation, dry mouth, somnolence, tremor, sweating, and abnormal ejaculation/orgasm. This profile is also the recognized common events profile for this drug. Evaluation of laboratory, vital signs, and ECG data did not reveal any drug-related changes not already recognized for venlafaxine. There are several outstanding requests for safety information that the sponsor has yet to respond to.

5.2.3 Conclusions Regarding Safety of Effexor XR in the Treatment of Panic Disorder

I agree with Dr. Chuen that all of the safety issues for this drug can be adequately addressed in labeling.

5.3 Clinical Sections of Labeling

We have made a number of modifications to the sponsor's proposed labeling.

6.0 WORLD LITERATURE

The sponsor provided a warrant that they reviewed the literature and found no relevant papers that would adversely affect conclusions about the safety of Effexor XR in the treatment of panic disorder.

7.0 FOREIGN REGULATORY ACTIONS

To my knowledge, Effexor XR is not approved anywhere at this time for the treatment of panic disorder.

8.0 PSYCHOPHARMACOLOGICAL DRUGS ADVISORY COMMITTEE (PDAC) MEETING

We decided not to take this application to the PDAC.

9.0 DSI INSPECTIONS

Inspections were conducted at 2 sites from study 354, the randomized withdrawal trial. These sites were David Sheehan and Evan Zimmer. Both sites were classified as VAI, and data from these sites were deemed to be acceptable.

10.0 LABELING AND APPROVABLE LETTER

10.1 Labeling

We have included a modified version of labeling with the approvable letter.

10.2 Foreign Labeling

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

10.3 Approvable Letter

The approvable letter includes our proposed labeling and requests for responses to numerous questions that were raised during the course of the review that the sponsor has not addressed as yet.

11.0 CONCLUSIONS AND RECOMMENDATIONS

I believe that Wyeth has submitted sufficient data to support the conclusion that Effexor XR is effective and acceptably safe in the treatment of panic disorder. However, before we can take an approval action, the sponsor needs to respond to various requests we have made and we need to reach agreement on labeling. Thus, we will issue the attached approvable letter along with our proposal for labeling, in anticipation of final approval.

cc:
Orig NDA 20-699/S-054 & 057 (Effexor XR/Panic Disorder)
HFD-120
HFD-120/TLaughren/MChuen/GDubitsky/RTaylor

DOC: Memo Effexor XR PD AE1.doc

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/s/

Thomas Laughren
7/10/05 12:31:44 PM
MEDICAL OFFICER

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
Food and Drug Administration
Rockville MD 20855

CLINICAL INSPECTION SUMMARY

DATE: 05/09/05

TO: Richardae Taylor, Pharm.D., Regulatory Project Manager
Michelle Chuen, M.D., Medical Officer
Division of Neuropharmacological Drug Products, HFD-120

THROUGH: Ni Khin, M.D., Branch Chief
Good Clinical Practice Branch I, HFD-46

FROM: Robert S. Stasko, M.D., Medical Officer
Good Clinical Practice Branch I, HFD-46
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspection

Re: **Drug**: Effexor ER
Therapeutic Classification: Type S
Chemical Classification: 6
Sponsor: Wyeth Pharmaceuticals
NDA: 20-699/SE1-054
Protocol: 0600B5-354-AU/CA/EU/ES CSR-50331 (354)
Proposed Indication: Panic Disorder
Adult Dosage Form/Route of Administration: capsules; 37.5-225mg
Type of Population: Adults

CONSULTATION REQUEST DATE: 12/15/04

PDUFA DATE: 7/29/05

I. BACKGROUND:

Venlafaxine (Effexor) is approved as an antidepressant for major depressive disorder and anxiolytic for generalized anxiety disorder (GAD) in adults. This supplement seeks an additional indication of panic disorder (PD) in adults. In this NDA application, the sponsor included results from **Protocol 0600B5-354-AU/CA/EU/ES CSR-50331 (354)** entitled A Double-Blind, Placebo-Controlled, Parallel-Group, Evaluation of the Long-Term Safety, Efficacy, and Prevention of Relapse in Adult Outpatients with Panic Disorder Who Respond to Open-Label Venlafaxine ER".

