Name: Effexor XR Extended-Release Capsules

Generic Name: venlafaxine hydrochloride

Sponsor: Wyeth Pharmaceuticals Inc.

Approval Date: 03/16/04

Indications: For the treatment of major depressive disorder, generalized anxiety disorder and social anxiety disorder.
CONTENTs

Reviews / Information Included in this NDA Review.

<table>
<thead>
<tr>
<th>Review Type</th>
<th>Included</th>
</tr>
</thead>
<tbody>
<tr>
<td>Approval Letter</td>
<td>X</td>
</tr>
<tr>
<td>Approvable Letter</td>
<td></td>
</tr>
<tr>
<td>Labeling</td>
<td>X</td>
</tr>
<tr>
<td>Summary Review</td>
<td></td>
</tr>
<tr>
<td>Officer/Employee List</td>
<td></td>
</tr>
<tr>
<td>Office Director Memo</td>
<td></td>
</tr>
<tr>
<td>Cross Discipline Team Leader Review</td>
<td></td>
</tr>
<tr>
<td>Medical Review(s)</td>
<td></td>
</tr>
<tr>
<td>Chemistry Review(s)</td>
<td>X</td>
</tr>
<tr>
<td>Environmental Assessment</td>
<td></td>
</tr>
<tr>
<td>Pharmacology Review(s)</td>
<td></td>
</tr>
<tr>
<td>Statistical Review(s)</td>
<td></td>
</tr>
<tr>
<td>Microbiology Review(s)</td>
<td></td>
</tr>
<tr>
<td>Clinical Pharmacology/Biopharmaceutics Review(s)</td>
<td></td>
</tr>
<tr>
<td>Risk Assessment and Risk Mitigation Review(s)</td>
<td></td>
</tr>
<tr>
<td>Proprietary Name Review(s)</td>
<td></td>
</tr>
<tr>
<td>Administrative/Correspondence Document(s)</td>
<td></td>
</tr>
</tbody>
</table>
Dear Mr. Bonk:

We acknowledge receipt of your supplemental new drug application dated September 29, 2003, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Effexor XR (venlafaxine hydrochloride) Extended Release Capsules.

We additionally acknowledge receipt of your amendments dated October 21, and December 22, 2003.

This application, submitted as a "Changes Being Effected" supplement, proposes 1) revisions to the Description section and Patient Brief Summary to reflect the inactive ingredient change in capsule shell caps, and 2) changes to the How Supplied section revising the Wyeth logo, corporate name, and address and removing the "Protect From Light" statement.

We have completed our review of this supplemental application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in your labeling submitted on September 29, 2003. Accordingly, this supplemental application is approved effective on the date of this letter.

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

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

Sincerely,

(See appended electronic signature page)

Russell Katz, M.D.
Director
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Russell Katz
3/16/04 11:38:44 AM
Effexor® XR
(venlafaxine hydrochloride)
Extended-Release Capsules

DESCRIPTION

Effexor XR is an extended-release capsule for oral administration that contains venlafaxine hydrochloride, a structurally novel antidepressant. It is designated (R/S)-1-(2-((dimethylamino)-1-(4-methoxyphenyl)cyclohexanol hydrochloride or (R/S)-1-((dimethylamino)methyl)-(p-methoxybenzyl)cyclohexanol hydrochloride and has the empirical formula of C17H21NO2 hydrochloride. Its molecular weight is 313.87. The structural formula is shown below.

\[
\text{venlafaxine hydrochloride}
\]

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, H1-histaminergic, or a2-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) U/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(1.9) U/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 Cmax (150 ng/mL for venlafaxine and 260 ng/mL for ODV) and later Tmax (5.5 hours for venlafaxine and 9 hours for ODV) than for immediate release venlafaxine tablets (Cmax's for immediate release 75 mg Q12 hours were 225 ng/mL for venlafaxine and 250 ng/mL for ODV; Tmax'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.

**Wyeth**
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. 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. Similarly, ODV elimination half-life was prolonged by about 40% and clearance was reduced by about 56% in renally impaired patients (GFR=10 to 70 mL/min), compared to normal subjects. 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, fixed-dose studies in adult outpatients meeting DSM-IV criteria for major depressive disorder.

A 12-week study utilizing Effexor XR doses in a range 75 to 225 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 227 mg/day) both demonstrated superior efficacy 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 item, 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/agitation factor, the cognitive disturbance factor, and the retardation factor, as well as for the psychomotor anxiety score.

