VENLAFAXINE HYDROCHLORIDE- venlafaxine hydrochloride capsule, extended release
Proficient Rx LP

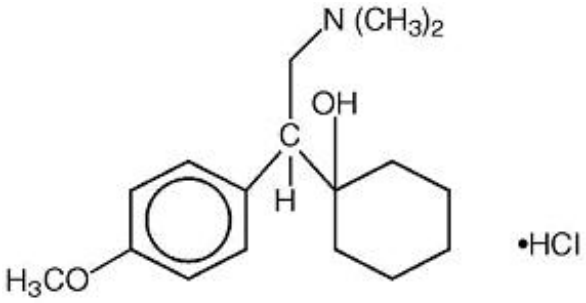
VENLAFAXINE HYDROCHLORIDE EXTENDED-RELEASE CAPSULES USP
Rx only

Suicidality and Antidepressant Drugs

Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of Major Depressive Disorder (MDD) and other psychiatric disorders. Anyone considering the use of venlafaxine hydrochloride extended-release capsules or any other antidepressant in a child, adolescent, or young adult must balance this risk with the clinical need. 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 in risk with antidepressants compared to placebo in adults aged 65 and older. Depression and certain other psychiatric disorders are themselves associated with increases in the risk of suicide. Patients of all ages who are started on antidepressant therapy should be monitored appropriately and observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. Venlafaxine hydrochloride extended-release capsules are not approved for use in pediatric patients (see WARNINGS, Clinical Worsening and Suicide Risk; PRECAUTIONS, Information for Patients; and PRECAUTIONS, Pediatric Use).

DESCRIPTION

Venlafaxine Hydrochloride Extended-Release Capsules USP for oral administration contain venlafaxine hydrochloride, USP 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. The structural formula is shown below.



venlafaxine hydrochloride

$C_{17}H_{27}NO_2$•HCl M.W. 313.87

Venlafaxine hydrochloride, USP 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.

Venlafaxine Hydrochloride Extended-Release Capsules USP are 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, USP equivalent to 37.5 mg, 75 mg, or 150 mg venlafaxine. Inactive ingredients consist of black iron oxide, dibutyl sebacate, ethylcellulose, gelatin, polyethylene glycol, povidone, propylene glycol, shellac, sugar spheres (which contain sucrose and corn starch), sunset yellow FCF FD&C yellow 6, talc, and titanium dioxide. The 37.5 mg capsules also contain D&C yellow 10 and potassium hydroxide, the 75 mg capsules also contain D&C yellow 10 and may contain potassium hydroxide, and the 150 mg capsules also contain potassium hydroxide.

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 venlafaxine hydrochloride extended-release capsules (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 venlafaxine hydrochloride tablets (immediate release) [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 venlafaxine hydrochloride extended-release capsule. Venlafaxine hydrochloride extended-release capsules, therefore, provide 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 venlafaxine hydrochloride extended-release 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 subjects 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 subjects compared to normal subjects. ODV elimination half-life was prolonged by about 60%, and clearance decreased by about 30% in cirrhotic subjects 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.

In a second study, venlafaxine was administered orally and intravenously in normal (n = 21) subjects, and in Child-Pugh A (n = 8) and Child-Pugh B (n = 11) subjects (mildly and moderately impaired, respectively). Venlafaxine oral bioavailability was increased 2 to 3 fold, oral elimination half-life was approximately twice as long and oral clearance was reduced by more than half, compared to normal subjects. In hepatically impaired subjects, ODV oral elimination half-life was prolonged by about 40%, while oral clearance for ODV was similar to that for normal subjects. A large degree of intersubject variability was noted.

Dosage adjustment is necessary in these hepatically impaired 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 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 venlafaxine hydrochloride extended-release capsule doses in a range 75 to 150 mg/day (mean dose for completers was 136 mg/day) and an 8 week study utilizing venlafaxine hydrochloride extended-release capsule doses in a range 75 to 225 mg/day (mean dose for completers was 177 mg/day) both demonstrated superiority of venlafaxine hydrochloride extended-release capsules 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, venlafaxine hydrochloride extended-release capsules were 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 venlafaxine hydrochloride tablets (immediate release) in a range of 150 to 375 mg/day (t.i.d. schedule) demonstrated superiority of venlafaxine hydrochloride tablets over placebo. The mean dose in completers was 350 mg/day.