This was a double-blind, randomized, multi-center, parallel-group, placebo-controlled, flexible-dose study with 4 study periods (baseline, open-label, double-blind, and taper). After a baseline period (14 days ±3 days) on no medications the frequency of panic attacks was determined. All subjects then entered an open-label 12-week phase were they could be dosed at a minimum of 75 mg/day or up to 225mg/day by day 22; there was no placebo in this 12 week period. At the end of the open-label period, nonresponders were tapered off the study medication for up to 2 weeks and did not enter the double-blind period. In the 6-month double-blind period, subjects ("responders") received either placebo or the same dose from the open-label phase. At the end of 6 months or upon withdrawal, responders received a taper period of up to 2 weeks, if necessary.

The primary efficacy variable in this long-term treatment study was time until panic disorder relapse for patients who responded to venlafaxine ER during the open phase. Relapse (panic attack frequency) was defined as ≥ 2 full-symptom panic attacks per week for 2 consecutive weeks which was extracted from Panic and Anticipatory Anxiety Scale (PAAS), or withdrawal from the study by the investigator because of a loss of efficacy.

Inspection assignment was issued in December 2004: Dr. Zimmer and Sheehan were chosen because of large enrollment of subjects in the study.

II. RESULTS (by site):

NAME	Protocol (Site #)	Location	ASSIGNED DATE	DATE EIR RECEIVED	CLASSIFICATION
David Sheehan, M.D.	354 #354013	Tampa, FL	12/15/04	2/14/05	VAI
Evan Zimmer, M.D.	354 #354081	North Miami, FL	12/15/04	2/18/05	VAI

1. David Sheehan, M.D., (Protocol 354, Site# 354013)

a. What was inspected: For protocol 354, 26 subjects were screened at the clinic but only 12 subjects were found to meet the inclusion/exclusion criteria and entered the open-label phase. Of these 12 subjects enrolled for the open label phase of this study only eight completed this section of the study. Six subjects continued on into the double-blind randomization phase, however none completed this final phase of the study. All subjects signed the informed consent. An in-depth audit of 8 subjects' records from the open-label trial and 3 from the double-blind phase was conducted.
b. Limitations of inspection: None
c. General observations/commentary: There were two instances of deviations from the

protocol. Per the Protocol's "Study Procedure", "Responders are defined as patients who have ≤ 1 full-symptom panic attacks per week during the last 2 weeks of open-label treatment. Responders are eligible to enter into the double-blind phase. Both subjects' records document two panic attacks in one week and for one subject two panic attacks occurred in one day. Neither of these subjects (#2763 and #2764) met the Sponsor's definition of "Responder."

There was no documentation that serum pregnancy tests were performed prior to accepting subjects #182 and #183 into the open-label treatment phase. Both are women of childbearing potential.

d. DSI suggests the review division consider excluding two subjects (#2763 and #2764)) who did not meet all eligibility criteria from efficacy data analysis, to determine if it may have any impact on study outcome.

2. Evan Zimmer, M.D., (Protocol 354, Site# 354081)

a. What was inspected: Dr. Zimmer conducts studies for BioQuan Research Group, Inc. Twenty-five subjects entered Study 354, 12 of whom completed the study. The following subjects did not complete the study: subjects #3518, #3521, and #3529 did not met the inclusion criteria for the double-blind portion of the study, subject 3502 was with drawn by sponsor due to abnormal labs, 3530 was withdrawn since meds were not taken, and 3509 was withdrawn by sponsor since the subject was out of the window time for visit 18. Subjects #3501, #3505, #3506, #3512, & #3514 withdrew consent and subjects #3527 and #3520 were lost to follow-up. Records of 8 subjects from the 25 subjects who entered in the study were reviewed in detail. All 25 subjects' records were reviewed for compliance with the informed consent requirements.
b. Limitations of inspection: None
c. General observations/commentary: A Form FDA-483 was issued at the end of inspection. Four subjects (#3517, #3522, #3502, and #3509) were enrolled and inclusion and exclusion criteria were evaluated using only check marks for yes and no answers. There are no evaluator initials, signatures or dates on these source forms. Without any signature of who the evaluator was, it is unclear if qualified personnel conducted the evaluation to determine eligibility of subjects to be enrolled in the study.
d. Recommendation: The review division should note without any signatures on inclusion/exclusion screening documents it is uncertain if the 4 subjects mentioned above did meet eligibility because it is uncertain if the evaluator was qualified to perform this task. The review division should consider any impact of these findings on study data. Otherwise, data appear acceptable.