A 4-week study of inpatients meeting DSM-IV criteria for major depressive disorder with melancholia utilizing Effexor (the immediate release form of venlafaxine) in a range of 150 to 375 mg/day (b.i.d. schedule) demonstrated superiority of Effexor over placebo. The mean dose in completers was 230 mg/day.

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

In one longer-term study, outpatients meeting DSM-IV criteria for major depressive disorder who had responded during an 8-week open trial on Effexor XR (75, 150, or 225 mg, b.i.d.) 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 ≤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) a 2 consecutive CGI Severity of Illness item scores of ≥4, or (3) a final CGI Severity of Illness item score of ≥4 for any patient who withdrew from the study for any reason. Patients receiving continued Effexor XR treatment experienced significantly lower relapse rates over the subsequent 26 weeks compared with those receiving placebo.

In a second longer-term trial, outpatients meeting DSM-IV criteria for major depressive disorder, recurrent type, who had responded (HAM-D-21 total score ≤10 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 with Effexor XR (100 to 200 mg/day, on a b.i.d. schedule) were randomized to continuation of their same Effexor XR dose or to placebo. The following factors were observed 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 (GAD)

The efficacy of Effexor XR capsules as a treatment for Generalized Anxiety Disorder (GAD) was established in two 8-week, placebo-controlled, fixed-dose studies in adult outpatients meeting DSM-IV criteria for Social Anxiety Disorder. Patients received Effexor XR capsules in a range of 75 to 225 mg/day. Effexor XR was significantly more effective than placebo on the Hamilton Rating Scale for Anxiety (HAMA) total score, both the HAMA-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 were not as consistently effective as the highest dose. A second 8-week study utilizing Effexor XR doses of 75 and 150 mg/day and placebo showed that both doses were significantly more effective than placebo on some of these same outcomes; however, the 75 mg/day dose was more consistently effective dose than placebo on the Hamilton Rating Scale for Anxiety (HAMA-A) total score, both the HAMA-A anxiety and tension items, and the CGI Global Improvement (CGI) scale. 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 highest dose.

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, fixed-dose studies in adult outpatients meeting DSM-IV criteria for Social Anxiety Disorder. Patients received Effexor XR capsules in a range of 75 to 225 mg/day. Effexor XR was assessed with the Liebowitz Social Anxiety Scale (LSAS). In these two trials, Effexor XR was significantly more effective than placebo on the LSAS total score at endpoint on the LSAS trial 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.

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

WARNINGS

Potential for Interaction with Monoamine Oxidase Inhibitors

Adverse reactions, some of which were serious, have been reported in patients who have recently been discontinued from a monoamine oxidase inhibitor (MAOI) and started on venlafaxine, or who have recently had venlafaxine therapy discontinued prior to initiation of an MAOI. These reactions have included tremor, myoclonus, diaphoresis, nausea, vomiting, flushing, dizziness, hyperthermia with features resembling neuroleptic malignant syndrome, seizures, and death. In patients receiving antidepressants with pharmacological properties similar to venlafaxine in combination with an MAOI, there have also been reports of serious, sometimes fatal, reactions. For a selective serotonin reuptake inhibitor, these reactions have included hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes that include extreme agitation progressing to delirium and coma. Some cases presented with features resembling neuroleptic malignant syndrome. Severe hyperthermia and seizures, sometimes fatal, have been reported in association with the combined use of tricyclic antidepressants and MAOIs. These reactions have also been reported in patients who have recently discontinued these drugs and have been started on an MAOI. The effects of combined use of venlafaxine and MAOIs have not been studied in humans or animals. Therefore, because venlafaxine is an inhibitor of both monoamine oxidase type A and type B 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 275 mg/day of Effexor XR in premarketing studies in patients with major depressive disorder, 3% (9/300) experienced sustained hypertension (defined as treatment-emergent supine diastolic blood pressure (SDBP) ≥ 20 mm Hg and ≥ 10 mm Hg above baseline for 3 consecutive on-treatment visits). Among patients treated with 37.5 to 225 mg/day of Effexor XR in premarketing GAD studies, 0.5% (3/601) 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. 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 15% 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, there was a final on-drug mean increase in SDBP of 0.3 mm Hg was observed for Effexor XR-treated patients compared with a mean increase of 0.5 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 and Social Anxiety Disorder studies, most increases were up to 8 mm Hg and in 0.7% (1/131) and 1.3% (2/153) 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; 26 to 45 mm Hg up to 6 months). In premarketing Social Anxiety Disorder studies up to 12 weeks, 0.4% (5/727) 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).