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

In one longer-term study, adult outpatients meeting DSM-IV criteria for major depressive disorder who had responded during an 8 week open trial on venlafaxine hydrochloride extended-release capsules (75, 150, or 225 mg, qAM) were randomized to continuation of their same venlafaxine hydrochloride extended-release capsule 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 venlafaxine hydrochloride extended-release capsule treatment experienced significantly lower relapse rates over the subsequent 26 weeks compared with those receiving placebo.

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

Panic Disorder

The efficacy of venlafaxine hydrochloride extended-release capsules as a treatment for

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

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

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

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

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

INDICATIONS AND USAGE

Major Depressive Disorder

Venlafaxine Hydrochloride Extended-Release Capsules USP are indicated for the treatment of major depressive disorder.

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

A major depressive episode (DSM-IV) implies a prominent and relatively persistent (nearly every day for at least 2 weeks) depressed mood or the loss of interest or pleasure in

nearly all activities, representing a change from previous functioning, and includes the presence of at least five of the following nine symptoms during the same two-week period: depressed mood, markedly diminished interest or pleasure in usual activities, significant change in weight and/or appetite, insomnia or hypersomnia, psychomotor agitation or retardation, increased fatigue, feelings of guilt or worthlessness, slowed thinking or impaired concentration, a suicide attempt or suicidal ideation.

The efficacy of Venlafaxine Hydrochloride Tablets USP (immediate release) in the treatment of major depressive disorder in adult inpatients meeting diagnostic criteria for major depressive disorder with melancholia was established in a 4 week controlled trial (see **Clinical Trials**). The safety and efficacy of Venlafaxine Hydrochloride Extended-Release Capsules USP in hospitalized depressed patients have not been adequately studied.

The efficacy of Venlafaxine Hydrochloride Extended-Release Capsules USP 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 Venlafaxine Hydrochloride Tablets USP (immediate release) 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 Venlafaxine Hydrochloride Tablets USP/Venlafaxine Hydrochloride Extended-Release Capsules USP for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient (see **DOSAGE AND ADMINISTRATION**).

Panic Disorder

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

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

The efficacy of Venlafaxine Hydrochloride Extended-Release Capsules USP in the treatment of panic disorder was established in two 12 week placebo-controlled trials in adult outpatients with panic disorder (DSM-IV). The efficacy of Venlafaxine Hydrochloride Extended-Release Capsules USP in prolonging time to relapse in panic disorder among responders following 12 weeks of open-label acute treatment was demonstrated in a placebo-controlled study (see **CLINICAL PHARMACOLOGY, Clinical Trials**). Nevertheless, the physician who elects to use Venlafaxine Hydrochloride Extended-Release Capsules USP 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.

The use of MAOIs intended to treat psychiatric disorders with venlafaxine hydrochloride or within 7 days of stopping treatment with venlafaxine hydrochloride is contraindicated because of an increased risk of serotonin syndrome. The use of venlafaxine hydrochloride within 14 days of stopping an MAOI intended to treat psychiatric disorders is also contraindicated (see **WARNINGS** and **DOSAGE AND ADMINISTRATION**).

Starting venlafaxine hydrochloride in a patient who is being treated with MAOIs such as linezolid or intravenous methylene blue is also contraindicated because of an increased risk of serotonin syndrome (see **WARNINGS** and **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 to 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 the younger patients for almost all drugs 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**.

Table

Age Range	Drug-Placebo Difference in Number of Cases of Suicidality per 1000 Patients Treated
	Increases Compared to Placebo
< 18	14 additional cases
18 to 24	5 additional cases
	Decreases Compared to Placebo
25 to 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, and unusual changes in behavior, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases.

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**, **Discontinuing Venlafaxine Hydrochloride Extended-Release Capsules**, for a description of the risks of discontinuation of venlafaxine hydrochloride extended-release capsules).

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 extended-release capsules should be written for the smallest quantity of capsules 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 extended-release capsules are not approved for use in treating bipolar depression.

Serotonin Syndrome

The development of a potentially life-threatening serotonin syndrome has been reported with SNRIs and SSRIs, including venlafaxine hydrochloride extended-release capsules, alone but particularly with concomitant use of other serotonergic drugs (including triptans, tricyclic antidepressants, fentanyl, lithium, tramadol, tryptophan, buspirone, and St. John's Wort) and with drugs that impair metabolism of serotonin (in particular, MAOIs, both those intended to treat psychiatric disorders and also others, such as linezolid and intravenous methylene blue).

