



Venlafaxine Hydrochloride Tablets

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 Weight

Adult Patients: A dose-dependent weight loss was noted in patients treated with venlafaxine for several weeks. 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 (1% venlafaxine-treated patients vs. 0% placebo-treated patients).

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

Pediatric Patients: Weight loss has been observed in pediatric patients (ages 6-17) receiving venlafaxine hydrochloride extended-release capsules. In a pooled analysis of four eight-week, double-blind, placebo-controlled, flexible dose outpatient trials for major depressive disorder (MDD) and generalized anxiety disorder (GAD), venlafaxine hydrochloride extended-release capsules-treated patients lost an average of 0.45 kg (n = 333), while placebo-treated patients gained an average of 0.77 kg (n = 333). More patients treated with venlafaxine hydrochloride extended-release capsules than with placebo experienced a weight loss of at least 3.5% in both the MDD and the GAD studies (18% of venlafaxine hydrochloride extended-release capsules-treated patients vs. 3% of placebo-treated patients; p<0.001). Weight loss was not limited to patients with treatment-emergent anorexia (see **PRECAUTIONS, General, Changes in Appetite**).

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

Changes in Height

Pediatric Patients: During the eight-week placebo-controlled GAD studies, venlafaxine hydrochloride extended-release capsules-treated patients (ages 6-17) grew an average of 0.3 cm (n = 122), while placebo-treated patients grew an average of 1.0 cm (n = 132); p=0.041. This difference in height suicidality symptoms that might be precursors to worsening depression or suicidality, especially if these symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms. If the decision has been made to discontinue treatment, medication should be tapered, as rapidly as is feasible, but with recognition that abrupt discontinuation can be associated with certain symptoms (see **PRECAUTIONS and DOSAGE AND ADMINISTRATION: Discontinuation of Treatment with Venlafaxine Hydrochloride Tablets**, for a description of the risks of discontinuation of venlafaxine hydrochloride tablets).

Changes in Appetite

Adult Patients: 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.

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

Activation of Mania/Hypomania

During 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, venlafaxine hydrochloride tablets should be used cautiously in patients with a history of mania.

Hypomania

Hypomania may occur as a result of treatment with SSRIs and SNRIs, including venlafaxine hydrochloride tablets. In many cases, this hypomania appears as a part of the syndrome of inappropriate antidiuretic hormone secretion (SIADH). Cases with serum sodium lower than 110 mEq/L have been reported. Elderly patients may be at greater risk of developing hypomania with SSRIs and SNRIs. Also, patients taking diuretics or who are otherwise volume depleted may be at greater risk (see **PRECAUTIONS, Geriatric Use**). Discontinuation of venlafaxine hydrochloride tablets should be considered in patients with symptomatic hypomania and appropriate medical intervention should be instituted.

Signs and symptoms of hypomania include headache, difficulty concentrating, memory impairment, confusion, weakness, and unsteadiness, which may lead to falls. Signs and symptoms associated with more severe and/or acute cases have included hallucination, syncope, seizure, coma, respiratory arrest, and death.

Seizures

In a 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. Venlafaxine hydrochloride tablets should be used cautiously in patients with a history of seizures. It should be discontinued in any patient who develops seizures.

Abnormal Bleeding

SSRIs and SNRIs, including venlafaxine, may increase the risk of bleeding events. Concomitant use of aspirin, nonsteroidal anti-inflammatory drugs, warfarin, and other anti-coagulants may add to this risk. Venlafaxine hydrochloride tablets should be used cautiously with concomitant use of serotonergic drugs (including triptans) with drugs which impair metabolism of serotonin (including MAOIs), or with antipsychotics or other dopamine antagonists. Serotonin syndrome symptoms may include mental status changes (e.g., agitation, hallucinations, coma), autonomic instability (e.g., tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (e.g., hyperreflexia, incoordination) and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea). See **PRECAUTIONS, Drug Interactions**.

Serotonin syndrome, in its most severe form can resemble neuroleptic malignant syndrome, which includes hyperthermia, muscle rigidity, autonomic instability with possible rapid fluctuation of vital signs, and mental status changes. Patients should be monitored for the emergence of serotonin syndrome or NMS-like signs and symptoms.