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

Invasive and Nervousness

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

Table 1

<table>
<thead>
<tr>
<th>Incidence of Invasive and Nervousness in Placebo-Controlled Major Depressive Disorder, GAD, and Social Anxiety Disorder Trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major Depressive</td>
</tr>
<tr>
<td>GAD</td>
</tr>
<tr>
<td>Social Anxiety</td>
</tr>
</tbody>
</table>
**INDICATIONS AND USAGE**

**Major Depressive Disorder**

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

The efficacy of Efexor XR in the treatment of major depressive disorder was established in 8- and 12-week controlled trials of outpatients whose diagnoses corresponded most closely to the DSM-IV-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 Efexor XR (the immediate release form of venlafaxine) in the treatment of major depressive disorder in inpatients meeting diagnostic criteria for major depressive disorder with melancholia was established in a 4-week controlled trial (see Clinical Trials). The safety and efficacy of Efexor XR in hospitalized depressed patients have not been adequately studied.

The efficacy of Efexor 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 Efexor XR 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 who 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 Efexor 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**

Efexor 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.

Efexor XR is indicated for the treatment of generalized anxiety disorder in adults who have also diagnosed with major depressive disorder (see Clinical Trials) and for the treatment of Social Anxiety Disorder as defined in DSM-IV (see Clinical Trials).

**Social Anxiety Disorder**

Efexor 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 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 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 phobia. Lesser degrees of performance anxiety or shyness generally do not require psychopharmacological treatment.

The efficacy of Efexor XR in the treatment of Social Anxiety Disorder was established in 12-weekplacebo-controlled trials in adult outpatients with Social Anxiety Disorder (DSM-IV). Efexor XR has not been studied in children or adolescents with Social Anxiety Disorder (see Clinical Trials).

The effectiveness of Efexor XR in the long-term treatment of Social Anxiety Disorder is, for more than 12 weeks, has not been systematically evaluated in adequate and well-controlled trials. Therefore, the physician who elects to use Efexor 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.

**INSERT PHARMACODE**
Serum Cholesterol Elevation
Clinically relevant increases in serum cholesterol were recorded in 5.3% of venlafaxine-treated patients and 0.0% of placebo-treated patients treated for at least 3 months in placebo-controlled trials (see ADVERSE REACTIONS—Laboratory Changes). Measurement of serum cholesterol levels should be considered during long-term treatment.

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

The same precautions observed when treating patients with major depressive disorder should be observed when treating patients with GAD or Social Anxiety Disorder.

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

Venlafaxine has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were systematically excluded from many clinical studies during venlafaxine’s premarketing testing. The electrocardiograms were analyzed for 275 patients who received Effexor XR and 229 patients who received placebo in 8- to 12-week double-blind, placebo-controlled trials or major depressive disorder studies, for 810 patients who received Effexor XR and 293 patients who received placebo in 8-week double-blind, placebo-controlled trials, for 165 patients who received Effexor XR and 228 patients who received placebo in 12-week double-blind, placebo-controlled trials in Social Anxiety Disorder. The mean change from baseline in corrected QT interval (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 1.6 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 2.6 msec for Effexor XR and decrease of 2.0 msec for placebo).

In these same trials, the mean change from baseline in heart rate for Effexor XR-treated patients in the major depressive disorder studies was significantly higher than that for placebo (a mean increase of 4 beats per minute for Effexor XR and 1 beat per minute for placebo). The mean change from baseline in heart rate for Effexor XR-treated patients in the GAD studies was significantly higher than that for placebo (a mean increase of 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 Social Anxiety Disorder studies was significantly higher than that for placebo (a mean increase of 5 beats per minute for Effexor XR and no change for placebo).

In a flexible-dose study, with Effexor doses in the range of 200 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 with underlying medical conditions that 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 novel, non-concomitant abnormalities did not differ from that with placebo.

In patients with renal impairment (GFR = 10 to 70 mL/min) or corshons of the fun, 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
Physicians are advised to discuss the following issues with patients for whom they prescribe Effexor XR (venlafaxine hydrochloride) extended-release capsules:

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

Concomitant Medication
Patients are 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.

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 desmethylorphan to desorphan.

