CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

NDA 20-151/S-028, 030, 032 & NDA 20-699/S-041, 048, 052

Name: Effexor Tablets & Effexor XR Extended-Release Capsules

Generic Name: venlafaxine hydrochloride

Sponsor: Wyeth Pharmaceuticals Inc.

Approval Date: 05/13/2004

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APPLICATION NUMBER:

NDA 20-151/S-028, 030, 032 &
NDA 20-699/S-041, 048, 052

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-151/S-028, 030, 032 &
NDA 20-699/S-041, 048, 052

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-151/S-028/S-030/S-032
NDA 20-699/S-041/S-048/S-052

Wyeth Pharmaceuticals, Inc.
Attention: Kenneth R. Bonk
Director, Worldwide Regulatory Affairs
P.O. Box 8299
Philadelphia, PA 19101-1245

Dear Mr. Bonk:

We acknowledge receipt of your supplemental new drug applications dated April 30, 2004, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Effexor (venlafaxine hydrochloride) Immediate Release Tablets (NDA 20-151/S-032) and Effexor XR (venlafaxine hydrochloride) Extended Release Capsules (NDA 20-699/S-052).

Your April 30, 2004, submission also constituted a complete response to our action letter dated March 19, 2004 for supplemental applications 20-151/S-028/S-030 and 20-699/S-041/S-048.

Reference is also made to a conference call dated April 28, 2004 between representatives of the Agency and yourself to discuss the Agency's class labeling initiatives.

The above supplemental applications provide for the following changes to product labeling:

NDAs 20-151/S-028 & 20-699/S-041

1. Revisions to the **PRECAUTIONS-Usage in Children** section to denote hostility and suicide related adverse events in pediatric clinical trials.
2. The addition of the term "tinnitus" to the **DOSAGE AND ADMINISTRATION-Discontinuing Effexor** or **Effexor XR** sections.
3. Revisions to the Patient Brief Summary.

We note your agreement to our request to remove your proposed addition of hostility and suicide related adverse events from the **PRECAUTIONS-Usage in Children** section. As discussed during that April 28, 2004 meeting, we continue to feel that it would not be helpful to include the language regarding reports of hostility and suicidality that you have proposed for the **Pediatric Use** section. As currently written, the language is uninterpretable, since it notes that there were increased reports, but without noting with reference to what data. If a reference to placebo data were added, this would suggest a causal association, however, this suggestion would be contradicted by the new language that follows. The difficulty, of course, is that it remains unclear at this point exactly what has been captured under the crude terms used to capture events. The currently proposed language for **WARNINGS** is intended to comprehensively address this complex issue and our current understanding of the available data, and we feel it would be confusing and potentially misleading to maintain your proposed language for the **Pediatric Use** section.

NDAs 20-151/S-030 & 20-699/S-048

These applications provide for revisions to the **DOSAGE and ADMINISTRATION/Discontinuing Effexor** or **Effexor XR** sections of product labeling.

Again, we note your agreement to revise product labeling to incorporate the class labeling initiative for all of the selective serotonin reuptake inhibitors (SSRIs) and serotonin and norepinephrine reuptake inhibitors (SNRIs), to change labeling in regards to discontinuation symptoms and to adverse events occurring in neonates exposed to any of the SSRIs or SNRIs late in the third trimester.

NDAs 20-151/S-032 & 20-699/S-052
These applications provide for antidepressant class labeling revisions to incorporate the following changes to product labeling:

1. The addition of a new subsection under **WARNINGS** entitled **Clinical Worsening and Suicide Risk**.
2. Revisions to the **PRECAUTIONS-Information for Patients** section.
3. Delete the section in **PRECAUTIONS-General** entitled "Suicide".
4. Add a reference to the **WARNINGS** section at the end of the **PRECAUTIONS- Pediatric Use** section, i.e., (see **WARNINGS-Clinical Worsening and Suicide Risk**).

We have completed the review of these supplemental applications 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 April 30, 2004 and as attached to this letter. Accordingly, these supplemental applications are approved effective on the date of this letter.

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Practitioner" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

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

Attachment

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
5/13/04 01:49:01 PM
Signed for Russell Katz, M.D.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-151/S-028, 030, 032 &
NDA 20-699/S-041, 048, 052

APPROVABLE LETTER(S)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-151/S-028/S-030
NDA 20-699/S-041/S-048

Wyeth Pharmaceuticals, Inc.
Attention: Kenneth R. Bonk
Director, Worldwide Regulatory Affairs
P.O. Box 8299
Philadelphia, PA 19101-1245

Dear Mr. Bonk:

We acknowledge receipt of your supplemental New Drug Applications (NDAs) dated August 8, 2003 (NDAs 20-151/S-028 & 20-699/S-041), and December 10, 2003 (NDAs 20-151/S-030 & 20-699/S-048), 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).

We additionally acknowledge receipt of your amendments to NDAs 20-151/S-028 & 20-699/S-041 dated August 25, and 29, 2003.

Reference is also made to the February 2, 2004 meeting of the Psychopharmacologic Drugs Advisory Committee and the Pediatric Subcommittee of the Anti-Infective Advisory Committee to discuss reports of the occurrence of suicidality in clinical trials for various antidepressant drugs in pediatric patients with major depressive disorder.

Supplemental applications 20-151/S-028 & 20-699/S-041 submitted under "Changes Being Effected in 30 days" provide for the following revisions to product labeling:

1. Revisions to the **PRECAUTIONS-Usage in Children** section to denote hostility and suicide related adverse events in pediatric clinical trials.
2. The addition of the term "tinnitus" to the **DOSAGE AND ADMINISTRATION-Discontinuing Effexor** or **Effexor XR** sections.
3. Revisions to the Patient Brief Summary.

Supplemental applications 20-151/S-030 & 20-699/S-048 submitted as "Prior Approval" applications provide for revisions to the **DOSAGE and ADMINISTRATION/Discontinuing Effexor** or **Effexor XR** sections of product labeling.

We completed our review of these applications, as amended, and they are approvable. Before these applications may be approved, however, you must submit final printed labeling revised as follows:

1. Based upon the recommendations made by the committee members, we believe that labeling changes are warranted in order to caution practitioners and patients about the need for close observation of patients being treated with antidepressants for clinical worsening, for the emergence of suicidality, and for the emergence of a variety of other symptoms that may represent a precursor to suicidality. The committees felt that it would be important to warn prescribers and families of the need to be vigilant for such behaviors, regardless of the role antidepressants may have in the emergence of suicidal ideation/attempts in patients taking antidepressants

   Because we do not believe that a causal association between children taking venlafaxine and the emergence of suicidality has as yet been definitively established, we do not agree with the labeling changes proposed in your August 8, 2003 submission. We feel that, both for the terms "suicide-related adverse events" and "hostility," there is a need for more clinically meaningful classification of the events subsumed under these very broad terms in order to interpret the findings from these trials in a meaningful way.

   As stated, later in this letter, we are requesting all sponsors of modern drugs to treat major depressive disorder to submit revisions to labeling, as a "Changes Being Effected in 30 days" supplemental new drug application, to incorporate this information.

2. The addition of the term "tinnitus" to the list of adverse experiences possibly related to venlafaxine dose reduction or discontinuation is acceptable. However, we do not concur with the addition of the phrase [ ] to the **DOSAGE and ADMINISTRATION/Discontinuing Effexor** or **Effexor XR** sections of product labeling since we are revising labeling, as stated later in this letter, in regard to discontinuation as part of a class labeling initiative.

   Additionally, since there are a number of cases of tinnitus which emerge during venlafaxine treatment, we request that tinnitus be added to the subsection **ADVERSE REACTIONS/Postmarketing Reports** section immediately following the mention of shock-like electrical sensations as follows: "shock-like electrical sensations <u>or tinnitus</u> (in some cases, subsequent to the discontinuation of venlafaxine or tapering of dose)."

3. The revisions to the Patient Brief Summary are acceptable.

As stated previously, and based upon our February 2, 2004 meeting, we are requesting revisions to your labeling in order to incorporate the committee's recommendations. Specifically, we are requesting the following revisions to product labeling.

1. Under **WARNINGS**, we are requesting the addition of a new subsection entitled **Clinical Worsening and Suicide**. Please note that the title of this new section should be bolded, as well as two statements embedded in this labeling language.

   WARNINGS-Clinical Worsening and Suicide

   Patients with major depressive disorder, both adult and pediatric, can experience worsening of their depression and/or the emergence of suicidal ideation and behavior (suicidality), whether or not they are taking antidepressant medications, and this risk may persist until significant remission occurs. Although 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, a causal role for antidepressants in inducing such behaviors has not been established. **Nevertheless, patients being treated with antidepressants should be observed closely for clinical worsening and suicidality, especially at the beginning of a course of drug therapy, or at the time of dose changes, either increases or decreases.** Consideration should be given to [ ]

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 [Insert EFFEXOR or EFFEXOR XR], for a description of the risks of discontinuation of [Insert EFFEXOR or EFFEXOR XR]).

It should be noted that [Insert EFFEXOR or EFFEXOR XR] is not approved for use in treating any indications in the pediatric population.

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 can 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 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 [Insert EFFEXOR or EFFEXOR XR] is not approved for use in treating bipolar depression.