Serotonin syndrome symptoms may include mental status changes (e.g., agitation, hallucinations, delirium, and coma), autonomic instability (e.g., tachycardia, labile blood pressure, dizziness, diaphoresis, flushing, hyperthermia), neuromuscular symptoms (e.g., tremor, rigidity, myoclonus, hyperreflexia, incoordination), seizures, and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea). Patients should be monitored for the emergence of serotonin syndrome.

The concomitant use of venlafaxine hydrochloride extended-release capsules with MAOIs intended to treat psychiatric disorders is contraindicated. Venlafaxine hydrochloride extended-release capsules should also not be started in a patient who is being treated with MAOIs such as linezolid or intravenous methylene blue. All reports with methylene blue that provided information on the route of administration involved intravenous administration in the dose range of 1 mg/kg to 8 mg/kg. No reports involved the administration of methylene blue by other routes (such as oral tablets or local tissue injection) or at lower doses. There may be circumstances when it is necessary to initiate treatment with a MAOI such as linezolid or intravenous methylene blue in a patient taking venlafaxine hydrochloride extended-release capsules. Venlafaxine hydrochloride extended-release capsules should be discontinued before initiating treatment with the MAOI (see **CONTRAINDICATIONS** and **DOSAGE AND ADMINISTRATION**).

If concomitant use of venlafaxine hydrochloride extended-release capsules with other

serotonergic drugs, including triptans, tricyclic antidepressants, fentanyl, lithium, tramadol, buspirone, tryptophan, and St. John's Wort is clinically warranted, patients should be made aware of a potential increased risk of serotonin syndrome, particularly during treatment initiation and dose increases.

Treatment with venlafaxine hydrochloride extended-release capsules and any concomitant serotonergic agents should be discontinued immediately if the above events occur and supportive symptomatic treatment should be initiated.

Angle-Closure Glaucoma: The pupillary dilation that occurs following use of many antidepressant drugs including Venlafaxine hydrochloride extended-release capsules may trigger an angle closure attack in a patient with anatomically narrow angles who does not have a patent iridectomy.

Sustained Hypertension

Venlafaxine hydrochloride extended-release capsule treatment is associated with 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) (see Table 2).

An analysis for patients in venlafaxine hydrochloride tablet (immediate release) studies meeting criteria for sustained hypertension revealed a dose-dependent increase in the incidence of sustained hypertension for venlafaxine hydrochloride tablets (immediate release) (see **Error! Hyperlink reference not valid.**).

An insufficient number of patients received mean doses of venlafaxine hydrochloride extended-release capsules over 300 mg/day to fully evaluate the incidence of sustained increases in blood pressure at these higher doses.

Table 1: Number (%) of Sustained Elevations in SDBP in Venlafaxine Hydrochloride Extended-Release Capsules Premarketing Studies by Indication

MDD (75 to 375 mg/day)	Panic Disorder (75 to 225 mg/day)
19/705 (3)	9/973 (0.9)

MDD = major depressive disorder

Table 2: Incidence (%) of Sustained Elevations in SDBP in Venlafaxine Hydrochloride Tablet Immediate Release Studies

Venlafaxine Hydrochloride Tablets mg/day	Incidence
< 100	3%
> 100 to ≤ 200	5%
> 200 to ≤ 300	7%
> 300	13%

In premarketing major depressive disorder studies, 0.7% (5/705) of the venlafaxine hydrochloride extended-release capsule-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 panic disorder studies up to 12 weeks, 0.5% (5/1001) of the venlafaxine hydrochloride extended-release capsule-treated patients discontinued treatment because of elevated blood pressure. In these patients, the blood pressure increases were in a modest range (7 to 19 mm Hg, SDBP).

Sustained increases of SDBP could have adverse consequences. Cases of elevated blood pressure requiring immediate treatment have been reported in postmarketing experience. Preexisting hypertension should be controlled before treatment with venlafaxine. It is recommended that patients receiving venlafaxine hydrochloride extended-release capsules 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.