Imipramine: Venlafaxine did not affect the pharmacokinetics of imipramine and 2-OH-imipramine. However, desipramine AUC, Cmax, and Cmin 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 DOX. 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 20% increase in risperidone AUC. However, venlafaxine coadministration did not significantly alter the pharmacokinetics of venlafaxine and DOX. The clinical significance of this finding is unknown.

CYP1A2: Venlafaxine did not inhibit CYP1A2 in vitro. This finding was confirmed in vivo by clinical drug interaction studies in which venlafaxine did not inhibit the metabolism of several CYP1A2 substrates, including alprazolam, diazepam, and tefencaine.

Warfarin: 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 50 mg oral dose of indoxyl and a 34% decrease in indomethacin AUC. Indinavir did not affect the pharmacokinetics of venlafaxine and DOX. The clinical significance of this finding is unknown.

CYP2C19: Venlafaxine did not inhibit CYP2C19 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.

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 tefencaine.

Monoamine Oxidase Inhibitors
See CONTRAINDICATIONS and WARNINGS.

CNS-Active Drugs
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 receptor blockers (5-HT3, 5-HT1B/1D, etc.), 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/m² 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 venlafaxine in patients receiving the maximum recommended human dose. Plasma levels of the 6-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 metabolites, 6-desmethylenefaxine (DOX), 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 vivo (7BLCr-313) mouse cell transformation assay, the sister chromatid exchange assay in cultured Chinese hamster ovary cells, or the in vivo chromosomal aberration assay in rats. Venlafaxine 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 rats.

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/m² basis.

Pregnancy
Neonatal 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/m² 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 rate of those deaths was not isolated. Those effects occurred at 0.2X.
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 13 healthy male subjects. Additionally, administration of venlafaxine in a stable regimen did not exaggerate the psychomotor and psychometric effects induced by ethanol in those 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 16 healthy subjects. The oral clearance of venlafaxine was reduced by about 43%, and the exposure (AUC) and maximum concentration (Cmax) 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, desmethylvenlafaxine, 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 (CLD) of a single 2 mg dose of haloperidol by 42%, which resulted in a 70% increase in haloperidol AUC. In addition, the haloperidol Cmax increased 88% when coadministered with venlafaxine, but the haloperidol elimination half-life (t1/2) 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 CYP2D6 and CYP3A4 Inhibitors

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 concurrent use of venlafaxine with drug treatments that potentially inhibit both CYP2D6 and CYP3A4, the primary metabolizing enzymes for venlafaxine, has not been studied.
<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Major Depressive Disorder Indication</th>
<th>GAD Indication</th>
<th>Social Anxiety Disorder Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Effexor XR (n=555)</td>
<td>Placebo (n=285)</td>
<td>Effexor XR (n=277)</td>
</tr>
<tr>
<td>Body as a Whole</td>
<td>--</td>
<td>--</td>
<td>3%</td>
</tr>
<tr>
<td>Anorexia</td>
<td>1%</td>
<td>&lt;1%</td>
<td>--</td>
</tr>
<tr>
<td>Vomiting</td>
<td>--</td>
<td>--</td>
<td>2%</td>
</tr>
<tr>
<td>Nervous System</td>
<td>4%</td>
<td>&lt;1%</td>
<td>8%</td>
</tr>
<tr>
<td>Headache</td>
<td>1%</td>
<td>&lt;1%</td>
<td>--</td>
</tr>
<tr>
<td>Dry Mouth</td>
<td>1%</td>
<td>0%</td>
<td>2%</td>
</tr>
<tr>
<td>Nausea</td>
<td>1%</td>
<td>&lt;1%</td>
<td>--</td>
</tr>
<tr>
<td>Vomiting</td>
<td>--</td>
<td>--</td>
<td>1%</td>
</tr>
<tr>
<td>Skin</td>
<td>2%</td>
<td>1%</td>
<td>--</td>
</tr>
<tr>
<td>Skin</td>
<td>2%</td>
<td>&lt;1%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Skin</td>
<td>--</td>
<td>2%</td>
<td>--</td>
</tr>
<tr>
<td>Skin</td>
<td>--</td>
<td>--</td>
<td>3%</td>
</tr>
<tr>
<td>Impotence</td>
<td>--</td>
<td>--</td>
<td>--</td>
</tr>
</tbody>
</table>

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

2. In U.S. placebo-controlled trials for major depressive disorder, the following were also common events leading to discontinuation and were considered to be drug-related for Effexor XR-treated patients (% Effexor XR (n = 555), % Placebo (n = 285)): Abnormal Ejaculation (male) 16% (placebo <1%); Impotence 4% (placebo <1%); Anorgasmia (female) 3% (placebo <1%).