2. Under **PRECAUTIONS-Information for Patients**, the following language should be added:

Patients and their families should be encouraged to be alert to the emergence of anxiety, agitation, panic attacks, insomnia, irritability, hostility, impulsivity, akathisia, hypomania, mania, worsening of depression, and suicidal ideation, especially early during antidepressant treatment. Such symptoms should be reported to the patient's physician if they are severe, abrupt in onset, or were not part of the

patient's presenting symptoms.

3. Delete the section in **PRECAUTIONS-General** entitled "Suicide".

Additionally, we are taking this opportunity, in a class labeling initiative for all of the selective serotonin reuptake inhibitors (SSRIs) and serotonin and norepinephrine reuptake inhibitors (SNRIs), to change labeling in regards to discontinuation symptoms and to adverse events occurring in neonates exposed to any of the SSRIs or SNRIs late in the third trimester.

Therefore, we are requesting the following revisions to labeling (double underline font denotes additions to labeling and strike through font denotes deletions to labeling):

4. Under **PRECAUTIONS-General**, please add the new subsection below:

Discontinuation of Treatment with [insert EFFEXOR or 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 [ ] 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 [insert EFFEXOR or EFFEXOR XR] and other SSRIs and SNRIs (Serotonin and Norepinephrine 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 [insert EFFEXOR or 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).

5. Under **PRECAUTIONS-PREGNANCY**, the following new class labeling subsection should be added (double underline font denotes class labeling):

PREGNANCY-Pregnancy-Nonteratogenic Effects

Neonates exposed to [insert EFFEXOR or EFFEXOR XR] and other SSRIs or serotonin and norepinephrine reuptake inhibitors (SNRIs), 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 [ ] When treating a pregnant woman with [insert EFFEXOR or EFFEXOR XR] during the third trimester, the physician should carefully consider the potential risks and benefits of treatment (see DOSAGE AND ADMINISTRATION).

6. Under **DOSAGE AND ADMINISTRATION**, please add a new section entitled **Special Populations**. Your current sections entitled **Patients with Hepatic Impairment, Patients with Renal Impairment,** and **Elderly Patients** may be placed in this section as well as the following new section entitled **Treatment of Pregnant Women During the Third Trimester** (double underline font denotes class labeling):

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

7. Under **DOSAGE AND ADMINISTRATION**, please revise the section entitled **Discontinuing EFFEXOR [EFFEXOR XR]** as follows:

   EFFEXOR LABELING
   Discontinuing Effexor (venlafaxine hydrochloride)
   Symptoms associated with discontinuation of Effexor and other SSRIs and SNRIs, 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.

EFFEXOR XR LABELING

Discontinuing Effexor XR

Symptoms associated with discontinuation of Effexor XR and other SSRIs and SNRIs, 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.

Within 10 days after the date of this letter, you are required to amend the supplemental applications, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.120. In the absence of any such action, FDA may proceed to withdraw these supplemental applications. 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.

Please submit twenty copies of final printed labeling, ten of which are individually mounted on heavyweight paper or similar material, exactly as specified above as a "**Supplement - Changes Being Effected**". Incorporate 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 the changes that are being made.

These supplements should be submitted within 30 days from the date of this letter.

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

Sincerely,

{See appended electronic signature page}

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

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

/s/

Russell Katz
3/19/04 04:06:47 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-151/S-028, 030, 032 &
NDA 20-699/S-041, 048, 052

LABELING

Wyeth®

Effexor®

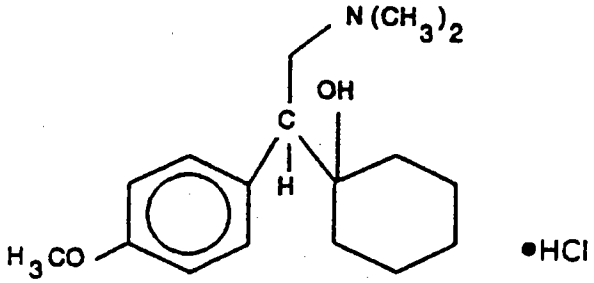
(venlafaxine hydrochloride)
Tablets

℞ 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.

DESCRIPTION

Effexor (venlafaxine hydrochloride) is a structurally novel antidepressant for oral administration. It is designated (R/S)-1-[2-(dimethylamino)-1-(4-methoxyphenyl)ethyl] cyclohexanol hydrochloride or (±)-1-[α-[(dimethyl-amino)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.

Compressed tablets contain venlafaxine hydrochloride equivalent to 25 mg, 37.5 mg, 50 mg, 75 mg, or 100 mg venlafaxine. Inactive ingredients consist of cellulose, iron oxides, lactose, magnesium stearate, and sodium starch glycolate.

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, 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

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 dose of venlafaxine is absorbed. Approximately 87% of a venlafaxine dose is recovered in the urine within 48 hours as either unchanged venlafaxine (5%), unconjugated ODV (29%), conjugated ODV (26%), or other minor inactive metabolites (27%). Renal elimination of venlafaxine and its metabolites is the primary route of excretion. The relative bioavailability of venlafaxine from a tablet was 100% when compared to an oral solution. Food has no significant effect on the absorption of venlafaxine or on the formation of ODV.

The degree of binding of venlafaxine to human plasma is 27% ± 2% at concentrations ranging from 2.5 to 2215 ng/mL. The degree of ODV binding to human plasma is 30% ± 12% at concentrations ranging from 100 to 500 ng/mL. Protein-binding-induced drug interactions with venlafaxine are not expected.

Steady-state concentrations of both venlafaxine and ODV in plasma were attained within 3 days of multiple-dose therapy. Venlafaxine and ODV exhibited linear kinetics over the dose range of 75 to 450 mg total dose per day (administered on a q8h schedule). Plasma clearance, elimination half-life and steady-state volume of distribution were unaltered for both venlafaxine and ODV after multiple-dosing. Mean ± SD steady-state plasma clearance of venlafaxine and ODV is 1.3 ± 0.6 and 0.4 ± 0.2 L/h/kg, respectively; elimination half-life is 5 ± 2 and 11 ± 2 hours, respectively; and steady-state volume of distribution is 7.5 ± 3.7 L/kg and 5.7 ± 1.8 L/kg, respectively. When equal daily doses of venlafaxine were administered as either b.i.d. or t.i.d. regimens, the drug exposure (AUC) and fluctuation in plasma levels of venlafaxine and ODV were comparable following both regimens.

Age and Gender

A 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 due to age or gender differences. Dosage adjustment based upon the age or gender of a patient is generally not necessary (see **DOSAGE AND ADMINISTRATION**).

Liver Disease

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

Dosage adjustment is necessary in these patients (see **DOSAGE AND ADMINISTRATION**).

Renal Disease

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

Dosage adjustment is necessary in these patients (see **DOSAGE AND ADMINISTRATION**).

CLINICAL TRIALS

The efficacy of Effexor (venlafaxine hydrochloride) as a treatment for major depressive disorder was established in 5 placebo-controlled, short-term trials. Four of these were 6-week trials in outpatients meeting DSM-III or DSM-III-R criteria for major depression: two involving dose titration with Effexor in a range of 75 to 225 mg/day (t.i.d. schedule), the third involving fixed Effexor doses of 75, 225, and 375 mg/day (t.i.d. schedule), and the fourth involving doses of 25, 75, and 200 mg/day (b.i.d. schedule). The fifth was a 4-week study of inpatients meeting DSM-III-R criteria for major depression with melancholia whose Effexor doses were titrated in a range of 150 to 375 mg/day (t.i.d. schedule). In these 5 studies, Effexor was shown to be significantly superior to placebo on at least 2 of the following 3 measures: Hamilton Depression Rating Scale (total score), Hamilton depressed mood item, and Clinical Global Impression-Severity of Illness rating. Doses from 75 to 225 mg/day were superior to placebo in outpatient studies and a mean dose of about 350 mg/day was effective in inpatients. Data from the 2 fixed-dose outpatient studies were suggestive of a dose-response relationship in the range of 75 to 225 mg/day. There was no suggestion of increased response with doses greater than 225 mg/day.

While there were no efficacy studies focusing specifically on an elderly population, elderly patients were included among the patients studied. Overall, approximately 2/3 of all patients in these trials were women. Exploratory analyses for age and gender effects on outcome did not suggest any differential responsiveness on the basis of age or sex.

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

continued Effexor XR treatment experienced significantly lower relapse rates over the subsequent 26 weeks compared with those receiving placebo.

In a second longer-term trial, outpatients meeting DSM-III-R criteria for major depression, 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.

INDICATIONS AND USAGE

Effexor (venlafaxine hydrochloride) is indicated for the treatment of major depressive disorder.

The efficacy of Effexor in the treatment of major depressive disorder was established in 6-week controlled trials of outpatients whose diagnoses corresponded most closely to the DSM-III or DSM-III-R category of major depression and in a 4-week controlled trial of inpatients meeting diagnostic criteria for major depression with melancholia (see **CLINICAL TRIALS**).

A major depressive episode implies a prominent and relatively persistent depressed or dysphoric mood that usually interferes with daily functioning (nearly every day for at least 2 weeks); it should include at least 4 of the following 8 symptoms: change in appetite, change in sleep, psychomotor agitation or retardation, loss of interest in usual activities or decrease in sexual drive, increased fatigue, feelings of guilt or worthlessness, slowed thinking or impaired concentration, and a suicide attempt or suicidal ideation.