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

For the two study sites that were inspected for Protocol 354, there was sufficient documentation to assure that all audited subjects did exist, that all enrolled subjects received the assigned study medication, and had their primary efficacy endpoint captured as specified in the protocol. As stated above, at Dr. Sheehan's site there were 2 subjects enrolled into the open-label phase who were not eligible to do so. At Dr. Zimmer's site there is insufficient documentation to ensure that qualified study personnel performed screening evaluations to determine eligibility of 4 subjects. Although it is unlikely that the above findings would affect the study outcome, the review division may wish to consider its overall impact. Otherwise, data appear acceptable for use in support of this pending NDA application.

Robert S. Stasko, M.D., Medical Officer
Good Clinical Practice Branch I, HFD-46
Division of Scientific Investigations

CONCURRENCE:

Ni Khin, M.D, Branch Chief
Good Clinical Practice Branch I, HFD-46
Division of Scientific Investigations

Key to Classifications
NAI = No deviation from regulations. Data acceptable
VAI = Minor deviations(s) from regulations. Data acceptable
VAI-RR= Deviation(s) form regulations, response received and reviewed. Data acceptable
OAI = Significant deviations for regulations. Data unreliable

cc:
NDA 21
HFD-45/Division File/Reading File
HFD-45/Program Management Staff (electronic copy)
HFD-46/Khin
HFD-46/Stasko

Page 5 CIS NDA20-699.054 Sheehan and Zimmer
HFD-46/Patague GCPB1 Files

rd:RSS5/4/05; 5/6/05; 5/10/05

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/s/

Robert S. Stasko
5/10/05 10:56:55 AM
MEDICAL OFFICER

Ni Aye Khin
5/10/05 03:46:04 PM
MEDICAL OFFICER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

NDA 20-699/S-054, 057

Wyeth Pharmaceuticals, Inc.
Attention: Bruce Bennett, R.Ph.
Associate Director II, Worldwide Regulatory Affairs
P.O. Box 8299
Philadelphia, PA 19101

Dear Mr. Bennett:
We have received your supplemental new drug applications (sNDA) 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

Review Priority Classification: Standard (S)

Date of Application: September 29, 2004

Date of Receipt: September 29, 2004

Our Reference Number: NDA 20-699/S-054(short-term) and S-057 (long term)

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application will be filed under section 505(b) of the Act on November 29, 2004 in accordance with 21 CFR 314.101(a).

In our filing review, we have identified the following potential review issues and request that you provide the information requested below:

1. Please provide a table of adverse event incidence by dose group (placebo, 75, 150, and 225mg) for the pool of the two fixed dose studies (studies 398 and 399). This should follow the format of Table 10.2.2A in the Study Report for study 398 but include all adverse events reported in at least 1% of Effexor XR-treated patients in any dose group in this study pool.

2. In your proposed labeling, under ADVERSE REACTIONS in the subsection entitled "Other Adverse Events Observed During the Premarketing Evaluation of Effexor and Effexor XR," it does not appear that you have incorporated adverse events from study 354. Please provide a revision of this subsection to include these events, as appropriate, and also a table of adverse event incidence for each specific adverse experience during premarketing studies to support your revision of this listing.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application.

Please respond only to the above requests for additional information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

Pediatric Research Equity Act (PREA)
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. We acknowledge receipt of your request for a waiver of pediatric studies for this application and have granted the waiver.

If you have any questions, call Richardae Taylor, Pharm.D., Regulatory Project Manager, at (301) 594-5793.

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
12/8/04 02:01:37 PM

NDA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

NDA # 20-699 Supplement # 054, 057 Efficacy Supplement Type SE- 1

Trade Name: Effexor XR
Established Name: venlafaxine HCL
Strengths: 37.5, 75, 100, 150mg Capsules

Applicant: Wyeth Pharmaceuticals, Inc.
Agent for Applicant:

Date of Application: 9/29/04
Date of Receipt: 9/29/04
Date clock started after UN:
Date of Filing Meeting: 11/10/04
Filing Date: 11/29/04
Action Goal Date (optional): User Fee Goal Date: 7/29/05

Indication(s) requested: Long-term and Short-term Panic Disorder

Type of Original NDA: (b)(1) ☐ (b)(2) ☐
OR
Type of Supplement: (b)(1) ☒ (b)(2) ☐

NOTE:

(1) If you have questions about whether the application is a 505(b)(1) or 505(b)(2) application, see Appendix A. A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). If the application is a (b)(2), complete Appendix B.