Elevations in Systolic and Diastolic Blood Pressure

In placebo-controlled premarketing studies, there were changes in mean blood pressure (see Table 4 for mean changes in supine systolic and supine diastolic blood pressure). Across most indications, a dose-related increase in supine systolic and diastolic blood pressure was evident in venlafaxine hydrochloride extended-release capsule-treated patients.

Table 3: Final On-Therapy Mean Changes From Baseline in Supine Systolic and Diastolic Blood Pressure (mm Hg) Results by Indication, Study Duration, and Dose in Placebo-Controlled Trials

	Venlafaxine Hydrochloride Extended-Release Capsules mg/day				Placebo	
	≤ 75		> 75			
	SSBP*	SDBP†	SSBP	SDBP	SSBP	SDBP
Major Depressive Disorder						
8 to 12 weeks	-0.28	0.37	2.93	3.56	-1.08	-0.10
Panic Disorder						
10 to 12 weeks	-1.15	0.97	-0.36	0.16	-1.29	-0.99

* Supine Systolic Blood Pressure
† Supine Diastolic Blood Pressure

Across all clinical trials in MDD, 1.4% of patients in the venlafaxine hydrochloride extended-release capsule-treated groups experienced a ≥ 15 mm Hg increase in supine diastolic blood pressure with blood pressure ≥ 105 mm Hg compared to 0.9% of patients in the placebo groups. Similarly, 1% of patients in the venlafaxine hydrochloride extended-release capsule-treated groups experienced a ≥ 20 mm Hg increase in supine systolic blood pressure with blood pressure ≥ 180 mm Hg compared to 0.3% of patients in the placebo groups.

PRECAUTIONS

General

Discontinuation of Treatment With Venlafaxine Hydrochloride Extended-Release Capsules

Discontinuation symptoms have been systematically evaluated in patients taking venlafaxine, to include 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, impaired coordination and balance, diarrhea, dizziness, dry mouth, dysphoric mood, fasciculation, fatigue, flu-like symptoms, headaches, hypomania, insomnia, nausea, nervousness, nightmares, sensory disturbances (including shock-like electrical sensations), somnolence, sweating, tremor, vertigo, and vomiting.

During marketing of venlafaxine hydrochloride extended-release capsules, 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 venlafaxine hydrochloride extended-release capsules. 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 venlafaxine hydrochloride extended-release capsules than with placebo in pooled analyses of short-term major depressive disorder and panic disorder studies as shown in **Table 5**.

Table 4: Incidence of Insomnia and Nervousness in Placebo-Controlled Major Depressive Disorder and Panic Disorder Trials

	Major Depressive Disorder		Panic Disorder	
	Venlafaxine Hydrochloride Extended-Release Capsules	Placebo	Venlafaxine Hydrochloride Extended-Release Capsules	Placebo
Symptom	n = 357	n = 285	n = 1001	n = 662
Insomnia	17%	11%	17%	9%

Nervousness	10%	5%	4%	6%

Insomnia and nervousness each led to drug discontinuation in 0.9% of the patients treated with venlafaxine hydrochloride extended-release capsules in major depressive disorder studies.

In panic disorder trials, insomnia and nervousness led to drug discontinuation in 1% and 0.1%, respectively, of the patients treated with venlafaxine hydrochloride extended-release capsules up to 12 weeks.

Changes in Weight

Adult Patients

A loss of 5% or more of body weight occurred in 7% of venlafaxine hydrochloride extended-release capsule-treated and 2% of placebo-treated patients in the short-term placebo-controlled major depressive disorder trials. The discontinuation rate for weight loss associated with venlafaxine hydrochloride extended-release capsules was 0.1% in major depressive disorder studies. In placebo-controlled panic disorder trials, 3% of the venlafaxine hydrochloride extended-release capsule-treated and 2% of the placebo-treated patients sustained a loss of 7% or more of body weight during up to 12 weeks of treatment. None of the patients receiving venlafaxine hydrochloride extended-release capsules in panic disorder studies discontinued for weight loss.

The safety and efficacy of venlafaxine therapy in combination with weight loss agents, including phentermine, have not been established. Coadministration of venlafaxine hydrochloride extended-release capsules and weight loss agents is not recommended. Venlafaxine hydrochloride extended-release capsules 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 to 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), venlafaxine hydrochloride extended-release capsule-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 the MDD study (18% of venlafaxine hydrochloride extended-release capsule-treated patients vs. 3.6% of placebo-treated patients; $p < 0.001$) (see **PRECAUTIONS**, **General**, *Changes in Appetite*).