The efficacy of Effexor XR in maintaining an antidepressant response for up to 26 weeks following 8 weeks of acute treatment was demonstrated in a placebo-controlled trial. The efficacy of Effexor in maintaining an antidepressant response in patients with recurrent depression 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.

CONTRAINDICATIONS

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

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

WARNINGS

Potential for Interaction with Monoamine Oxidase Inhibitors

Adverse reactions, some of which were serious, have been reported in patients who have recently been discontinued from a monoamine oxidase inhibitor (MAOI) and started on Effexor, or who have recently had Effexor 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 a monoamine oxidase inhibitor, 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. Therefore, it is recommended that Effexor 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 Effexor, at least 7 days should be allowed after stopping Effexor before starting an MAOI.

Clinical Worsening and Suicide Risk

Patients with major depressive disorder, both adult and pediatric, may experience worsening of their depression and/or the emergence of suicidal ideation and behavior (suicidality), whether or not they are taking antidepressant medications, and this risk may persist until significant remission occurs. Although 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, a causal role for antidepressants in inducing such behaviors has not been established. **Nevertheless, patients being treated with antidepressants should be observed closely for clinical worsening and suicidality, especially at the beginning of a course of drug therapy, or at the time of dose changes, either increases or decreases.** Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients whose depression is persistently worse or whose emergent suicidality is severe, abrupt in onset, or was not part of the patient's presenting symptoms.

Because of the possibility of co-morbidity between major depressive disorder and other psychiatric and nonpsychiatric disorders, the same precautions observed when treating patients with major depressive disorder should be observed when treating patients with other psychiatric and nonpsychiatric disorders.

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, consideration should be given to changing the therapeutic regimen, including possibly discontinuing the

medication, in patients for whom such symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms.

Families and caregivers of 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, and the other symptoms described above, as well as the emergence of suicidality, and to report such symptoms immediately to health care providers. Prescriptions for Effexor should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose.

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, Discontinuing Effexor**, for a description of the risks of discontinuation of Effexor).

It should be noted that Effexor is not approved for use in treating any indications in the pediatric population.

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 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 is not approved for use in treating bipolar depression.

Sustained Hypertension

Venlafaxine treatment is associated with sustained increases in blood pressure in some patients. (1) In a premarketing study comparing three fixed doses of venlafaxine (75, 225, and 375 mg/day) and placebo, a mean increase in supine diastolic blood pressure (SDBP) of 7.2 mm Hg was seen in the 375 mg/day group at week 6 compared to essentially no changes in the 75 and 225 mg/day groups and a mean decrease in SDBP of 2.2 mm Hg in the placebo group. (2) An analysis for patients meeting criteria for sustained hypertension (defined as treatment-emergent SDBP ≥ 90 mm Hg *and* ≥ 10 mm Hg above baseline for 3 consecutive visits) revealed a dose-dependent increase in the incidence of sustained hypertension for venlafaxine:

Probability of Sustained Elevation in SDBP (Pool of Premarketing Venlafaxine Studies)	
Treatment Group	Incidence of Sustained Elevation in SDBP
Venlafaxine	
< 100 mg/day	3%
101-200 mg/day	5%
201-300 mg/day	7%
> 300 mg/day	13%
Placebo	2%

An analysis of the patients with sustained hypertension and the 19 venlafaxine patients who were discontinued from treatment because of hypertension (<1% of total venlafaxine-treated group) revealed that most of the blood pressure increases were in a modest range (10 to 15 mm Hg, SDBP). Nevertheless, sustained increases of this magnitude could have adverse consequences. Therefore, it is recommended that patients receiving venlafaxine 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

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, 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. 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**).

Anxiety and Insomnia

Treatment-emergent anxiety, nervousness, and insomnia were more commonly reported for venlafaxine-treated patients compared to placebo-treated patients in a pooled analysis of short-term, double-blind, placebo-controlled depression studies:

Symptom	Venlafaxine n = 1033	Placebo n = 609
Anxiety	6%	3%
Nervousness	13%	6%
Insomnia	18%	10%

Anxiety, nervousness, and insomnia led to drug discontinuation in 2%, 2%, and 3%, respectively, of the patients treated with venlafaxine in the Phase 2 and Phase 3 depression studies.

Changes in Appetite and Weight

Treatment-emergent anorexia was more commonly reported for venlafaxine-treated (11%) than placebo-treated patients (2%) in the pool of short-term, double-blind, placebo-controlled depression studies. A dose-dependent weight loss was often noted in patients treated with venlafaxine for several weeks. Significant weight loss, especially in underweight depressed patients, may be an undesirable result of venlafaxine treatment. A loss of 5% or more of body weight occurred in 6% of patients treated with venlafaxine compared with 1% of patients treated with placebo and 3% of patients treated with another antidepressant. However, discontinuation for weight loss associated with venlafaxine was uncommon (0.1% of venlafaxine-treated patients in the Phase 2 and Phase 3 depression trials).

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

Activation of Mania/Hypomania

During Phase 2 and Phase 3 trials, hypomania or mania occurred in 0.5% of patients treated with venlafaxine. Activation of mania/hypomania has also been reported in a small proportion of patients with major affective disorder who were treated with other marketed antidepressants. As with all antidepressants, Effexor (venlafaxine hydrochloride) 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 at risk of acute narrow angle glaucoma should be monitored.

Seizures
During premarketing testing, seizures were reported in 0.26% (8/3082) of venlafaxine-treated patients. Most seizures (5 of 8) occurred in patients receiving doses of 150 mg/day or less. Effexor should be used cautiously in patients with a history of seizures. It 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
Clinical experience with Effexor in patients with concomitant systemic illness is limited. Caution is advised in administering Effexor to patients with diseases or conditions that could affect hemodynamic responses or metabolism.

Effexor 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 the product's premarketing testing. Evaluation of the electrocardiograms for 769 patients who received Effexor in 4- to 6-week double-blind placebo-controlled trials, however, showed that the incidence of trial-emergent conduction abnormalities did not differ from that with placebo. The mean heart rate in Effexor-treated patients was increased relative to baseline by about 4 beats per minute.

The electrocardiograms for 357 patients who received Effexor XR (the extended-release form of venlafaxine) and 285 patients who received placebo in 8- to 12-week double-blind, placebo-controlled trials were analyzed. The mean change from baseline in corrected QT interval (QTc) for Effexor XR-treated patients 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). In these same trials, the mean change from baseline in heart rate for Effexor XR-treated patients 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). 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.

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

Information for Patients

Physicians are advised to discuss the following issues with patients for whom they prescribe Effexor:

Patients and their families should be encouraged to be alert to the emergence of anxiety, agitation, panic attacks, insomnia, irritability, hostility, impulsivity, akathisia, hypomania, mania, worsening of depression, and suicidal ideation, especially early during antidepressant treatment. Such symptoms should be reported to the patient's physician, especially if they are severe, abrupt in onset, or were not part of the patient's presenting symptoms.

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 Effexor therapy does not adversely affect their ability to engage in such activities.

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.

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 Effexor 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 Effexor.

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

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 ODV when venlafaxine was administered at 150 mg/day in 15 healthy male subjects. Additionally, administration of venlafaxine in a stable regimen did not exaggerate the psychomotor and psychometric effects induced by ethanol in these same subjects when they were not receiving venlafaxine.

Cimetidine
Concomitant administration of cimetidine and venlafaxine in a steady-state study for both drugs resulted in inhibition of first-pass metabolism of venlafaxine in 18 healthy subjects. The oral clearance of venlafaxine was reduced by about 43%, and the exposure (AUC) and maximum concentration (C_{max}) of the drug were increased by about 60%. However, co-administration of cimetidine had no apparent effect on the pharmacokinetics of ODV, which is present in much greater quantity in the circulation than is 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. O-desmethylvenlafaxine (ODV) also was unaffected. Venlafaxine had no effect on the pharmacokinetics of lithium (see also *CNS-Active Drugs*, below).

Drugs Highly Bound to Plasma Protein

Venlafaxine is not highly bound to plasma proteins; therefore, administration of Effexor 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 and venlafaxine. However, although imipramine partially inhibited the CYP2D6-mediated metabolism of venlafaxine, resulting in higher plasma concentrations of venlafaxine and lower plasma concentrations of ODV, the total concentration of active compounds (venlafaxine plus ODV) was not affected. Additionally, in a clinical study involving CYP2D6-poor and -extensive metabolizers, the total concentration of active compounds (venlafaxine plus ODV), was similar in the two metabolizer groups. Therefore, no dosage adjustment is required when venlafaxine is coadministered with a CYP2D6 inhibitor.

CYP3A4 Inhibitors: In vitro studies indicate that venlafaxine is likely metabolized to a minor, less active metabolite, N-desmethylvenlafaxine, by CYP3A4. Because CYP3A4 is typically a minor pathway relative to CYP2D6 in the metabolism of venlafaxine, the potential for a clinically significant drug interaction between drugs that inhibit CYP3A4-mediated metabolism and venlafaxine is small.

The concomitant use of venlafaxine with a drug treatment(s) that potently 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 potent 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 to that of fluoxetine on the CYP2D6-mediated metabolism of dextromethorphan to dextrorphan.

<u>Imipramine</u>—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 AUCs 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 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 16 times, on a mg/kg basis, and 1.7 times on a mg/m^2 basis, the maximum recommended human dose. 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 levels of venlafaxine were 1 times (male rats) and 6 times (female rats) the plasma levels 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.