3. 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, injury, injury, back pain, chest pain, dizziness, dysmenorrhea, dyspepsia, flu syndrome, headache, infection, infection, infection, infection, rash, rhinitis, and sinusitis.

4. <1% indicates an incidence greater than zero but less than 1%.


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### Table 3 (continued)

<table>
<thead>
<tr>
<th>Body System</th>
<th>Effexor XR (n=555)</th>
<th>Placebo (n=285)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urogenital System</td>
<td>Abnormal Ejaculation (male) 4%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Cardiovascular System</td>
<td>Vasodilatation 3%</td>
<td>2%</td>
</tr>
<tr>
<td>Nervous System</td>
<td>Stiffness 16%</td>
<td>11%</td>
</tr>
<tr>
<td>Insomnia</td>
<td>16%</td>
<td>6%</td>
</tr>
<tr>
<td>Somnolence</td>
<td>10%</td>
<td>10%</td>
</tr>
<tr>
<td>Nervousness</td>
<td>14%</td>
<td>8%</td>
</tr>
<tr>
<td>Libido Decreased</td>
<td>6%</td>
<td>4%</td>
</tr>
<tr>
<td>Tremor</td>
<td>4%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Abnormal Dreams</td>
<td>3%</td>
<td>2%</td>
</tr>
<tr>
<td>Hypertonia</td>
<td>3%</td>
<td>2%</td>
</tr>
<tr>
<td>Paresthesia</td>
<td>1%</td>
<td>1%</td>
</tr>
<tr>
<td>Respiratory System</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Skin</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Skin</td>
<td>10%</td>
<td>3%</td>
</tr>
<tr>
<td>Skin</td>
<td>4%</td>
<td>1%</td>
</tr>
<tr>
<td>Anorgasmia</td>
<td>11%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Impotence</td>
<td>5%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Anorgasmia (female)</td>
<td>2%</td>
<td>0%</td>
</tr>
</tbody>
</table>

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 (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 adverse events occurred in at least 5% of patients:
Erectile dysfunction was rare and occurred at a rate of less than 0.5% of the placebo group. Abnormalities of sexual function (impotence in men, anorgasmia in women, and libido decreased), gastrointestinal complaints (constipation and flatulence), and problems of special senses (abnormal vision), cardiovascular effects (hypertension and vasodilatation), and yawning were reported.

**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**

Table 5: Treatment-Emergent Adverse Event Incidence in Short-Term Placebo-Controlled Effexor XR Clinical Trials in Social Anxiety Disorder Patients

<table>
<thead>
<tr>
<th>Body System</th>
<th>Effexor XR</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>34%</td>
<td>33%</td>
</tr>
<tr>
<td>Anxiety</td>
<td>17%</td>
<td>8%</td>
</tr>
<tr>
<td>Abdominal Pain</td>
<td>6%</td>
<td>5%</td>
</tr>
<tr>
<td>Hematologic</td>
<td>4%</td>
<td>3%</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>3%</td>
<td>1%</td>
</tr>
<tr>
<td>Nervousness</td>
<td>20%</td>
<td>9%</td>
</tr>
<tr>
<td>Incontinence</td>
<td>12%</td>
<td>11%</td>
</tr>
<tr>
<td>Insomnia</td>
<td>12%</td>
<td>8%</td>
</tr>
<tr>
<td>Nervousness</td>
<td>10%</td>
<td>6%</td>
</tr>
<tr>
<td>Tremor</td>
<td>7%</td>
<td>6%</td>
</tr>
<tr>
<td>Depression</td>
<td>9%</td>
<td>7%</td>
</tr>
<tr>
<td>Nausea</td>
<td>3%</td>
<td>3%</td>
</tr>
<tr>
<td>Paresthesia</td>
<td>3%</td>
<td>2%</td>
</tr>
<tr>
<td>Abnormal Vision</td>
<td>3%</td>
<td>1%</td>
</tr>
<tr>
<td>Anxiety</td>
<td>5%</td>
<td>4%</td>
</tr>
<tr>
<td>Agitation</td>
<td>4%</td>
<td>3%</td>
</tr>
<tr>
<td>Tic</td>
<td>3%</td>
<td>2%</td>
</tr>
<tr>
<td>Nervousness</td>
<td>3%</td>
<td>2%</td>
</tr>
<tr>
<td>Dizziness</td>
<td>2%</td>
<td>1%</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>5%</td>
<td>3%</td>
</tr>
</tbody>
</table>

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 Social Anxiety Disorder indication (Table 5): Abnormalities of sexual function (abnormal ejaculation, orgasmic dysfunction, impotence), yawning, sweating, and abnormal vision.