(2) If the application is a supplement to an NDA, please indicate whether the NDA is a (b)(1) or a (b)(2) application:

☒ NDA is a (b)(1) application OR ☐ NDA is a (b)(2) application

Therapeutic Classification: S ☒ P ☐
Resubmission after withdrawal? ☐ Resubmission after refuse to file? ☐
Chemical Classification: (1,2,3 etc.) 3
Other (orphan, OTC, etc.)

Form 3397 (User Fee Cover Sheet) submitted: YES ☒ NO ☐

User Fee Status: Paid ☒ Exempt (orphan, government) ☐
Waived (e.g., small business, public health) ☐

NOTE: *If the NDA is a 505(b)(2) application, and the applicant did not pay a fee in reliance on the 505(b)(2) exemption (see box 7 on the User Fee Cover Sheet), confirm that a user fee is not required. The applicant is required to pay a user fee if: (1) the product described in the 505(b)(2) application is a new molecular entity or (2) the applicant claims a new indication for a use that that has not been approved under section 505(b). Examples of a new indication for a use include a new indication, a new dosing regime, a new patient population, and an Rx-to-OTC switch. The best way to determine if the applicant is claiming a new indication for a use is to compare the applicant's proposed labeling to labeling that has already been approved for the product described in the application. Highlight the differences between the proposed and approved labeling.*

If you need assistance in determining if the applicant is claiming a new indication for a use, please contact the user fee staff.

- Is there any 5-year or 3-year exclusivity on this active moiety in an approved (b)(1) or (b)(2) application? YES ☒ NO ☐
  If yes, explain: Yes, for an approved b1 supplement for social anxiety disorder.

- Does another drug have orphan drug exclusivity for the same indication? YES ☐ NO ☒

- If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? YES ☐ NO ☐

  If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

- Is the application affected by the Application Integrity Policy (AIP)? YES ☐ NO ☒
  If yes, explain:

- If yes, has OC/DMPQ been notified of the submission? YES ☐ NO ☐

- Does the submission contain an accurate comprehensive index? YES ☒ NO ☐

- Was form 356h included with an authorized signature? YES ☒ NO ☐
  If foreign applicant, both the applicant and the U.S. agent must sign.

- Submission complete as required under 21 CFR 314.50? YES ☒ NO ☐
  If no, explain:

- If an electronic NDA, does it follow the Guidance? N/A ☐ YES ☒ NO ☐
  If an electronic NDA, all forms and certifications must be in paper and require a signature.
  Which parts of the application were submitted in electronic format? All except administrative forms that require signature.

  Additional comments:

- If an electronic NDA in Common Technical Document format, does it follow the CTD guidance? N/A ☐ YES ☐ NO ☐

- Is it an electronic CTD (eCTD)? N/A ☐ YES ☐ NO ☐
  If an electronic CTD, all forms and certifications must either be in paper and signed or be electronically signed.

  Additional comments:

- Patent information submitted on form FDA 3542a? YES ☒ NO ☐

- Exclusivity requested? YES, 3 Years NO ☐
  NOTE: *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*

- Correctly worded Debarment Certification included with authorized signature? YES ☒ NO ☐
  If foreign applicant, both the applicant and the U.S. Agent must sign the certification.

NOTE: *Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as "To the best of my knowledge . . . ."*

- Financial Disclosure forms included with authorized signature? YES ☒ NO ☐
  (Forms 3454 and 3455 must be included and must be signed by the APPLICANT, not an agent.)
  NOTE: *Financial disclosure is required for bioequivalence studies that are the basis for approval.*

- Field Copy Certification (that it is a true copy of the CMC technical section)? Y ☒ NO ☐

- PDUFA and Action Goal dates correct in COMIS? YES ☒ NO ☐
  If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.

- Drug name and applicant name correct in COMIS? If not, have the Document Room make the corrections. Ask the Doc Rm to add the established name to COMIS for the supporting IND if it is not already entered.