The risks associated with longer-term venlafaxine hydrochloride extended-release capsule use were assessed in an open-label MDD 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 MDD studies, venlafaxine hydrochloride extended-release capsule-treated patients grew an average of 0.8 cm (n = 146), while placebo-treated patients grew an average of 0.7 cm (n = 147). In the six-month, open-label MDD study, children and adolescents had height increases that were less than expected based on data from age- and sex-matched peers. The difference between observed growth rates and expected growth rates was larger for children (< 12 years old) than for adolescents (≥ 12 years old).

Changes in Appetite

Adult Patients

Treatment-emergent anorexia was more commonly reported for venlafaxine hydrochloride extended-release capsule-treated (8%) than placebo-treated patients (4%) in the pool of short-term, double-blind, placebo-controlled major depressive disorder studies. The discontinuation rate for anorexia associated with venlafaxine hydrochloride extended-release capsules was 1.0% in major depressive disorder studies. Treatment-emergent anorexia was more commonly reported for venlafaxine hydrochloride extended-release capsule-treated (8%) than placebo-treated patients (3%) in the pool of short-term, double-blind, placebo-controlled panic disorder studies. The discontinuation rate for anorexia was 0.4% for patients receiving venlafaxine hydrochloride extended-release capsules for up to 12 weeks in panic disorder studies.

Pediatric Patients

Decreased appetite has been observed in pediatric patients receiving venlafaxine hydrochloride extended-release capsules. In the placebo-controlled trials for MDD, 10% of patients aged 6 to 17 treated with venlafaxine hydrochloride extended-release capsules for up to eight 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 premarketing major depressive disorder studies, mania or hypomania occurred in 0.3% of venlafaxine hydrochloride extended-release capsule-treated patients and no placebo patients. In premarketing panic disorder studies, 0.1% of venlafaxine hydrochloride extended-release capsules-treated patients and no placebo-treated patients experienced mania or hypomania. In all premarketing major depressive disorder trials with venlafaxine hydrochloride tablets (immediate release), mania or hypomania occurred in 0.5% of venlafaxine-treated patients compared with no 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, venlafaxine hydrochloride extended-release capsules should be used cautiously in patients with a history of mania.

Hyponatremia

Hyponatremia may occur as a result of treatment with SSRIs and SNRIs, including

venlafaxine hydrochloride extended-release capsules. In many cases, this hyponatremia appears to be the result of the syndrome of inappropriate antidiuretic hormone secretion (SIADH). Cases with serum sodium lower than 110 mmol/L have been reported. Elderly patients may be at greater risk of developing hyponatremia 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 extended-release capsules should be considered in patients with symptomatic hyponatremia and appropriate medical intervention should be instituted.

Signs and symptoms of hyponatremia 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

During premarketing experience, no seizures occurred among 705 venlafaxine hydrochloride extended-release capsule-treated patients in the major depressive disorder studies. In panic disorder studies, 1 seizure occurred among 1,001 venlafaxine hydrochloride extended-release capsule-treated patients. In all premarketing major depressive disorder trials with venlafaxine hydrochloride tablets (immediate release), seizures were reported at various doses in 0.3% (8/3082) of venlafaxine-treated patients. Venlafaxine hydrochloride extended-release capsules, 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

SSRIs and SNRIs, including venlafaxine hydrochloride extended-release capsules, may increase the risk of bleeding events, ranging from ecchymoses, hematomas, epistaxis, petechiae, and gastrointestinal hemorrhage to life-threatening hemorrhage. Concomitant use of aspirin, non-steroidal anti-inflammatory drugs, warfarin, and other anti-coagulants or other drugs known to affect platelet function may add to this risk. Case reports and epidemiological studies (case-control and cohort design) have demonstrated an association between use of drugs that interfere with serotonin reuptake and the occurrence of gastrointestinal bleeding.

Patients should be cautioned about the risk of bleeding associated with the concomitant use of venlafaxine hydrochloride extended-release capsules and NSAIDs, aspirin, or other drugs that affect coagulation.

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.