The concomitant use of venlafaxine hydrochloride tablets with MAOIs used to treat depression is contraindicated (see **CONTRAINDICATIONS**). If concomitant treatment of venlafaxine hydrochloride tablets with a 5-hydroxytryptamine receptor agonist (triptan) is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases (see **PRECAUTIONS, Drug Interactions**).

The concomitant use of venlafaxine hydrochloride tablets with serotonin precursors (such as tryptophan) is not recommended (see **PRECAUTIONS, Drug Interactions**).

Treatment with venlafaxine hydrochloride tablets and any concomitant serotonergic or sympathomimetic agents, including antipsychotics, should be discontinued immediately if the above events occur and supportive symptomatic treatment should be initiated.

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 group 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 \geq 90 mm Hg and \geq 10 mm Hg above baseline for 3 consecutive visits) revealed a dose-dependent increase in the incidence of sustained hypertension for venlafaxine:

Treatment Group	Probability of Sustained Elevation in SDBP (Pool of Premarketing Venlafaxine Studies)
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. Cases of elevated blood pressure requiring immediate treatment have been reported in post marketing experience. Pre-existing hypertension should be controlled before treatment with venlafaxine. 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.

Mydriasis:
Mydriasis has been reported in association with venlafaxine; therefore patients with raised intraocular pressure or at risk of acute narrow-angle glaucoma (angle-closure glaucoma) should be monitored (see **PRECAUTIONS, Information for Patients**).

PRECAUTIONS
General
Discontinuation of Treatment with Venlafaxine Hydrochloride Tablets
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:

Information for Patients
Prescribers or other health professionals should inform patients, their families, and their caregivers about the benefits and risks associated with treatment with venlafaxine hydrochloride tablets and should counsel them in its appropriate use. A patient Medication Guide about "Antidepressant Medicines, Depression and Other Serious Mental Illness, and Suicidal Thoughts or Actions" is available for patients and their families and caregivers of patients should be advised to look for the emergence of such symptoms on a day-to-day basis, since changes may be abrupt. Such symptoms should be reported to the patient's prescriber or health professional, especially if they are severe, abrupt in onset, or were not part of the patient's presenting symptoms. Symptoms such as these may be associated with an increased risk for suicidal thinking and behavior and indicate a need for very close monitoring and possible changes in the medication.

Interference with Cognitive and Motor Performance
Clinical studies were performed to examine the effects of venlafaxine on behavioral performance of healthy individuals. The results revealed no clinically significant impairment of psychomotor, cognitive, or complex behavior performance. However, since any psychoactive drug may impair judgment, thinking, or motor skills, patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that venlafaxine hydrochloride tablets 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
Breasts should be advised to notify their physician if they are breast-feeding an infant.

Mydriasis
Mydriasis (prolonged dilation of the pupils of the eye) has been reported with venlafaxine. Patients should be advised to notify their physician if they have a history of glaucoma or a history of increased intraocular pressure (see **WARNINGS**).

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 and nutritional supplements, since there is a potential for interactions.

Patients should be cautioned about the risk of serotonin syndrome with the concomitant use of venlafaxine hydrochloride tablets and triptans, tramadol, tryptophan supplements or other serotonergic agents (see **WARNINGS, Serotonin Syndrome and PRECAUTIONS, Drug Interactions, CNS-Active Drugs**).

Patients should be cautioned about the concomitant use of venlafaxine hydrochloride tablets and NSAIDs, aspirin, warfarin, or other agents that affect coagulation. The potential for interactions with psychotropic drugs that interfere with serotonin reuptake and these agents has been associated with an increased risk of bleeding (see **PRECAUTIONS, Abnormal Bleeding**).

Alcohol

Although venlafaxine hydrochloride tablets have 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 hydrochloride tablets.

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 pharmacologic 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

In 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

Haloperidol 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 venlafaxine hydrochloride tablets in combination with another drug that is highly protein bound should not cause increased free concentrations of the other drug.

Drugs that Interfere with Hemostasis (e.g., NSAIDs, Aspirin, and Warfarin)

Serotonin release by platelets plays an important role in hemostasis. Epidemiological studies of the case-control and cohort design that have demonstrated an association between use of psychotropic drugs that interfere with serotonin reuptake and the occurrence of upper gastrointestinal bleeding have shown that the risk of bleeding is increased with concomitant use of aspirin, NSAIDs, or other agents with anticoagulant effects, including increased bleeding, have been reported when SSRIs and SNRIs are coadministered with warfarin. Patients receiving warfarin therapy should be carefully monitored when venlafaxine is initiated or discontinued.