Mutagenicity

Venlafaxine and the major human metabolite, O-desmethylvenlafaxine (ODV), were not mutagenic in the Ames reverse mutation assay in Salmonella bacteria or the CHO/HGPRT mammalian cell forward gene mutation assay. Venlafaxine was also not mutagenic in the in vitro BALB/c-3T3 mouse cell transformation assay, the sister chromatid exchange assay in cultured CHO cells, or the in vivo chromosomal aberration assay in rat bone marrow. ODV was not mutagenic in the in vitro CHO cell chromosomal aberration assay. There was a clastogenic response in the in vivo chromosomal aberration assay in rat bone marrow in male rats receiving 200 times, on a mg/kg basis, or 50 times, on a mg/m^2 basis, the maximum human daily dose. The no effect dose was 67 times (mg/kg) or 17 times (mg/m^2) the human dose.

Impairment of Fertility

Reproduction and fertility studies in rats showed no effects on male or female fertility at oral doses of up to 8 times the maximum recommended human daily dose on a mg/kg basis, or up to 2 times 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 11 times (rat) or 12 times (rabbit) the maximum recommended human daily dose on a mg/kg basis, or 2.5 times (rat) and 4 times (rabbit) the 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 10 times (mg/kg) or 2.5 times (mg/m^2) the maximum human daily dose. The no effect dose for rat pup mortality was 1.4 times the human dose on a mg/kg basis or 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, 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 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 Effexor® (venlafaxine hydrochloride) 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, 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.

Usage in Children
Safety and effectiveness in individuals below 18 years of age have not been established. (See **WARNINGS-Clinical Worsening and Suicide Risk**).

Geriatric Use
Of the 2,897 patients in Phase 2 and Phase 3 depression studies with Effexor, 12% (357) were 65 years of age or over. No overall differences in effectiveness or safety were observed between these 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

Associated with Discontinuation of Treatment

Nineteen percent (537/2897) of venlafaxine patients in Phase 2 and Phase 3 depression studies discontinued treatment due to an adverse event. The more common events (≥ 1%) associated with discontinuation and considered to be drug-related (ie, those events associated with dropout at a rate approximately twice or greater for venlafaxine compared to placebo) included:

CNS	Venlafaxine	Placebo
Somnolence	3%	1%
Insomnia	3%	1%
Dizziness	3%	—
Nervousness	2%	—
Dry mouth	2%	—
Anxiety	2%	1%
Gastrointestinal		
Nausea	6%	1%
Urogenital		
Abnormal ejaculation*	3%	—
Other		
Headache	3%	1%
Asthenia	2%	—
Sweating	2%	—

* Percentages based on the number of males.
— Less than 1%

Incidence in Controlled Trials

Commonly Observed Adverse Events in Controlled Clinical Trials

The most commonly observed adverse events associated with the use of Effexor® (incidence of 5% or greater) and not seen at an equivalent incidence among placebo-treated patients (ie, incidence for Effexor at least twice that for placebo), derived from the 1% incidence table below, were asthenia, sweating, nausea, constipation, anorexia, vomiting, somnolence, dry mouth, dizziness, nervousness, anxiety, tremor, and blurred vision as well as abnormal ejaculation/orgasm and impotence in men.

Adverse Events Occurring at an Incidence of 1% or More Among Effexor-Treated Patients

The table that follows enumerates adverse events that occurred at an incidence of 1% or more, and were more frequent than in the placebo group, among Effexor-treated patients who participated in short-term (4- to 8-week) placebo-controlled trials in which patients were administered doses in a range of 75 to 375 mg/day. This 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.

TABLE 1

Treatment-Emergent Adverse Experience Incidence in 4- to 8-Week Placebo-Controlled Clinical Trials[1]

Body System	Preferred Term	Effexor (n=1033)	Placebo (n=609)
Body as a Whole	Headache	25%	24%
	Asthenia	12%	6%
	Infection	6%	5%
	Chills	3%	—
	Chest pain	2%	1%
	Trauma	2%	1%
Cardiovascular	Vasodilatation	4%	3%
	Increased blood pressure/hypertension	2%	—
	Tachycardia	2%	—
	Postural hypotension	1%	—
Dermatological	Sweating	12%	3%
	Rash	3%	2%
	Pruritus	1%	—
Gastrointestinal	Nausea	37%	11%
	Constipation	15%	7%
	Anorexia	11%	2%
	Diarrhea	8%	7%
	Vomiting	6%	2%
	Dyspepsia	5%	4%
	Flatulence	3%	2%
Metabolic	Weight loss	1%	—

Body System	Preferred Term	Effexor (n=1033)	Placebo (n=609)
Nervous System	Somnolence	23%	9%
	Dry mouth	22%	11%
	Dizziness	19%	7%
	Insomnia	18%	10%
	Nervousness	13%	6%
	Anxiety	6%	3%
	Tremor	5%	1%
	Abnormal dreams	4%	3%
	Hypertonia	3%	2%
	Paresthesia	3%	2%
	Libido decreased	2%	—
	Agitation	2%	—
	Confusion	2%	1%
	Thinking abnormal	2%	1%
	Depersonalization	1%	—
	Depression	1%	—
	Urinary retention	1%	—
	Twitching	1%	—
Respiration	Yawn	3%	—
Special Senses	Blurred vision	6%	2%
	Taste perversion	2%	—
	Tinnitus	2%	—
	Mydriasis	2%	—
Urogenital System	Abnormal ejaculation/ orgasm	12%[2]	—[2]
	Impotence	6%[2]	—[2]
	Urinary frequency	3%	2%
	Urination impaired	2%	—
	Orgasm disturbance	2%[3]	—[3]

[1] Events reported by at least 1% of patients treated with Effexor (venlafaxine hydrochloride) are included, and are rounded to the nearest %. Events for which the Effexor incidence was equal to or less than placebo are not listed in the table, but included the following: abdominal pain, pain, back pain, flu syndrome, fever, palpitation, increased appetite, myalgia, arthralgia, amnesia, hypesthesia, rhinitis, pharyngitis, sinusitis, cough increased, and dysmenorrhea[3].

— Incidence less than 1%.

[2] Incidence based on number of male patients.

[3] Incidence based on number of female patients.

Dose Dependency of Adverse Events

A comparison of adverse event rates in a fixed-dose study comparing Effexor (venlafaxine hydrochloride) 75, 225, and 375 mg/day with placebo revealed a dose dependency for some of the more common adverse events associated with Effexor use, as shown in the table that follows. The rule for including events was to enumerate those that occurred at an incidence of 5% or more for at least one of the venlafaxine groups and for which the incidence was at least twice the placebo incidence for at least one Effexor group. Tests for potential dose relationships for these events (Cochran-Armitage Test, with a criterion of exact 2-sided p-value ≤ 0.05) suggested a dose-dependency for several adverse events in this list, including chills, hypertension, anorexia, nausea, agitation, dizziness, somnolence, tremor, yawning, sweating, and abnormal ejaculation.

TABLE 2
Treatment-Emergent Adverse Experience Incidence in a Dose Comparison Trial

Body System/ Preferred Term	Effexor (mg/day)			
	Placebo (n=92)	75 (n=89)	225 (n=89)	375 (n=88)
Body as a Whole				
Abdominal pain	3.3%	3.4%	2.2%	8.0%
Asthenia	3.3%	16.9%	14.6%	14.8%
Chills	1.1%	2.2%	5.6%	6.8%
Infection	2.2%	2.2%	5.6%	2.3%
Cardiovascular System				
Hypertension	1.1%	1.1%	2.2%	4.5%
Vasodilatation	0.0%	4.5%	5.6%	2.3%
Digestive System				
Anorexia	2.2%	14.6%	13.5%	17.0%
Dyspepsia	2.2%	6.7%	6.7%	4.5%
Nausea	14.1%	32.6%	38.2%	58.0%
Vomiting	1.1%	7.9%	3.4%	6.8%
Nervous System				
Agitation	0.0%	1.1%	2.2%	4.5%
Anxiety	4.3%	11.2%	4.5%	2.3%
Dizziness	4.3%	19.1%	22.5%	23.9%
Insomnia	9.8%	22.5%	20.2%	13.6%
Libido decreased	1.1%	2.2%	1.1%	5.7%
Nervousness	4.3%	21.3%	13.5%	12.5%
Somnolence	4.3%	16.9%	18.0%	26.1%
Tremor	0.0%	1.1%	2.2%	10.2%
Respiratory System				
Yawn	0.0%	4.5%	5.6%	8.0%
Skin and Appendages				
Sweating	5.4%	6.7%	12.4%	19.3%
Special Senses				
Abnormality of accommodation	0.0%	9.1%	7.9%	5.6%
Urogenital System				
Abnormal ejaculation/orgasm	0.0%	4.5%	2.2%	12.5%
Impotence	0.0%	5.8%	2.1%	3.6%
(Number of men)	(n=63)	(n=52)	(n=48)	(n=56)

Adaptation to Certain Adverse Events

Over a 6-week period, there was evidence of adaptation to some adverse events with continued therapy (eg, dizziness and nausea), but less to other effects (eg, abnormal ejaculation and dry mouth).