Interstitial Lung Disease and Eosinophilic Pneumonia

Interstitial lung disease and eosinophilic pneumonia associated with venlafaxine therapy have been rarely reported. The possibility of these adverse events should be considered

in venlafaxine-treated patients who present with progressive dyspnea, cough or chest discomfort. Such patients should undergo a prompt medical evaluation, and discontinuation of venlafaxine therapy should be considered.

Use in Patients With Concomitant Illness

Premarketing experience with venlafaxine in patients with concomitant systemic illness is limited. Caution is advised in administering venlafaxine hydrochloride extended-release capsules 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 venlafaxine hydrochloride extended-release capsules and 220 patients who received placebo in 8 to 12 week double-blind, placebo-controlled trials in major depressive disorder, and for 661 patients who received venlafaxine hydrochloride extended-release capsules and 395 patients who received placebo in three 10 to 12 week double-blind, placebo-controlled trials in panic disorder. The mean change from baseline in corrected QT interval (QT_C) for venlafaxine hydrochloride extended-release capsule-treated patients in major depressive disorder studies was increased relative to that for placebo-treated patients (increase of 4.7 msec for venlafaxine hydrochloride extended-release capsules and decrease of 1.9 msec for placebo). The mean change from baseline in QT_C interval for venlafaxine hydrochloride extended-release capsule-treated patients in the panic disorder studies was increased relative to that for placebo-treated patients (increase of 1.5 msec for venlafaxine hydrochloride extended-release capsules and decrease of 0.7 msec for placebo).

In these same trials, the mean change from baseline in heart rate for venlafaxine hydrochloride extended-release capsule-treated patients in the major depressive disorder studies was significantly higher than that for placebo (a mean increase of 4 beats per minute for venlafaxine hydrochloride extended-release capsules and 1 beat per minute for placebo). The mean change from baseline in heart rate for venlafaxine hydrochloride extended-release capsule-treated patients in the panic disorder studies was significantly higher than that for placebo (a mean increase of 3 beats per minute for venlafaxine hydrochloride extended-release capsules and a mean decrease of less than 1 beat per minute for placebo).

In a flexible-dose study, with venlafaxine hydrochloride tablet (immediate release) doses in the range of 200 to 375 mg/day and mean dose greater than 300 mg/day, venlafaxine hydrochloride tablet-treated patients had a mean increase in heart rate of 8.5 beats per minute compared with 1.7 beats per minute in the placebo group.

As increases in heart rate were observed, caution should be exercised in patients whose underlying medical conditions might be compromised by increases in heart rate (e.g., patients with hyperthyroidism, heart failure, or recent myocardial infarction).

Evaluation of the electrocardiograms for 769 patients who received venlafaxine hydrochloride tablets (immediate release) 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**). Venlafaxine hydrochloride extended-release capsules, like all drugs effective in the treatment of major depressive disorder, should be used with caution in such patients.

Information for Patients

Prescribers or other health professionals should inform patients, their families, and their caregivers about the benefits and risks associated with treatment with venlafaxine hydrochloride extended-release capsules 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 venlafaxine hydrochloride extended-release capsules. The prescriber or health professional should instruct patients, their families, and their caregivers to read the Medication Guide and should assist them in understanding its contents. Patients should be given the opportunity to discuss the contents of the Medication Guide and to obtain answers to any questions they may have. The complete text of the Medication Guide is reprinted at the end of this document.

Patients should be advised of the following issues and asked to alert their prescriber if these occur while taking venlafaxine hydrochloride extended-release capsules.

Clinical Worsening and Suicide Risk

Patients, their families, and their caregivers should be encouraged to be alert to the emergence of anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, mania, other unusual changes in behavior, worsening of depression, and suicidal ideation, especially early during antidepressant treatment and when the dose is adjusted up or down. Families and caregivers of patients should be advised to 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 possibly changes in the medication.

Interference With Cognitive and Motor Performance

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

Concomitant Medication

Patients should be advised to inform their physicians if they are taking, or plan to take,

any prescription or over-the-counter drugs, including herbal preparations 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 extended-release capsules and triptans, tramadol, tryptophan supplements or other serotonergic agents (see **CONTRAINDICATIONS** and **WARNINGS**, **Serotonin Syndrome** and **PRECAUTIONS**, **Drug Interactions**, *CNS-Active Drugs*, Serotonergic Drugs).