- List referenced IND numbers: 41,412

- End-of-Phase 2 Meeting(s)? Date(s) 3/21/01 NO ☐
  If yes, distribute minutes before filing meeting.

- Pre-NDA Meeting(s)? Date(s) _____ NO ☒
  If yes, distribute minutes before filing meeting.

Project Management

- Was electronic "Content of Labeling" submitted? YES ☒ NO ☐
  If no, request in 74-day letter.

- All labeling (PI, PPI, MedGuide, carton and immediate container labels) consulted to DDMAC?
  YES ☐ NO ☒

- Risk Management Plan consulted to ODS/IO? N/A ☒ YES ☐ NO ☐

- Trade name (plus PI and all labels and labeling) consulted to ODS/DMETS? Y ☐ NO ☒

- MedGuide and/or PPI (plus PI) consulted to ODS/DSRCS? N/A ☒ YES ☐ NO ☐

- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling, submitted?
  N/A ☒ YES ☐ NO ☐

If Rx-to-OTC Switch application:

- OTC label comprehension studies, all OTC labeling, and current approved PI consulted to ODS/DSRCS? N/A ☒ YES ☐ NO ☐

- Has DOTCDP been notified of the OTC switch application? YES ☐ NO ☐

Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff? YES ☐ NO ☒

Chemistry

- Did applicant request categorical exclusion for environmental assessment? YES ☐ NO ☒
  If no, did applicant submit a complete environmental assessment? YES ☒ NO ☐
  If EA submitted, consulted to Florian Zielinski (HFD-357)? YES ☒ NO ☐
- Establishment Evaluation Request (EER) submitted to DMPQ? YES ☐ NO ☐
- If a parenteral product, consulted to Microbiology Team (HFD-805)? YES ☐ NO ☒

ATTACHMENT

MEMO OF FILING MEETING

DATE: 11/10/04

BACKGROUND: Supplemental apllication for Panic Disorder (Short-term and Long-term)
(Provide a brief background of the drug, e.g., it is already approved and this NDA is for an extended-release formulation; whether another Division is involved; foreign marketing history; etc.)

ATTENDEES: Dr. Laughren (Clinical Team Leader), Dr. Oliver (Chemistry Team Leader), Dr. Andreason (Clinical Team Leader), Dr. Katz (Division Director), Dr. Dubitsky (Mentor, clinical reviewer), Dr. Chuen (Clinical reviewer), Dr. Jin (statistical team leader), Dr. Soldatova (Chemistry reviewer), Dr. Siddiqui (statistical reviewer), Dr. Stasko (DSI), Dr. Taylor (P

ASSIGNED REVIEWERS (including those not present at filing meeting) : see above

Discipline	**Reviewer**
Medical:	
Secondary Medical:	
Statistical:	
Pharmacology:	
Statistical Pharmacology:	
Chemistry:	
Environmental Assessment (if needed):	
Biopharmaceutical:	
Microbiology, sterility:	
Microbiology, clinical (for antimicrobial products only):	
DSI:	
Regulatory Project Management:	
Other Consults:	

Per reviewers, are all parts in English or English translation? YES ☒ NO ☐
If no, explain:

CLINICAL FILE ☒ REFUSE TO FILE ☐

- Clinical site inspection needed? YES ☒ NO ☐
- Advisory Committee Meeting needed? YES, date if known _____ NO ☒
- If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? N/A ☒ YES ☐ NO ☐

CLINICAL MICROBIOLOGY N/A ☒ FILE ☐ REFUSE TO FILE ☐

STATISTICS N/A ☐ FILE ☒ REFUSE TO FILE ☐

BIOPHARMACEUTICS FILE ☐ REFUSE TO FILE ☐

- Biopharm. inspection needed? YES ☐ NO ☐

PHARMACOLOGY N/A ☒ FILE ☐ REFUSE TO FILE ☐

- GLP inspection needed? YES ☐ NO ☐

CHEMISTRY FILE ☒ REFUSE TO FILE ☐

- Establishment(s) ready for inspection? YES ☐ NO ☐
- Microbiology YES ☐ NO ☐

ELECTRONIC SUBMISSION:
Any comments:

REGULATORY CONCLUSIONS/DEFICIENCIES:
(Refer to 21 CFR 314.101(d) for filing requirements.)