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*Adverse events for which the Effexor XR (venlafaxine hydrochloride) 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, infection, myalgia, pain, palpitation, pharyngitis, rhinitis, tinnitus, and urinary frequency.

* <1% means greater than zero but less than 1%.

* Mostly “hot flashes.”

* Mostly “vivid dreams,” “nightmares,” and “increased dreaming.”

* Mostly “blurred vision” and “difficulty focusing eyes.”

* Includes “delayed ejaculation” and “anorgasmia.”

* Includes “delayed orgasm,” “abnormal orgasm,” and “anorgasmia.”

* Percentage based on the number of males (Effexor XR=525, placebo=220).

* Percentage based on the number of females (Effexor XR=856, placebo=335).
Table 5 (continued)

Treatment-Emergent Adverse Event Incidence in Short-Term Placebo-Controlled
Effexor XR Clinical Trials in Social Anxiety Disorder Patients

<table>
<thead>
<tr>
<th>Body System</th>
<th>Effexor XR (% Reporting Event)</th>
<th>Placebo (% Reporting Event)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Special Senses</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abnormal Vision</td>
<td>6%</td>
<td>3%</td>
</tr>
<tr>
<td>Urogenital System</td>
<td>16%</td>
<td>1%</td>
</tr>
<tr>
<td>Abnormal Ejaculation*</td>
<td>10%</td>
<td>1%</td>
</tr>
<tr>
<td>Impotence</td>
<td>8%</td>
<td>0%</td>
</tr>
<tr>
<td>Orgasmic Dysfunction**</td>
<td>8%</td>
<td>0%</td>
</tr>
</tbody>
</table>

*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, dysphoria, infection, miosis, pain, pharyngitis, rash, rhinitis, and upper respiratory infection.

**<1% means greater than zero but less than 1%.

- Mostly "hot flashes."
- Mostly "decreased appetite" and "loss of appetite."
- Mostly "vivid dreams."
- "Nightmares."
- "Increased dreaming."

- Includes "delayed ejaculation." *Anorgasimia.*

- Based on the number of males (Effexor XR=158, placebo=153).

Vital Sign Changes

Effexor XR (venlafaxine hydrochloride) extended-release capsules treatment for up to 12 weeks in premarketing placebo-controlled major depressive disorder trials was associated with a mean final on-therapy increase in pulse rate of approximately 2 beats per minute, compared with 1 beat per minute for placebo, Effexor XR treatment for up to 8 weeks in premarketing placebo-controlled GAD trials was associated with a mean final on-therapy increase in pulse rate of approximately 2 beats per minute, compared with less than 1 beat per minute for placebo, Effexor XR treatment for up to 12 weeks in premarketing placebo-controlled Social Anxiety Disorder trials was associated with mean final on-therapy increase in pulse rate of approximately 4 beats per minute, compared with no change for placebo. (See the Sustained Hypertension section 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 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.

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 0.1 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 ≥201 mg/dL, or 2) an average increase in serum cholesterol ≥50 mg/dL from baseline to a value ≥221 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 fixed-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 7.6 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 95 patients. During its premarketing assessment, multiple...
doses of Effexor XR were also administered to 1311 patients in Phase 3 (SAD) studies and 277 patients in Phase 3 Social Anxiety Disorder studies. In addition, in premarketing assessment of Effexor, multiple doses were administered to 897 patients in Phase 1 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, incident (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 adverse event categories.

In the tabulations that follow, reported adverse events are classified using a standard COSTART-based Dictionary terminology. The frequencies presented, therefore, represent the proportion of the 5356 patient exposed to multiple doses of either formulation of venlafaxine who experienced an event of the type cited on at least one occasion while receiving venlafaxine. All reported events are included except those already listed in Tables 3, 4, and 5 and those events for which a drug cause was remote. If the "COSTART" term for an event was so general as to be uninformative, it was replaced with a more informative specific term. Management of Overdosage

Treatment should consist of those general measures employed in the management of overdose 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 if symptoms of a delayed nature. Activated charcoal should be administered. Due to the large volume of distribution of this drug, forced diuresis, hemoperfusion, and exchange transfusion are unlikely to be of benefit. No specific antidotes for venlafaxine are known.