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, the total concentration of venlafaxine plus ODV increased on average by approximately 23% in EMs and 53% in PMs (range in PMs = 4% to 134%).

Concomitant use of CYP3A4 inhibitors and venlafaxine may increase levels of venlafaxine and ODV. Therefore, caution is advised if a patient's therapy includes a CYP3A4 inhibitor and venlafaxine concomitantly.

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 for venlafaxine, the potential for a clinically significant drug interaction between venlafaxine and CYP3A4 inhibitors is small. The concomitant use of venlafaxine with a drug treatment(s) that potently inhibits both CYP2D6 and CYP3A4, the primary metabolic 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
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 dextrophan.

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 AUCs increased by about 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.

Metoprolol-Concomitant administration of venlafaxine (50 mg every 8 hours for 5 days) and metoprolol (100 mg every 24 hours for 5 days) to 18 healthy male subjects in a pharmacokinetic interaction study for both drugs resulted in an increase of plasma concentrations of metoprolol by approximately 30-40% without altering the plasma concentrations of its active metabolite, o-hydroxy metoprolol. Metoprolol did not affect the pharmacokinetics of venlafaxine or ODV. In *in vitro* studies, venlafaxine did not affect the pharmacokinetics of venlafaxine. Venlafaxine appeared to reduce the blood pressure lowering effect of metoprolol in this study. The clinical relevance of this finding for hypertensive patients is unknown. Caution should be exercised with co-administration of venlafaxine and metoprolol.

Venlafaxine treatment has been associated with dose-related increases in blood pressure in some patients. In the concomitant administration of venlafaxine and such drugs is required. Venlafaxine appeared to reduce the blood pressure lowering effect of metoprolol in this study. The clinical relevance of this finding for hypertensive patients is unknown. Caution should be exercised with co-administration of venlafaxine and metoprolol.

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 11 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.

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.

Serotonergic Drugs: Based on the mechanism of action of venlafaxine and the potential for serotonin syndrome, caution is advised when venlafaxine is co-administered with other drugs that may affect the serotonergic neurotransmitter systems, such as triptans, SSRIs, other SNRIs, linezolid (an antibiotic which is a reversible non-selective MAOI), lithium, tramadol, or St. John's Wort (see **WARNINGS, Serotonin Syndrome**). If concomitant treatment of venlafaxine hydrochloride tablets with these drugs is warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases (see **WARNINGS, Serotonin Syndrome**). The concomitant use of venlafaxine hydrochloride tablets with tryptophan supplements is not recommended (see **WARNINGS, Serotonin Syndrome**).

Triptans: There have been rare postmarketing reports of serotonin syndrome with use of an SSRI and a triptan. If concomitant treatment of venlafaxine hydrochloride tablets with a triptan is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases (see **WARNINGS, Serotonin Syndrome**).

Electroconvulsive Therapy

There are no clinical data establishing the benefit of electroconvulsive therapy combined with venlafaxine hydrochloride tablets 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 an mg/m² 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

drug interactions with SNRIs or SSRI treatment or with other serotonergic drugs. These interactions have been associated with symptoms that include tremor, myoclonus, diaphoresis, nausea, vomiting, flushing, dizziness, hyperthermia with features resembling neuroleptic malignant syndrome, seizures, rigidity, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes that include extreme agitation progressing to delirium and coma. Based on the half-life of venlafaxine, at least 7 days should be allowed after stopping venlafaxine hydrochloride tablets before starting an MAOI (see **DOSAGE AND ADMINISTRATION**).

WARNINGS

Clinical Worsening and Suicide Risk
Patients with major depressive disorder (MDD), both adult and pediatric, may experience worsening of their depression and/or the emergence of suicidal ideation and behavior (suicidality) or unusual changes in behavior, whether or not they are taking antidepressant medications, and this risk may persist until significant remission occurs. Suicide is a known risk of depression and certain other psychiatric disorders, and these disorders themselves are the strongest predictors of suicide. There has been a long standing concern, however, that antidepressants may have a role in inducing worsening of depression and the emergence of suicidality in certain patients during the early phases of treatment. Pooled analyses of short-term placebo-controlled trials of antidepressant drugs (SSRIs and others) showed that these drugs increase the risk of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults (ages 18-24) with major depressive disorder (MDD) and other psychiatric disorders. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction with antidepressants compared to placebo in adults aged 65 and older.