Vital Sign Changes

Effexor (venlafaxine hydrochloride) treatment (averaged over all dose groups) in clinical trials was associated with a mean increase in pulse rate of approximately 3 beats per minute, compared to no change for placebo. In a flexible-dose study, with 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.

In controlled clinical trials, Effexor was associated with mean increases in diastolic blood pressure ranging from 0.7 to 2.5 mm Hg averaged over all dose groups, compared to mean decreases ranging from 0.9 to 3.8 mm Hg for placebo. However, there is a dose dependency for blood pressure increase (see **WARNINGS**).

Laboratory Changes

Of the serum chemistry and hematology parameters monitored during clinical trials with Effexor, a statistically significant difference with placebo was seen only for serum cholesterol. In premarketing trials, treatment with Effexor tablets was associated with a mean final on-therapy increase in total cholesterol of 3 mg/dL.

Patients treated with Effexor tablets for at least 3 months in placebo-controlled 12-month extension trials had a mean final on-therapy increase in total cholesterol of 9.1 mg/dL 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 an analysis of ECGs obtained in 769 patients treated with Effexor and 450 patients treated with placebo in controlled clinical trials, the only statistically significant difference observed was for heart rate, ie, a mean increase from baseline of 4 beats per minute for Effexor. In a flexible-dose study, with 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 **PRECAUTIONS, General,** *Use in Patients with Concomitant Illness*).

Other Events Observed During the Premarketing Evaluation of Venlafaxine

During its premarketing assessment, multiple doses of Effexor were administered to 2897 patients in Phase 2 and Phase 3 studies. In addition, in premarketing assessment of Effexor XR (the extended release form of venlafaxine), multiple doses were administered to 705 patients in Phase 3 major depressive disorder studies and Effexor was administered to 96 patients. During its premarketing assessment for Generalized Anxiety Disorder, multiple doses of Effexor XR were administered to 476 patients in Phase 3 studies. The conditions and duration of exposure to venlafaxine in both development programs varied greatly, and included (in overlapping categories) open and double-blind studies, uncontrolled and controlled studies, inpatient (Effexor only) and outpatient studies, fixed-dose and titration studies. Untoward events associated with

this exposure were recorded by clinical investigators using terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of untoward events into a smaller number of standardized event categories.

In the tabulations that follow, reported adverse events were classified using a standard COSTART-based Dictionary terminology. The frequencies presented, therefore, represent the proportion of the 4174 patients exposed to multiple doses of either formulation of venlafaxine who experienced an event of the type cited on at least one occasion while receiving venlafaxine. All reported events are included except those already listed in Table 1 and those events for which a drug cause was remote. If the COSTART term for an event was so general as to be uninformative, it was replaced with a more informative term. It is important to emphasize that, although the events reported occurred during treatment with venlafaxine, they were not necessarily caused by it.

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

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

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

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

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

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

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

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

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

Respiratory system—**Frequent:** bronchitis, 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—**Infrequent:** acne, alopecia, brittle nails, contact dermatitis, dry skin, eczema, skin hypertrophy, maculopapular rash, psoriasis, urticaria; **Rare:** erythema nodosum, exfoliative dermatitis, lichenoid dermatitis, hair discoloration, skin discoloration, furunculosis, hirsutism, leukoderma, pustular rash, vesiculobullous rash, seborrhea, skin atrophy, skin striae.

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

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

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* 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 extrasystole, 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 (venlafaxine hydrochloride) 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 Effexor 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 Effexor (eg, development of tolerance, incrementation of dose, drug-seeking behavior).

OVERDOSAGE

Human Experience

There were 14 reports of acute overdose with Effexor (venlafaxine hydrochloride), either alone or in combination with other drugs and/or alcohol, among the patients included in the premarketing evaluation. The majority of the reports involved ingestions in which the total dose of Effexor 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

Initial Treatment

The recommended starting dose for Effexor is 75 mg/day, administered in two or three divided doses, taken with food. Depending on tolerability and the need for further clinical effect, the dose may be increased to 150 mg/day. If needed, the dose should be further increased up to 225 mg/day. When increasing the dose, increments of up to 75 mg/day should be made at intervals of no less than 4 days. In outpatient settings there was no evidence of usefulness of doses greater than 225 mg/day for moderately depressed patients, but more severely depressed inpatients responded to a mean dose of 350 mg/day. Certain patients, including more severely depressed patients, may therefore respond more to higher doses, up to a maximum of 375 mg/day, generally in three divided doses (see **PRECAUTIONS, General**, *Use in Patients with Concomitant Illness*).

Special Populations

Treatment of Pregnant Women During the Third Trimester

Neonates exposed to Effexor, 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 during the third trimester, the physician should carefully consider the potential risks and benefits of treatment. The physician may consider tapering Effexor in the third trimester.

Dosage for 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 to normal subjects (see **CLINICAL PHARMACOLOGY**), it is recommended that the total daily dose be reduced by 50% in patients with moderate hepatic impairment. Since there was much individual variability in clearance between patients with cirrhosis, it may be necessary to reduce the dose even more than 50%, and individualization of dosing may be desirable in some patients.

Dosage for 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 to normals (see **CLINICAL PHARMACOLOGY**), it is recommended that the total daily dose be reduced by 25% in patients with mild to moderate renal impairment. It is recommended that the total daily dose be reduced by 50% and the dose be withheld until the dialysis treatment is completed (4 hrs) in patients undergoing hemodialysis. Since there was much individual variability in clearance between patients with renal impairment, individualization of dosing may be desirable in some patients.

Dosage for Elderly Patients

No dose adjustment is recommended for elderly patients on the basis of age. As with any antidepressant, however, caution should be exercised in treating the elderly. When individualizing the dosage, extra care should be taken when increasing the dose.

Maintenance Treatment

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 an antidepressant response in patients with recurrent depression 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**). 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.

Discontinuing Effexor (venlafaxine hydrochloride)

Symptoms associated with discontinuation of Effexor, 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.

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. In addition, at least 7 days should be allowed after stopping Effexor before starting an MAOI (see **CONTRAINDICATIONS** and **WARNINGS**).

HOW SUPPLIED

Effexor® (venlafaxine hydrochloride) Tablets are available as follows:

25 mg, peach, shield-shaped tablet with "25" and a "W" on one side and "701" on scored reverse side.

NDC 0008-0701-01, bottle of 100 tablets.

NDC 0008-0701-02, carton of 10 Redipak® blister strips of 10 tablets each.

37.5 mg, peach, shield-shaped tablet with "37.5" and a "W"on one side and "781" on scored reverse side.

NDC 0008-0781-01, bottle of 100 tablets.

NDC 0008-0781-02, carton of 10 Redipak® blister strips of 10 tablets each.

50 mg, peach, shield-shaped tablet with "50" and a "W" on one side and "703" on scored reverse side.

NDC 0008-0703-01, bottle of 100 tablets.

NDC 0008-0703-02, carton of 10 Redipak® blister strips of 10 tablets each.

75 mg, peach, shield-shaped tablet with "75" and a "W" on one side and "704" on scored reverse side.

NDC 0008-0704-01, bottle of 100 tablets.

NDC 0008-0704-02, carton of 10 Redipak® blister strips of 10 tablets each.

100 mg, peach, shield-shaped tablet with "100" and a "W" on one side and "705" on scored reverse side.

NDC 0008-0705-01, bottle of 100 tablets.

NDC 0008-0705-02, carton of 10 Redipak® blister strips of 10 tablets each.

The appearance of these tablets is a trademark of Wyeth Pharmaceuticals.

Store at controlled room temperature 20° to 25°C (68° to 77°F) in a dry place.

Dispense in a well-closed container as defined in the USP.

Wyeth®

Wyeth Pharmaceuticals Inc.
Philadelphia, PA 19101

W10402C007
ET01
Rev 04/04

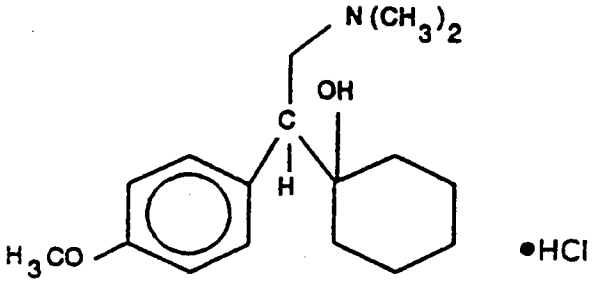
Wyeth®

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.

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



venlafaxine hydrochloride

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

Effexor XR is formulated as an extended-release capsule for once-a-day oral administration. Drug release is controlled by diffusion through the coating membrane on the spheroids and is not pH dependent. Capsules contain venlafaxine hydrochloride equivalent to 37.5 mg, 75 mg, or 150 mg venlafaxine. Inactive ingredients consist of cellulose, ethylcellulose, gelatin, 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, 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, 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 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.