Patients should be advised that taking venlafaxine hydrochloride extended-release capsules can cause mild pupillary dilation, which in susceptible individuals, can lead to an episode of angle closure glaucoma. Preexisting glaucoma is almost always open-angle glaucoma because angle closure glaucoma, when diagnosed, can be treated definitively with iridectomy. Open-angle glaucoma is not a risk factor for angle closure glaucoma. Patients may wish to be examined to determine whether they are susceptible to angle closure, and have a prophylactic procedure (e.g., iridectomy), if they are susceptible.

Patients should be cautioned about the concomitant use of venlafaxine hydrochloride extended-release capsules and NSAIDs, aspirin, warfarin, or other drugs that affect coagulation since combined use of 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 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 preexisting 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 venlafaxine hydrochloride extended-release capsules to a patient taking 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 also shown that concurrent use of an NSAID or aspirin may potentiate this risk of bleeding. Altered 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 hydrochloride extended-release capsules are 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 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 **CLINICAL PHARMACOLOGY**, *Metabolism and Excretion*). Therefore, no dosage adjustment is required when venlafaxine is coadministered with a CYP2D6 inhibitor.

Ketoconazole

A pharmacokinetic study with ketoconazole 100 mg b.i.d. with a single dose of venlafaxine 50 mg in extensive metabolizers (EM; n = 14) and 25 mg in poor metabolizers (PM; n = 6) of CYP2D6 resulted in higher plasma concentrations of both venlafaxine and O-desmethylvenlafaxine (ODV) in most subjects following administration of ketoconazole. Venlafaxine C_{max} increased by 26% in EM subjects and 48% in PM subjects. C_{max} values for ODV increased by 14% and 29% in EM and PM subjects, respectively.

Venlafaxine AUC increased by 21% in EM subjects and 70% in PM subjects (range in PMs -2% to 206%), and AUC values for ODV increased by 23% and 33% in EM and PM (range in PMs -38% to 105%) subjects, respectively. Combined AUCs of venlafaxine and 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.

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.

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 to 40% without altering the plasma concentrations of its active metabolite, α-hydroxymetoprolol. Metoprolol did not alter the pharmacokinetic profile of venlafaxine or its active metabolite, O-desmethylvenlafaxine.

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 coadministration of venlafaxine and metoprolol.

Venlafaxine treatment has been associated with dose-related increases in blood pressure in some patients. It is recommended that patients receiving venlafaxine hydrochloride extended-release capsules have regular monitoring of blood pressure (see **WARNINGS**).

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, WARNINGS,** and **DOSAGE AND ADMINISTRATION**.

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 (see **CONTRAINDICATIONS** and **WARNINGS**, **Serotonin Syndrome**).

Serotonergic Drugs

See **CONTRAINDICATIONS**, **WARNINGS**, and **DOSAGE AND ADMINISTRATION**.

Triptans

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

Drug-Laboratory Test Interactions

False-positive urine immunoassay screening tests for phencyclidine (PCP) and amphetamine have been reported in patients taking venlafaxine. This is due to lack of specificity of the screening tests. False positive test results may be expected for several days following discontinuation of venlafaxine therapy. Confirmatory tests, such as gas chromatography/mass spectrometry, will distinguish venlafaxine from PCP and amphetamine.

Electroconvulsive Therapy

There are no clinical data establishing the benefit of electroconvulsive therapy combined with 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 of venlafaxine in rats showed no adverse effects on male or female fertility at oral doses of up to 2 times the maximum recommended human dose of 225 mg/day on a mg/m^2 basis.

However, reduced fertility was observed in a study in which male and female rats were treated with O-desmethylvenlafaxine (ODV), the major human metabolite of venlafaxine, prior to and during mating and gestation. This occurred at an ODV exposure (AUC) approximately 2 to 3 times that associated with a human venlafaxine dose of 225 mg/day.

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.

Nonteratogenic Effects

Neonates exposed to venlafaxine hydrochloride extended-release capsules, 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 venlafaxine hydrochloride extended-release capsules 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 venlafaxine hydrochloride extended-release capsules, 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 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 extended-release capsules 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 capsules' 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 extended-release capsules, 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 capsule 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 to 17), the occurrence of blood pressure and cholesterol increases considered to be clinically relevant in pediatric patients was similar to that observed in adult patients. Consequently, the precautions for adults apply to pediatric patients (see **WARNINGS**, **Sustained Hypertension** and **PRECAUTIONS**, **General**, *Serum Cholesterol Elevation*).