The pooled analyses of placebo-controlled trials in children and adolescents with MDD, obsessive compulsive disorder (OCD), or other psychiatric disorders included a total of 24 short-term trials of 9 antidepressant drugs in over 4400 patients. The pooled analyses of placebo-controlled trials in adults with MDD or other psychiatric disorders included a total of 295 short-term trials (median duration of 2 months) of 11 antidepressant drugs in over 77,000 patients. There was considerable variation in risk of suicidality among drugs, but a tendency toward an increase in risk among the younger patients who were studied. There were differences in absolute risk of suicidality across the different indications, with the highest incidence in MDD. The risk differences (drug vs. placebo), however, were relatively stable within age strata and across indications. These risk differences (drug-placebo difference in the number of cases of suicidality per 1000 patients treated) are provided in Table 1.

Age Range	Drug-Placebo Difference in Number of Cases of Suicidality per 1000 Patients Treated
	Increases Compared to Placebo
<18	14 additional cases
18-24	5 additional cases
	Decreases Compared to Placebo
25-64	1 fewer case
>65	6 fewer cases

No suicides occurred in any of the pediatric trials. There were suicides in the adult trials, but the number was not sufficient to reach any conclusion about drug effect on suicide.

It is unknown whether the suicidality risk extends to longer-term use, i.e., beyond several months. However, there is substantial evidence from placebo-controlled maintenance trials in adults with depression that the use of antidepressants can delay the recurrence of depression.

All patients being treated with antidepressants for any indication should be monitored appropriately and observed closely for clinical worsening, suicidality, or unusual changes in behavior, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases.

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

Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients whose depression is persistently worse, or who are experiencing emergent suicidality or symptoms that might be precursors to worsening depression or suicidality, especially if these symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms. If the decision has been made to discontinue treatment, medication should be tapered, as rapidly as is feasible, but with recognition that abrupt discontinuation can be associated with certain symptoms (see **PRECAUTIONS and DOSAGE AND ADMINISTRATION: Discontinuation of Treatment with Venlafaxine Hydrochloride Tablets**, for a description of the risks of discontinuation of venlafaxine hydrochloride tablets).

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, unusual changes in behavior, and the other symptoms described above, as well as the emergence of suicidality, and to report such symptoms immediately to health care providers. Such monitoring should include daily observation by families and caregivers. Prescriptions for venlafaxine hydrochloride tablets should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose.

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

Serotonin Syndrome or Neuroleptic Malignant Syndrome (NMS)-like Reactions
The development of a potentially life-threatening serotonin syndrome or Neuroleptic Malignant Syndrome (NMS)-like reactions have been reported with SNRIs and SSRIs alone, including venlafaxine hydrochloride tablets treatment, but particularly with concomitant use of serotonergic drugs (including triptans) with drugs which impair metabolism of serotonin (including MAOIs), or with antipsychotics or other dopamine antagonists. Serotonin syndrome symptoms may include mental status changes (e.g., agitation, hallucinations, coma), autonomic instability (e.g., tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (e.g., hyperreflexia, incoordination) and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea). See **PRECAUTIONS, Drug Interactions**.

Serotonin syndrome, in its most severe form can resemble neuroleptic malignant syndrome, which includes hyperthermia, muscle rigidity, autonomic instability with possible rapid fluctuation of vital signs, and mental status changes. Patients should be monitored for the emergence of serotonin syndrome or NMS-like signs and symptoms.

The concomitant use of venlafaxine hydrochloride tablets with MAOIs used to treat depression is contraindicated (see **CONTRAINDICATIONS**). If concomitant treatment of venlafaxine hydrochloride tablets with a 5-hydroxytryptamine receptor agonist (triptan) is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases (see **PRECAUTIONS, Drug Interactions**).