INDICATIONS AND USAGE

Major Depressive Disorder

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

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

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

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

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

CONTRAINDICATIONS

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

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

WARNINGS

Potential for Interaction with Monoamine Oxidase Inhibitors

Adverse reactions, some of which were serious, have been reported in patients who have recently been discontinued from a monoamine oxidase inhibitor (MAOI) and started on venlafaxine, or who have recently had venlafaxine therapy discontinued prior to initiation of an MAOI. These reactions have included tremor, myoclonus, diaphoresis, nausea, vomiting, flushing, dizziness, hyperthermia with features resembling neuroleptic malignant syndrome, seizures, and death. In patients receiving antidepressants with pharmacological properties similar to venlafaxine in combination with an MAOI, there have also been reports of serious, sometimes fatal, reactions. For a selective serotonin reuptake inhibitor, these reactions have included hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes that include extreme agitation progressing to delirium and coma. Some cases presented with features resembling neuroleptic malignant syndrome. Severe hyperthermia and seizures, sometimes fatal, have been reported in association with the combined use of tricyclic antidepressants and MAOIs. These reactions have also been reported in patients who have recently discontinued these drugs and have been started on an MAOI. The effects of combined use of venlafaxine and MAOIs have not been evaluated in humans or animals. Therefore, because venlafaxine is an inhibitor of both norepinephrine and serotonin reuptake, it is recommended that Effexor XR (venlafaxine hydrochloride) extended-release capsules not be used in combination with an MAOI, or within at least 14 days of discontinuing treatment with an MAOI. Based on the half-life of venlafaxine, at least 7 days should be allowed after stopping venlafaxine before starting an MAOI.

Clinical Worsening and Suicide Risk

Patients with major depressive disorder, both adult and pediatric, may experience worsening of their depression and/or the emergence of suicidal ideation and behavior (suicidality), whether or not they are taking antidepressant medications, and this risk may persist until significant remission occurs. Although 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, a causal role for antidepressants in inducing such behaviors has not been established. **Nevertheless, patients being treated with antidepressants should be observed closely for clinical worsening and suicidality, especially at the beginning of a course of drug therapy, or at the time of dose changes, either increases or decreases.** Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients whose depression is persistently worse or whose emergent suicidality is severe, abrupt in onset, or was not part of the patient's presenting symptoms.

Because of the possibility of co-morbidity between major depressive disorder and other psychiatric and nonpsychiatric disorders, the same precautions observed when treating patients with major depressive disorder should be observed when treating patients with other psychiatric and nonpsychiatric disorders.

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, consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients for whom such symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms.

Families and caregivers of 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, and the other symptoms described above, as well as the emergence of suicidality, and to report such symptoms immediately to health care providers. 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.

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, Discontinuing Effexor XR**, for a description of the risks of discontinuation of Effexor XR).

It should be noted that Effexor XR is not approved for use in treating any indications in the pediatric population.

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 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.

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. 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 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).

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

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

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

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

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

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

Changes in Appetite and Weight

Treatment-emergent anorexia was more commonly reported for Effexor XR treated (8%) than placebo treated patients (4%) in the pool of short-term studies in major depressive disorder. Significant weight loss, especially in underweight depressed patients, may be an undesirable effect of Effexor XR treatment. A loss of 5% or more of body weight occurred in 7% of Effexor XR-treated and 2% of placebo-treated patients in placebo-controlled major depressive

disorder trials. Discontinuation rates for anorexia and weight loss associated with Effexor XR were low (1.0% and 0.1%, respectively, of Effexor XR treated patients in major depressive disorder studies).

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

In the pool of Social Anxiety Disorder studies, treatment emergent anorexia was reported in 20% and 2% of patients receiving Effexor XR and placebo up to 12 weeks, respectively. A loss of 7% or more of body weight occurred in 3% of the Effexor XR-treated and 0.4% of the placebo-treated patients up to 12 weeks in these trials. Discontinuation rates for anorexia and weight loss were low for patients receiving Effexor XR up to 12 weeks (0.4% and 0.0%, respectively).

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.

Activation of Mania/Hypomania

During premarketing major depressive disorder studies, mania or hypomania occurred in 0.3% of Effexor XR-treated patients and 0.0% placebo patients. In premarketing GAD studies, 0.0% of Effexor XR-treated patients and 0.2% of placebo-treated patients experienced mania or hypomania. In premarketing Social Anxiety Disorder studies, no Effexor XR-treated patients and no placebo-treated patients experienced mania or hypomania. In all premarketing major depressive disorder trials with Effexor, mania or hypomania occurred in 0.5% of venlafaxine-treated patients compared with 0% of placebo patients. Mania/hypomania has also been reported in a small proportion of patients with mood disorders who were treated with other 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 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, and for 195 patients who received Effexor XR and 228 patients who received placebo in 12-week double-blind, placebo-controlled trials in Social Anxiety Disorder. The mean change from baseline in corrected QT interval (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).

In these same trials, the mean change from baseline in heart rate for Effexor XR-treated patients in the major depressive disorder studies was significantly higher than that for placebo (a mean increase of 4 beats per minute for Effexor XR and 1 beat per minute for placebo). The mean change from baseline in heart rate for Effexor XR-treated patients in the GAD studies was significantly higher than that for placebo (a mean increase of 3 beats per minute for Effexor XR and no change for placebo). The mean change from baseline in heart rate for Effexor XR-treated patients in the Social Anxiety Disorder studies was significantly higher than that for placebo (a mean increase of 5 beats per minute for Effexor XR and no change for placebo).

In a flexible-dose study, with Effexor doses in the range of 200 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

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

Patients and their families should be encouraged to be alert to the emergence of anxiety, agitation, panic attacks, insomnia, irritability, hostility, impulsivity, akathisia, hypomania, mania, worsening of depression, and suicidal ideation, especially early during antidepressant treatment. Such symptoms should be reported to the patient's physician, especially if they are severe, abrupt in onset, or were not part of the patient's presenting symptoms.

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 pediatric patients have not been established. (See **WARNINGS-Clinical Worsening and Suicide Risk**).

Geriatric Use

Approximately 4% (14/357), 6% (77/1381), and 2% (6/277) of Effexor XR-treated patients in placebo-controlled premarketing major depressive disorder, GAD, and Social Anxiety Disorder trials, respectively, were 65 years of age or over. Of 2,897 Effexor-treated patients in premarketing phase major depressive disorder studies, 12% (357) were 65 years of age or over. No overall differences in effectiveness or safety were observed between geriatric patients and younger patients, and other reported clinical experience generally has not identified differences in response between the elderly and younger patients. However, greater sensitivity of some older

individuals cannot be ruled out. As with other antidepressants, several cases of hyponatremia and syndrome of inappropriate antidiuretic hormone secretion (SIADH) have been reported, usually in the elderly.

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

ADVERSE REACTIONS

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

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

Adverse Events Associated with Discontinuation of Treatment

Approximately 11% of the 357 patients who received Effexor® XR (venlafaxine hydrochloride) extended-release capsules in placebo-controlled clinical trials for major depressive disorder discontinued treatment due to an adverse experience, compared with 6% of the 285 placebo-treated patients in those studies. Approximately 18% of the 1381 patients who received Effexor XR capsules in placebo-controlled clinical trials for GAD discontinued treatment due to an adverse experience, compared with 12% of the 555 placebo-treated patients in those studies. Approximately 17% of the 277 patients who received Effexor XR capsules in placebo-controlled clinical trials for Social Anxiety Disorder discontinued treatment due to an adverse experience, compared with 5% of the 274 placebo-treated patients in those studies. The most common events leading to discontinuation and considered 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 either indication) are shown in Table 2.

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

Adverse Event	Percentage of Patients Discontinuing Due to Adverse Event					
	Major Depressive Disorder Indication[2]		GAD Indication[3,4]		Social Anxiety Disorder Indication	
	Effexor XR n = 357	Placebo n = 285	Effexor XR n = 1381	Placebo n = 555	Effexor XR n = 277	Placebo n = 274
Body as a Whole						
Asthenia	--	--	3%	<1%	1%	<1%
Headache	--	--	--	--	2%	<1%
Digestive System						
Nausea	4%	<1%	8%	<1%	4%	0%
Anorexia	1%	<1%	--	--	--	--
Dry Mouth	1%	0%	2%	<1%	--	--
Vomiting	--	--	1%	<1%	--	--
Nervous System						
Dizziness	2%	1%	--	--	2%	0%
Insomnia	1%	<1%	3%	<1%	3%	<1%
Somnolence	2%	<1%	3%	<1%	2%	<1%
Nervousness	--	--	2%	<1%	--	--
Tremor	--	--	1%	0%	--	--
Anxiety	--	--	--	--	1%	<1%
Skin						
Sweating	--	--	2%	<1%	1%	0%
Urogenital System						
Impotence[5]	--	--	--	--	3%	0%

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

[2] In U.S. placebo-controlled trials for major depressive disorder, the following were also common events leading to discontinuation and were considered to be drug-related for Effexor XR-treated patients (% Effexor XR [n = 192], % Placebo [n = 202]): hypertension (1%, <1%); diarrhea (1%, 0%); paresthesia (1%, 0%); tremor (1%, 0%); abnormal vision, mostly blurred vision (1%, 0%); and abnormal, mostly delayed, ejaculation (1%, 0%).

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

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

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

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

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

Major Depressive Disorder

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

Generalized Anxiety Disorder

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

Social Anxiety Disorder

Note in particular the following adverse events that occurred in at least 5% of the Effexor XR patients and at a rate at least twice that of the placebo group for the 2 placebo-controlled trials for the Social Anxiety Disorder indication (Table 5): Asthenia, gastrointestinal complaints (anorexia, dry mouth, nausea), CNS complaints (anxiety, insomnia, libido decreased, nervousness, somnolence, dizziness), abnormalities of sexual function (abnormal ejaculation, orgasmic dysfunction, impotence), yawn, sweating, and abnormal vision.