In managing overdose, consider the possibility of multiple drug involvement. The physician should consider contacting a poison control center or regional poison control center is 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; it may be administered by carefully opening the capsule and sprinkling the entire contents on a spoonful of apple sauce. 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 efficacy for 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. 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 for up to 2 weeks or more; the average dose was about 140 to 150 mg/day (see Edilect 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 the clinical trials establishing efficacy of Effexor XR in outpatients with Generalized Anxiety Disorder (SAD), 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 SAD was not clearly established in fixed-dose studies, certain patients not responding to the initial 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 4 days. (See the Use in Patients with Concomitant

INSERT PHARMACODE
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).

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 twice-a-day to 75 mg Effexor XR once daily. However, individual dosage adjustments may be necessary.

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

Patients with Renal Impairment
Given the decrease in clearance for venlafaxine and the increase in elimination half-life for both venlafaxine and ODV that is observed in patients with renal impairment (GFR = 10 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, or Social Anxiety Disorder, however, caution should be exercised in treating the elderly. When individualizing the dosage, extra care should be taken when increasing the dose.

Maintenance Treatment
There is no body of evidence available from controlled trials to indicate how long patients with major depressive disorder, Generalized Anxiety Disorder, or Social Anxiety Disorder should be treated with Effexor XR. It is generally agreed that acute episodes of major depressive disorder require several months or longer of sustained pharmacological therapy beyond response to the acute episode. In one study, in which patients responding during 8 weeks of acute treatment with Effexor XR were assigned randomly to placebo or to the same dose of Effexor XR (75, 150, or 225 mg/day, qAM) during 26 weeks of maintenance treatment as they had received during the acute stabilization phase, longer-term efficacy was demonstrated. A second longer-term study has demonstrated the efficacy of Effexor in maintaining a response in patients with recurrent major depressive disorder who had responded and continued to be improved during an initial 26 weeks of treatment and were then randomly assigned to placebo or Effexor for periods of up to 52 weeks on the same dose (100 to 225 mg/day, on a q.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 is no efficacy data beyond 12 weeks of treatment with Effexor XR. The need for continuing medication in patients with Social Anxiety Disorder who improve with Effexor XR treatment should be periodically reassessed.

Discontinuing Effexor XR
When discontinuing Effexor XR after more than 1 week of therapy, it is generally recommended that the dose be tapered to minimize the risk of discontinuation symptoms. Patients who have received Effexor XR for 6 weeks or more should have their dose tapered over at least a 2-week period. In clinical trials with Effexor XR, tapering was achieved by reducing the dose by 75 mg/day, as needed.
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 of 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, diarrhoea, dizziness, dry mouth, dysphoric mood, fasciculation, fatigue, headaches, hypomania, insomnia, nausea, nervousness, nightmares, seizures, sensory disturbances (including shock-like electrical sensations), somnolence, sweating, tinnitus, tremor, vertigo, and vomiting. It is therefore recommended that the dosage of Effexor XR be tapered gradually and the patient monitored. The period required for tapering may depend on the dose, duration of therapy and the individual patient. Discontinuation effects are well known to occur with antidepressants.

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

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

- 37.5 mg, grey cap/pink body with "W" and "Effexor XR" on the cap and "37.5" on the body.
- NDC 0008-0837-01, bottle of 100 capsules.
- NDC 0008-0837-03, carton of 10 Redipak® blister strips of 10 capsules each.

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

- 75 mg, peach cap and body with "W" and "Effexor XR" on the cap and "75" on the body.
- NDC 0008-0833-01, bottle of 100 capsules.
- NDC 0008-0833-03, carton of 10 Redipak® blister strips of 10 capsules each.

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

- 150 mg, dark orange cap and body with "W" and "Effexor XR" on the cap and "150" on the body.
- NDC 0008-0836-01, bottle of 100 capsules.
- NDC 0008-0836-03, carton of 10 Redipak® blister strips of 10 capsules each.