The concomitant use of venlafaxine hydrochloride tablets with serotonin precursors (such as tryptophan) is not recommended (see **PRECAUTIONS, Drug Interactions**).

Treatment with venlafaxine hydrochloride tablets and any concomitant serotonergic or sympathomimetic agents, including antipsychotics, should be discontinued immediately if the above events occur and supportive symptomatic treatment should be initiated.

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 group 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 \geq 90 mm Hg and \geq 10 mm Hg above baseline for 3 consecutive visits) revealed a dose-dependent increase in the incidence of sustained hypertension for venlafaxine:

Treatment Group	Probability of Sustained Elevation in SDBP (Pool of Premarketing Venlafaxine Studies)
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).

(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/m³ basis, the maximum human daily dose. The no effect dose was 67 times (mg/kg) or 17 times (mg/m³) 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/ m³ basis.

Pregnancy

Toxicologic 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/m³ 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 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/m³) 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/m³ 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 venlafaxine hydrochloride tablets, 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-Active Drugs**). When treating a pregnant woman with venlafaxine hydrochloride tablets 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 hydrochloride tablets 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 venlafaxine hydrochloride tablets, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

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

Anyone considering the use of venlafaxine hydrochloride tablets in a child or adolescent must balance the potential risks with the clinical need.

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

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

Of the 2,897 patients in Phase 2 and Phase 3 depression studies with venlafaxine hydrochloride tablets, 12% (357) were 65 years of age or over. No clear differences in efficacy 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. SSRIs and SNRIs, including venlafaxine, have been associated with cases of clinically significant hyponatremia in elderly patients, who may be at greater risk for this adverse effect (see **PRECAUTIONS, Hyponatremia**).

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 (i.e., 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%	—
Dizziness	3%	—
Nervousness	2%	—
Dry mouth	2%	1%
Anxiety	2%	—
Gastrointestinal	6%	—
Nausea	2%	1%
Urogenital	—	—
Abnormal ejaculation	3%	—
Other	—	—
Headache	3%	1%
Asthenia	2%	—
Sweating	2%	—

¹ Percentages based on the number of males.

² 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 venlafaxine hydrochloride tablets (incidence of 5% or greater) and not seen at an equivalent incidence among placebo-treated patients (i.e., incidence for venlafaxine hydrochloride tablets 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 Venlafaxine Hydrochloride Tablets - 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 venlafaxine hydrochloride tablets-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 2 Treatment-Emergent Adverse Experience Incidence in 4- to 8-Week Placebo-Controlled Clinical Trials ¹			
Body System	Preferred Term	Venlafaxine Hydrochloride Tablets (n=1033)	Placebo (n=609)
Body as a Whole	Headache	25%	24%
	Asthenia	12%	6%
	Chills	8%	5%
	Chills	3%	-
	Chest pain	2%	1%
Cardiovascular	Trauma	2%	1%
	Vasodilatation	4%	3%
	Increased blood pressure/hypertension	2%	-
Dermatological	Tachycardia	2%	-
	Postural hypotension	1%	-
	Sweating	12%	3%
	Pruritus	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%	-
	Somnolence	23%	9%
Nervous System	Dry mouth	22%	11%
	Dizziness	19%	7%
	Insomnia	10%	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%

Body System	Preferred Term	Venlafaxine Hydrochloride Tablets (n=1033)	Placebo (n=609)
Respiration	Thinking abnormal	2%	1%
	Depersonalization	1%	—
	Depression	1%	—
	Urinary retention	1%	—
	Twitching	1%	—
	Yawn	1%	—
	Blurred vision	6%	2%
Special Senses	Taste perversion	2%	—
	Tinnitus	2%	—
	Mydriasis	2%	—
Urogenital System	Abnormal ejaculation/ Orgasm	12% ²	— ³
	Impotence	6% ²	— ³
	Urinary frequency	3%	2%
	Urination impaired	2%	—
	Orgasm disturbance	2%	— ³

¹ Events reported by at least 1% of patients treated with venlafaxine hydrochloride tablets are included, and are rounded to the nearest %. Events for which the venlafaxine hydrochloride tablets incidence was equal to or less than placebo are not listed in the table, but included the following: abdominal pain, pain, back pain, hip syndrome, fever, palpitation, increased appetite, myalgia, arthralgia, amnesia, hypesthesia, rhinitis, pharyngitis, sinusitis, cough increased, and dysmenorrhea⁴.