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

	% 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%
Respiratory System		
Pharyngitis	7%	6%
Yawn	3%	0%
Skin		
Sweating	14%	3%
Special Senses		
Abnormal Vision[5]	4%	<1%

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

Body System Preferred Term	% Reporting Event Effexor XR (n = 277)	 Placebo (n = 274)
Body as a Whole		
Headache	34%	33%
Asthenia	17%	8%
Flu Syndrome	6%	5%
Accidental Injury	5%	3%
Abdominal Pain	4%	3%
Cardiovascular System		
Hypertension	5%	4%
Vasodilatation[3]	3%	1%
Palpitation	3%	1%
Digestive System		
Nausea	29%	9%
Anorexia[4]	20%	1%
Constipation	8%	4%
Diarrhea	6%	5%
Vomiting	3%	2%
Eructation	2%	0%
Metabolic/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).

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. (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.

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 1381 patients in Phase 3 GAD studies and 277 patients in Phase 3 Social Anxiety Disorder studies. In addition, in premarketing assessment of Effexor, multiple doses were administered to 2897 patients in Phase 2 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 5356 patients exposed to multiple doses of either formulation of venlafaxine who experienced an event of the type cited on at least one occasion while receiving venlafaxine. All reported events are included except those already listed in Tables 3, 4, and 5 and those events for which a drug cause was remote. If the COSTART term for an event was so general as to be uninformative, it was replaced with a more informative term. It is important to emphasize that,

although the events reported occurred during treatment with venlafaxine, they were not necessarily caused by it.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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.

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**).

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, 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 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.

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.

Wyeth®

Wyeth Pharmaceuticals Inc.
Philadelphia, PA 19101

W10404C009
ET01
Rev 04/04

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-151/S-028, 030, 032 &
NDA 20-699/S-041, 048, 052

MEDICAL REVIEW(S)

Review and Evaluation of Clinical Data
NDA #20-151

Sponsor:	Wyeth Pharmaceuticals
Drug:	Effexor (venlafaxine)
Indication:	Depression
Material Submitted:	SLR-028: Special Supplement-CBE
Correspondence Date:	August 8, 2003
Date Received:	August 11, 2003

I. Background

The sponsor is submitting this CBE (Changes Being Effected) supplement to add specific safety information to two sections of Effexor labeling:

1) PRECAUTIONS/Usage in Children and
2) DOSAGE AND ADMINISTRATION/Discontinuing Effexor.

The sponsor planned to implement these changes in August 2003.

II. Review of Labeling Changes

A. PRECAUTIONS/Usage in Children

The sponsor's pediatric development program consisted of 2 pharmacokinetic trials (one with Effexor and one with Effexor XR), 3 studies in Major Depressive Disorder (MDD) with Effexor XR, and 2 trials in Generalized Anxiety Disorder (GAD) with Effexor XR. The results of these studies were submitted as S-024 to this NDA on 9-25-02. This supplement was reviewed by Dr. Glenn Mannheim and was deemed non-approvable (NA) due to lack of a demonstration of efficacy. An NA letter was issued on 3-20-03.

The sponsor has amended this subsection of labeling to reflect findings from the MDD and GAD trials in children and adolescents which indicate an increased reporting rate of hostility and suicidal ideation in the Effexor XR group versus placebo. These findings are summarized in Table 1 below.

TABLE 1 REPORTING RATES OF TREATMENT-EMERGENT HOSTILITY AND SUICIDAL IDEATION IN PLACEBO-CONTROLLED PEDIATRIC TRIALS		
	N/n(%) Reporting AE	
	Effexor XR	Placebo
Hostility		
MDD	7/182(4%)	2/179(1%)
GAD	2/157(1%)	0/163(0%)
All	9/339(3%)*	2/342(<1%)
Suicidal Ideation		
MDD	6/182(3%)*	0/179(0%)
GAD	0/157(0%)	0/163(0%)
All	6/339(2%)*	0/342(0%)

* p-value ≤0.05 for the comparison of Effexor XR vs. placebo.[1]

Based on these data, Wyeth has revised this subsection as follows (added text double-underlined):

Usage in Children
Safety and effectiveness in individuals below 18 years of age have not been established.

<u>In pediatric clinical trials, there were increased reports of hostility and, especially in Major Depressive Disorder, suicide-related adverse events such as suicidal ideation and self-harm.</u>

B. DOSAGE AND ADMINISTRATION/Discontinuing Effexor (venlafaxine hydrochloride)

Wyeth indicates that in the eighth Periodic Safety Update Report (May 6, 2000-May 5, 2001), a comprehensive review of tinnitus through May 5, 2001, was performed. Based on that review, reports of tinnitus continued to be monitored. Subsequently, the sponsor undertook an analysis of all reports of tinnitus associated with venlafaxine from their Global Safety Surveillance and Epidemiology (GSSE) database during the period between May 6, 2001, and May 5, 2002.

This analysis revealed 35 reports, only one of which was considered serious. Twelve were confounded by medical

[1] P-values determined by the undersigned reviewer using the Statcalc function of EpiInfo version 6.

conditions or concomitant medications associated with tinnitus. Three reports had little information.

Of the remaining 20 reports, 9 emerged during venlafaxine treatment. Of these 9 cases, one involved a positive dechallenge and 2 reported continuation of tinnitus after dose reduction or discontinuation.

Eleven of the cases report the onset of tinnitus associated with dose reduction or discontinuation. In 3 of these cases, tinnitus abated when venlafaxine was reintroduced. In one of these 3 cases, the patient discontinued venlafaxine a second time and the symptom reappeared; when venlafaxine was restarted, the tinnitus abated in this patient.

Based on these findings, the sponsor has added the adverse event term "tinnitus" to this subsection of labeling.

III. Conclusions and Recommendations

The Division has undertaken an extensive effort to thoroughly investigate a potential association between the use of recently approved antidepressants, including venlafaxine, and suicidality among pediatric patients, to include a meeting of the Psychopharmacological Drugs Advisory Committee on 2-2-04. This effort was prompted by data from the use of another antidepressant drug in pediatric patients; this data was similar to that cited here.

The outcome of this investigation is unknown at this time point. One possibility is a class labeling action for most, if not all, recently approved antidepressant drugs. Nonetheless, in the meantime, I do not object to the mention of these findings in Effexor labeling.

The addition of tinnitus to the list of adverse experiences possibly related to venlafaxine dose reduction or discontinuation is felt to be reasonable based on the above data. However, since the previously mentioned events were derived from clinical trials and retrospective surveys, I do recommend that the first sentence of the second paragraph in this subsection be modified as follows to indicate that these events are also derived from spontaneous [ ] reports (added text double-underlined):

Discontinuation symptoms have been systematically evaluated in patients taking venlafaxine, to include prospective analyses of clinical trials in Generalized Anxiety Disorder, retrospective surveys of trials in [ ]
[ ]

Additionally, since the sponsor describes a number of cases of tinnitus which emerge during venlafaxine treatment, it is recommended that tinnitus be added to the subsection ADVERSE REACTIONS/Postmarketing Reports immediately following the mention of shock-like electrical sensations as follows: "shock-like electrical sensations <u>or tinnitus</u> (in some cases, subsequent to the discontinuation of venlafaxine or tapering of dose)."

This supplement may be approved once the sponsor agrees to the above changes.

Gregory M. Dubitsky, M.D.
January 23, 2004

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

Greg Dubitsky
1/23/04 08:27:51 PM
MEDICAL OFFICER

Thomas Laughren
1/25/04 11:07:13 AM
MEDICAL OFFICER
I agree with Dr. Dubitsky's comments re: tinnitus; however, re: the language pertinent to suicidality, it is my view that our action on these proposed changes should await our more comprehensive review of suicidality; of course, they are CBE.--TPL

Review and Evaluation of Clinical Data
NDA #20-699

Sponsor:	Wyeth Pharmaceuticals
Drug:	Effexor XR
Indication:	Major Depression, GAD, SAD,
Material Submitted:	SLR-041: Special Supplement-CBE
Correspondence Date:	August 8, 2003
Date Received:	August 11, 2003

The sponsor is submitting this CBE (Changes Being Effected) supplement to add specific safety information to two sections of Effexor XR labeling:

1) PRECAUTIONS/Pediatric Use and
2) DOSAGE AND ADMINISTRATION/Discontinuing Effexor XR.

Additionally, the Patient Brief Summary for Effexor XR has been revised to reflect the above labeling changes.

The sponsor planned to implement these changes in August 2003.

A CBE supplement for identical changes to Effexor labeling was submitted on 8-8-03 (SLR-028 to NDA 20-151). This supplement was reviewed by the undersigned on 1-23-04 and deemed to be approvable pending agreement by the sponsor to make minor modifications to the implemented changes (see Review and Evaluation of Clinical Data). Those recommendations apply to this supplement as well.

Changes to the Patient Brief Summary for Effexor XR were reviewed and found to be acceptable.