☐ The application is unsuitable for filing. Explain why:

☐ The application, on its face, appears to be well-organized and indexed. The application appears to be suitable for filing.

☐ No filing issues have been identified.

☒ Filing issues to be communicated by Day 74. List (optional):

ACTION ITEMS:

1.☐ If RTF, notify everybody who already received a consult request of RTF action. Cancel the EER.

2.☐ If filed and the application is under the AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.

3.☒ Convey document filing issues/no filing issues to applicant by Day 74.

Chardae Taylor, Pharm.D.
Regulatory Project Manager, HFD-120

Appendix A to NDA Regulatory Filing Review

An application is likely to be a 505(b)(2) application if:

(1) it relies on literature to meet any of the approval requirements (unless the applicant has a written right of reference to the underlying data)
(2) it relies on the Agency's previous approval of another sponsor's drug product (which may be evidenced by reference to publicly available FDA reviews, or labeling of another drug sponsor's drug product) to meet any of the approval requirements (unless the application includes a written right of reference to data in the other sponsor's NDA)
(3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)
(4) it seeks approval for a change from a product described in an OTC monograph and relies on the monograph to establish the safety or effectiveness of one or more aspects of the drug product for which approval is sought (see 21 CFR 330.11).

Products that may be likely to be described in a 505(b)(2) application include combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations), OTC monograph deviations, new dosage forms, new indications, and new salts.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, please consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

Appendix B to NDA Regulatory Filing Review
Questions for 505(b)(2) Applications

1. Does the application reference a listed drug (approved drug)? YES ☐ NO ☐

   *If "**No**," skip to question 3.*

2. Name of listed drug(s) referenced by the applicant (if any) and NDA/ANDA #(s):

3. The purpose of this and the questions below (questions 3 to 5) is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval and that should be referenced as a listed drug in the pending application.

   (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved?

   YES ☐ NO ☐

   (***Pharmaceutical equivalents*** are drug products in identical dosage forms that: **(1)** contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; **(2)** do not necessarily contain the same inactive ingredients; **and** **(3)** meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c))

   *If "**No**," skip to question 4. Otherwise, answer part (b).*

   (b) Is the approved pharmaceutical equivalent(s) cited as the listed drug(s)? YES ☐ NO ☐
   (The approved pharmaceutical equivalent(s) should be cited as the listed drug(s).)

   *If "**Yes**," skip to question 6. Otherwise, answer part (c).*

   (c) Have you conferred with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (ORP) (HFD-007)? YES ☐ NO ☐

   *If "**No**," please contact the Director, Division of Regulatory Policy II, ORP. Proceed to question 6.*

4. (a) Is there a pharmaceutical alternative(s) already approved? YES ☐ NO ☐

   (***Pharmaceutical alternatives*** are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)

   *If "**No**," skip to question 5. Otherwise, answer part (b).*

   (b) Is the approved pharmaceutical alternative(s) cited as the listed drug(s)? YES ☐ NO ☐
   (The approved pharmaceutical alternative(s) should be cited as the listed drug(s).)

NOTE: *If there is more than one pharmaceutical alternative approved, consult the Director, Division of*

Regulatory Policy II, Office of Regulatory Policy (ORP) (HFD-007) to determine if the appropriate pharmaceutical alternatives are referenced.

*If "**Yes**," skip to question 6. Otherwise, answer part (c).*

(c) Have you conferred with the Director, Division of Regulatory Policy II, ORP? YES ☐ NO ☐

*If "**No**," please contact the Director, Division of Regulatory Policy II, ORP. Proceed to question 6.*

5. (a) Is there an approved drug product that does not meet the definition of "pharmaceutical equivalent" or "pharmaceutical alternative," as provided in questions 3(a) and 4(a), above, but that is otherwise very similar to the proposed product?

YES ☐ NO ☐

*If "**No**," skip to question 6.*

*If "**Yes**," please describe how the approved drug product is similar to the proposed one and answer part (b) of this question. Please also contact the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007), to further discuss.*

(b) Is the approved drug product cited as the listed drug? YES ☐ NO ☐

6. Describe the change from the listed drug(s) provided for in this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsules to solution").

7. Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? (Normally, FDA will refuse-to-file such NDAs (see 21 CFR 314.101(d)(9)). YES ☐ NO ☐

8. Is the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (See 314.54(b)(1)). If yes, the application should be refused for filing under 21 CFR 314.101(d)(9)). YES ☐ NO ☐

9. Is the rate at which the product's active ingredient(s) is absorbed or otherwise made available to the site of action unintentionally less than that of the RLD (see 21 CFR 314.54(b)(2))? If yes, the application should be refused for filing under 21 CFR 314.101(d)(9). YES ☐ NO ☐

10. Are there certifications for each of the patents listed for the listed drug(s)? YES ☐ NO ☐

11. Which of the following patent certifications does the application contain? (Check all that apply and identify the patents to which each type of certification was made, as appropriate.)

☐ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)
Patent number(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)
Patent number(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)
Patent number(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification)
Patent number(s):

NOTE: *IF FILED, and if the applicant made a "Paragraph IV" certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must* ***subsequently*** *submit a signed certification stating that the NDA holder and patent owner(s) were notified the NDA was filed [21 CFR 314.52(b)]. The applicant must also submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)].*

☐ 21 CFR 314.50(i)(1)(ii): No relevant patents.

☐ 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)
Patent number(s):

☐ 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above).
Patent number(s):

☐ Written statement from patent owner that it consents to an immediate effective date upon approval of the application.
Patent number(s):

12. Did the applicant:

- Identify which parts of the application rely on information (e.g. literature, prior approval of another sponsor's application) that the applicant does not own or to which the applicant does not have a right of reference?

  YES ☐ NO ☐

- Submit a statement as to whether the listed drug(s) identified has received a period of marketing exclusivity?

  YES ☐ NO ☐

- Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug?

  N/A ☐ YES ☐ NO ☐

- Certify that it is seeking approval only for a new indication and not for the indications approved for the listed drug if the listed drug has patent protection for the approved indications and the applicant is requesting only the new indication (21 CFR 314.54(a)(1)(iv).?

  N/A ☐ YES ☐ NO ☐

13. If the (b)(2) applicant is requesting 3-year exclusivity, did the applicant submit the following information required by 21 CFR 314.50(j)(4):

    - Certification that at least one of the investigations included meets the definition of "new clinical investigation" as set forth at 314.108(a).

      YES ☐ NO ☐

    - A list of all published studies or publicly available reports that are relevant to the conditions for which the applicant is seeking approval.

      YES ☐ NO ☐

    - EITHER

      The number of the applicant's IND under which the studies essential to approval were conducted.

      IND# _____ NO ☐

      OR

      A certification that the NDA sponsor provided substantial support for the clinical investigation(s) essential to approval if it was not the sponsor of the IND under which those clinical studies were conducted?

      YES ☐ NO ☐

14. Has the Associate Director for Regulatory Affairs, OND, been notified of the existence of the (b)(2) application?

    YES ☐ NO ☐

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

/s/

Richardae Taylor
7/11/05 02:52:47 PM
CSO

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION	**REQUEST FOR CONSULTATION**

TO *(Division/Office)*:	FROM:
HFD-357/Environmental Assessment **Attention: Florian Zielinski, Room 1048 RKW2** **(5515 Security La)**	**HFD-120/Division of Neuropharmacological Drug Products**

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
October 6, 2004		20-699/SE1-054	Efficacy Supplement	September 29, 2004

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Effexor (venlafaxine HCl) Extended Release Capsules		Panic Disorder	See Below User Fee Due Date

NAME OF FIRM: Wyeth Pharmaceuticals, Inc.

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*:

COMMENTS/SPECIAL INSTRUCTIONS:

The HFD-120 has received a new efficacy supplement for Effexor (venlafaxine HCl) NDA 20-699/SE1-054 in the treatment of Panic Disorder. The User Fee due date on this application is 7/29/05. The documents may be found in the EDR: \\CDSESUB1\N20699\S_054\2004-09-29.

Please review and comment on the EA aspects of this submission. The reviewing chemist is Dr. Lyudmila Soldatova and the PM is Chardae Taylor, 301-594-5793.

Thanks!

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one)
Richardae Taylor, Pharm.D. Regulatory Project Manager 301-594-5793 taylorr@cder.fda.gov	X MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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

/s/

Richardae Taylor
10/6/04 10:34:23 AM