² Incidence less than 1%.

³ Incidence based on number of male patients.

⁴ Incidence based on number of female patients.

Dose Dependency of Adverse Events

A comparison of adverse event rates in a fixed-dose study comparing venlafaxine hydrochloride tablets 75, 225, and 375 mg/day with placebo revealed a dose dependency for some of the more common adverse events associated with venlafaxine hydrochloride tablets 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 venlafaxine hydrochloride tablets 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 3 Treatment-Emergent Adverse Experience Incidence in a Dose Comparison Trial				
Body System/ Preferred Term	Venlafaxine Hydrochloride Tablets (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%	14.8%	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%	18.0%	12.5%
Somnolence	4.3%	16.9%	16.9%	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 (e.g., dizziness and nausea), but less to other effects (e.g., abnormal ejaculation and dry mouth).

Vital Sign Changes

Venlafaxine hydrochloride tablets 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, venlafaxine hydrochloride tablets were 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 total blood pressure increase (see **WARNINGS**).

Laboratory Changes

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

Patients treated with venlafaxine hydrochloride 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**).

In an analysis of ECGs obtained in 769 patients treated with venlafaxine hydrochloride tablets and 450 patients treated with placebo in controlled clinical trials, the only statistically significant difference observed was for heart rate, i.e., a mean increase from baseline of 4 beats per minute for venlafaxine hydrochloride tablets. 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 venlafaxine hydrochloride tablets were administered to 2897 patients in Phase 2 and Phase 3 studies. In addition, in premarketing assessment of venlafaxine hydrochloride extended-release capsules, multiple doses were administered to 705 patients in Phase 3 major depressive disorder studies and venlafaxine hydrochloride tablets were administered to 96 patients. During its premarketing assessment, multiple doses of venlafaxine hydrochloride extended-release capsules were also administered to 1381 patients in Phase 3 GAD studies and 277 patients in Phase 3 Social Anxiety Disorder 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 (venlafaxine hydrochloride tablets 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 Table 2 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: **requent** 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: accidental injury, chest pain substernal, neck pain; **Infrequent:** face edema, intentional injury, malaise, moniliae, neck rigidity, pelvic pain, photosensitivity reaction, suicide attempt, withdrawal syndrome; **Rare:** angiodermatitis, bacteremia, carcinoma, cellulitis.

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, aortic, first-degree atrioventricular block, bigeminy, bradycardia, bundle branch block, capillary fragility, cardiovascular disorder (mitral valve and circulatory disturbance), cerebral ischemia, coronary artery disease, congestive heart failure, heart arrest, mucocutaneous hemorrhage, myocardial infarct, palpox.

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

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

Musculoskeletal system-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: 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, loss of consciousness, delusions, dementia, dystonia, facial paralysis, feeling drunk, abnormal gait, Guillain-Barre Syndrome, hyperchloredia, hypokinesia, impulse control difficulties, nurems, nystagmus, paranoid reaction, 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, maculopular 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, abnormal vision; **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), vaginitis; **Infrequent:** albuminuria, amenorrhea, urethritis, dysuria, hematuria, leukorrhea, menorrhagia, nocturia, bladder pain, breast pain, polyuria, pyuria, urinary incontinence, urinary urgency, vaginitis, hematuria; **Rare:** abortion, anuria, urinary bladder discharge, breast engorgement, breast enlargement, endometriosis, fibrocystic breast, calcium crystalluria, cervicitis, ovarian cyst, prolonged erection, gynecomasia (male), hypomenorrhea, kidney calculus, kidney pain, kidney function abnormal, female lactation⁵, mastitis, menopause, oliguria, orchitis, pyelonephritis, salpingitis, urolithiasis, uterine hemorrhage⁶, uterine spasm⁷, vaginal dryness⁸.

⁵Based 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 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**).

DRUG ABUSE AND DEPENDENCE

Controlled Substance Class

Venlafaxine hydrochloride tablets are not a controlled substance.

Physical and Psychological Dependence

In vitro studies revealed that venlafaxine has virtually no affinity for opiate, benzodiazepine, phenylcycidine (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 hydrochloride tablets have 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 hydrochloride tablets (e.g.,