Gregory M. Dubitsky, M.D.
January 23, 2004

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Greg Dubitsky
1/23/04 09:08:25 PM
MEDICAL OFFICER

Thomas Laughren
1/25/04 11:12:42 AM
MEDICAL OFFICER
See my comments re: Dr. Dubitsky's review of SLR-028 for NDA 20-151.--TPL

Review and Evaluation of Clinical Data
NDA #20-151

Sponsor:	Wyeth Pharmaceuticals
Drug:	Effexor (venlafaxine)
Indication:	Depression
Material Submitted:	SLR-030: Prior Approval Supplement
Correspondence Date:	December 10, 2003
Date Received:	December 11, 2003

I. Background

On 4-16-03, Wyeth submitted a CBE labeling supplement (SLR-027) to add safety information to Effexor labeling regarding: 1) drug interactions possibly resulting in serotonin syndrome, 2) postmarketing spontaneous reports of dyskinesia and rhabdomyolysis, and 3) reports of seizures when discontinuing Effexor.

We issued a letter on 9-16-03 which indicated that this supplement was approvable. Before approval, we stated that the sponsor would need to make specific revisions to their proposed labeling changes (under the PRECAUTIONS, OVERDOSAGE, and DOSAGE AND ADMINISTRATION sections). In this letter, we also asked that they submit additional data regarding reports of rhabdomyolysis and dyskinesia.[1]

Two of the above issues were addressed in a response dated 12-9-03 (i.e., revisions to the Drug Interactions subsection under PRECAUTIONS regarding CNS-active drugs and the addition of an adverse event term to the Human Experience subsection under OVERDOSAGE). Wyeth's response to these two items was deemed to be acceptable by me in a review dated 1-20-04. However, I indicated that the response was incomplete in that it did not address the third issue in the approvable letter (a revision to the subsection Discontinuing Effexor under DOSAGE AND ADMINISTRATION regarding seizures associated with discontinuation of Effexor).

This separate supplement (SLR-030) addresses the latter issue.

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[1] See the approvable letter for details.

II. Review of Labeling Proposal

Based on a number of reports of seizures during taper or after abrupt discontinuation of venlafaxine from their global safety database, the sponsor had proposed to add the adverse event term "seizures" to the listing of events observed during taper or after stopping venlafaxine in the subsection Discontinuing Effexor under DOSAGE AND ADMINISTRATION. In our 9-16-03 approvable letter, we requested that they add the mention of [ ]

This submission contains Wyeth's counterproposal. [ ] [ ] [ ], the sponsor prefers to maintain one combined list of discontinuation symptoms since some events from clinical trials have also been reported in the postmarketing experience. Thus, they propose that 1) [ ] [ ] [ ] and 2) one combined list of events, that includes "seizures," be presented in labeling. Their proposal is incorporated on page 23 of the labeling under Tab 1 of this submission.

III. Conclusions and Recommendations

I have no strong objection to the sponsor's proposal as described in this submission.

However, it should be noted that there is a class labeling initiative regarding discontinuation-related experiences with SSRI's and SNRI's currently underway. This initiative will include Effexor as well as Effexor XR. Therefore, it is recommended that the above proposal from Wyeth be incorporated, as appropriate, into the labeling revisions that will be requested pursuant to this initiative.

Furthermore, although a corresponding supplement for Effexor XR has not yet been submitted, the issue reviewed above will pertain to that product as well and it is recommended that a similar labeling revision be requested for Effexor XR as part of the class labeling request.

Gregory M. Dubitsky, M.D.
March 5, 2004

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

Greg Dubitsky
3/5/04 12:20:46 PM
MEDICAL OFFICER

Thomas Laughren
3/5/04 01:30:30 PM
MEDICAL OFFICER

Review and Evaluation of Clinical Data
NDA #20-151

Sponsor:	Wyeth
Drug:	Effexor (venlafaxine)
Indication:	Depression
Material Submitted:	Dear Health Care Professional Letter (SLR-032-C)
Date Submitted:	June 2, 2004
Date Received:	June 3, 2004
Related Supplement:	NDA #20-699/SLR-052-C (Effexor XR)

S-032 to NDA 20-151 provided for the addition of the following information to Effexor labeling:

- warnings about the potential for clinical worsening and suicide risk associated with Effexor therapy,
- discontinuation-associated adverse events, and
- neonatal effects when pregnant women had been treated with Effexor during the third trimester.

These changes, as well as the corresponding changes to Effexor XR labeling which were submitted as S-052 to NDA 20-699, were approved on 5-13-04.

This submission also references labeling changes regarding changes in height, weight, and appetite in pediatric patients treated with Effexor or Effexor XR. These were submitted under SE5-024 to NDA 20-151 and SE5-030 to NDA 20-699 and were approved on 5-5-04.

This submission conveys a Dear Health Care Professional letter, issued on 6-3-04, to communicate the above important labeling revisions to prescribers.

This letter, provided as an attachment, was reviewed and is acceptable. No further action is recommended at this time.

Gregory M. Dubitsky, M.D.
June 16, 2004

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NDA #20-699
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Greg Dubitsky
6/16/04 06:29:45 PM
MEDICAL OFFICER

Thomas Laughren
6/17/04 07:57:59 AM
MEDICAL OFFICER

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-151/S-028, 030, 032 &
NDA 20-699/S-041, 048, 052

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

REGULATORY PROJECT MANAGER
LABELING REVIEW

Date: May 12, 2004
DRUG/NDA: Effexor (venlafaxine hydrochloride) Immediate Release Tablets (NDA 20-151) and Effexor XR (venlafaxine hydrochloride) Extended Release Capsules (NDA 20-699)
Sponsor: Wyeth
Indication: Major Depressive Disorder/Panic Disorder

NDA	Supplement	Dated	Action
Effexor (venlafaxine hydrochloride) Immediate Release Tablets (NDA 20-151)			
20-151	SLR-027	4-16-03, and amended on 12-9-03	AE Letter dated 9-16-03 AP Letter dated 3-19-04
20-151	SLR-028	8-8-03, and amended on 4-2-04, and 4-30-04	AE Letter dated 3-19-04 Open
20-151	SLR-029	10-31-03	AP Letter dated 4-8-04
20-151	SLR-030	12-10-03, and amended on 4-30-03	AE Letter dated 3-19-04 Open
20-151	SLR-032	4-30-04	Open
Effexor XR (venlafaxine hydrochloride) Extended Release Capsules (NDA 20-699)			
20-699	SLR-038	4-16-03	AP Letter Dated 9-20-03
20-699	SLR-039	4-16-03, and amended on 12-3-03	AE Letter dated 9-16-03 AP Letter dated 3-19-04
20-699	SLR-041	8-8-03, and amended on 4-2-04, and 4-30-04	AE Letter dated 3-19-04 Open
20-699	SLR-043	3-7-03	AP Letter Dated 9-20-03
20-699	SLR-045	9-29-03, and amended on 10-21-03, and 12-22-03	AP Letter Dated 3-16-04
20-699	SLR-046	10-31-03	AP Letter Dated 4-8-04
20-699	SLR-048	12-10-03, and amended on 4-30-03	AE Letter dated 3-19-04 Open
20-699	SLR-050	2-13-04	AP Letter dated 3-19-04
20-699	SLR-052	4-30-04	Open

Review:

There are 6 open labeling supplements. They are as follows:

NDAs 20-151/S-028 & 20-699/S-041

1. Revisions to the **PRECAUTIONS-Usage in Children** section to denote hostility and suicide related adverse events in pediatric clinical trials.
2. The addition of the term "tinnitus" to the **DOSAGE AND ADMINISTRATION-Discontinuing Effexor** or **Effexor XR** sections.
3. Revisions to the Patient Brief Summary.

The major point of contention was that we did not agree with the addition of hostility and suicide in the **Pediatric Use** section. Wyeth subsequently agreed to our request to remove their proposed addition of hostility and suicide related adverse events from the **PRECAUTIONS-Usage in Children** section.

NDAs 20-151/S-030 & 20-699/S-048
These applications provide for revisions to the **Dosage And Administration/Discontinuing Effexor** or **Effexor XR** sections of product labeling.

There was a class labeling initiative for all of the selective serotonin reuptake inhibitors (SSRIs) and serotonin and norepinephrine reuptake inhibitors (SNRIs) drugs to incorporate labeling regarding discontinuation and nonteratogenic effects. Again, Wyeth subsequently agreed to revise product labeling to incorporate the class labeling initiative for all of the SSRI and SNRI drugs changing labeling in regards to discontinuation symptoms and to adverse events occurring in neonates exposed to any of the SSRIs or SNRIs late in the third trimester.

NDAs 20-151/S-032 & 20-699/S-052
These applications provide for antidepressant class labeling revisions to incorporate the following changes to product labeling:

1. The addition of a new subsection under **WARNINGS** entitled **Clinical Worsening and Suicide Risk**.
2. Revisions to the **PRECAUTIONS-Information for Patients** section.
3. Delete the section in **PRECAUTIONS-General** entitled "Suicide".
4. Add a reference to the **WARNINGS** section at the end of the **PRECAUTIONS-Pediatric Use** section, i.e., (see **WARNINGS-Clinical Worsening and Suicide Risk**).

These changes were requested in a letter dated 3-19-04, and revised in an e-mail dated 4-19-04.

Conclusions

1. The sponsor and the Agency have come to final agreement on all of the outstanding labeling issues, and the sponsor has implemented these revisions.

2. Therefore, I recommend that the open labeling supplements, NDAs 20-151/SLR-028/SLR-030/SLR-032 & 20-699/SLR-041/SLR-048/SLR-052, be approved.

{See appended electronic signature page}

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

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/s/

Paul David
5/13/04 09:53:00 AM
CSO