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

The appearance of these capsules is a trademark of Wyeth Pharmaceuticals.
APPLICATION NUMBER:
NDA 20-699/S-045

CHEMISTRY REVIEW(S)
CHEMIST REVIEW
OF SUPPLEMENT

1. ORGANIZATION: HFD-120
   2. NDA 20-699
   3. SUPPLEMENT NUMBER AND DATES:
      LETTER DATE: SLR-045
      STAMP DATE: 09-29-03
   4. AMENDMENT/REPORTS/DATES
      RECEIVED BY CHEMIST: 10-10-03

6. APPLICANT NAME & ADDRESS:
   Wyeth-Ayerst Laboratories
   P.O. Box 8299
   Philadelphia, PA 19101-8299
   Effexor® XR

7. NAME OF DRUG:
   8. NONPROPRIETARY NAME:
   Effexor
   Venlafaxine hydrochloride

9. CHEMICAL NAME and STRUCTURE:
   (R,S)-1-(2-(dimethylamino)-1-(4-methoxyphenyl)ethyl) cyclohexanol hydrochloride

10. DOSAGE FORMS:
11. POTENCY:
12. PHARMACOLOGICAL CATEGORY:
   anti-depressant/ general anti-anxiety disorder
13. HOW DISPENSED:
   X R(x) (OTC)
14. RECORD and REPORTS CURRENT:
   X Yes No
15. RELATED IND/INDA/DMF:
   SCM-006 and SCM-006 (C)

16. SUPPLEMENT PROVIDES FOR: This supplement provides for a change in the labeling for the drug product.

17. ADDITIONAL COMMENTS: In the original NDA the applicant was approved to use grey opaque capsule shell cap which contained titanium dioxide, Iron Oxide and gelatin (formula ). After approval of the application, the applicant learned that the grey capsule shell cap that was being used for the drug product (formula ) was not the grey capsule shell cap which was approved in the original application. The applicant spoke with the agency and was advised to submit the appropriate data (i.e. stability and dissolution data) to support the use of the new grey capsule shell cap (formula ). The applicant submitted this information in Supplement 006. In this application, the applicant seeks to use the grey capsule shell cap (formula ) that was approved in the original NDA. The applicant indicates that the labeling will be changed to omit the three colorants ( ) that were used in the formulation. The applicant indicates that the description of the 37.5 mg capsule in the “HOW SUPPLIED Section” will not be changed as both capsules are described as grey, however, the “HOW SUPPLIED Section” was changed to include the revised Wyeth corporate name, logo and address.

18. CONCLUSIONS & RECOMMENDATIONS:
   Evaluation: ACCEPTABLE

Sherita D. McLamore, Ph.D
Review Chemist

Thomas Oliver, Ph.D
Chemistry Team Leader
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Sherita McLamore
11/12/03 01:20:50 PM
CHEMIST

Thomas Oliver
11/12/03 02:02:28 PM
CHEMIST
6. APPLICANT NAME & ADDRESS:

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

7. NAME OF DRUG:

Effexor® XR

8. NONPROPRIETARY NAME:

Venlafaxine hydrochloride

9. CHEMICAL NAME and STRUCTURE:

(R,S)-1-[2-(dimethylamino)-1-(4-methoxyphenyl)ethyl] cyclohexanol hydrochloride

10. DOSAGE FORMS:

Extended Release Capsules

11. POTENCY:

37.5 mg; 75 mg, 100 mg, 150 mg

12. PHARMACOLOGICAL CATEGORY:

anti-depressant/ general anti-anxiety disorder

13. HOW DISPENSED:

X Rx (OTC)

14. RECORD and REPORTS CURRENT:

X Yes  No

15. RELATED IND/INDA/DMF:

SCM-006 and SCM-006 (C)

16. SUPPLEMENT PROVIDES FOR: This supplement provides for a change in the labeling for the drug product.

17. ADDITIONAL COMMENTS: In addition to the aforementioned changes submitted in the original application, the applicant has requested the removal of the "Protect from Light Statement" in the HOW SUPPLIED section of the labeling. The "Protect from Light Statement" statement was added in the December 20, 1999 submission following the change from capsule color code to capsule color code.

18. CONCLUSIONS & RECOMMENDATIONS:

Evaluation: ACCEPTABLE

Sherita D. McLamore, Ph.D
Review Chemist

Signature

Date Completed 03-01-04

Thomas Oliver, Ph.D
Chemistry Team Leader

Signature

Date
Redacted 2 page(s)
of trade secret and/or
confidential commercial
information from

Chemistry Review #2
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/s/

Sherita McLamore
3/8/04 02:38:42 PM
CHEMIST

Thomas Oliver
3/9/04 07:45:35 AM
CHEMIST