Geriatric Use

Approximately 4% (14/357) and 2% (16/1001) of venlafaxine hydrochloride extended-release capsule-treated patients in placebo-controlled premarketing major depressive disorder and panic disorder trials, respectively, were 65 years of age or over. Of 2,897 venlafaxine hydrochloride tablet-treated (immediate release) 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. SSRIs and SNRIs, including venlafaxine hydrochloride extended-release capsules have been associated with cases of clinically significant hyponatremia in elderly patients, who may be at greater risk for this adverse event (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

The information included in the **Adverse Findings Observed in Short-Term, Placebo-Controlled Studies With Venlafaxine Hydrochloride Extended-Release Capsules** 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), and on data up to 12 weeks from a pool of four controlled clinical trials in panic disorder. Information on additional adverse events associated with venlafaxine hydrochloride extended-release capsules in the entire development program for the formulation and with venlafaxine hydrochloride tablets (immediate release) is included in the **Other Adverse Events Observed During the Premarketing Evaluation of Venlafaxine Hydrochloride Tablets and Venlafaxine Hydrochloride Extended-Release Capsules** subsection (see also **WARNINGS** and **PRECAUTIONS**).

Adverse Findings Observed in Short-Term, Placebo-Controlled Studies With Venlafaxine Hydrochloride Extended-Release Capsules

Adverse Events Associated With Discontinuation of Treatment

Approximately 11% of the 357 patients who received 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 7% of the 1,001 patients who received venlafaxine hydrochloride extended-release capsules in placebo-controlled clinical trials for panic disorder discontinued treatment due to an adverse experience, compared with 6% of the 662 placebo-treated patients in those studies. The most common events leading to discontinuation and considered to be drug-related (i.e., leading to discontinuation in at least 1% of the venlafaxine hydrochloride extended-release capsule-treated patients at a rate at least twice that of placebo) are shown in **Table 6**.

Table 5: Common Adverse Events Leading to Discontinuation of Treatment in Placebo-Controlled Trials*

	Percentage of Patients Discontinuing Due to Adverse Event			
Adverse Event	**Major Depressive Disorder Indication†**		**Panic Disorder Indication**	
	Venlafaxine Hydrochloride Extended-Release Capsules	**Placebo**	**Venlafaxine Hydrochloride Extended-Release Capsules**	**Placebo**
	n = 357	**n = 285**	**n = 1001**	**n = 662**
Body as a Whole				
Asthenia	--	--	1%	0%
Headache	--	--	--	--
Digestive System				
Nausea	4%	< 1%	2%	< 1%
Anorexia	1%	< 1%	--	--
Dry Mouth	1%	0%	--	--
Vomiting	--	--	--	--
Nervous System				
Dizziness	2%	1%	--	--
Insomnia	1%	< 1%	1%	< 1%
Somnolence	2%	< 1%	--	--
Nervousness	--	--	--	--
Tremor	--	--	--	--
Skin				
Sweating	--	--	--	--
Urogenital System				
Impotence‡	--	--	--	--

* Two of the major depressive disorder studies were flexible dose and one was fixed dose. Two of the panic disorder studies were flexible dose and two were fixed dose.

† 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 venlafaxine hydrochloride extended-release capsule-treated patients (% venlafaxine hydrochloride extended-release capsules [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%).

‡ Incidence is based on the number of men (venlafaxine hydrochloride extended-release capsules = 454, placebo = 357).

Adverse Events Occurring at an Incidence of 2% or More Among Venlafaxine Hydrochloride Extended-Release Capsule-Treated Patients

Tables 7 and 10 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), and of panic disorder (up to 12 weeks; dose range of 37.5 to 225 mg/day), respectively, in 2% or more of patients treated with venlafaxine hydrochloride extended-release capsules where the incidence in patients treated with venlafaxine hydrochloride extended-release capsules 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 7 and 10

Major Depressive Disorder

Note in particular the following adverse events that occurred in at least 5% of the venlafaxine hydrochloride extended-release capsule patients and at a rate at least twice that of the placebo group for all placebo-controlled trials for the major depressive disorder indication (**Table 7**): 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 venlafaxine hydrochloride extended-release capsule-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.

Panic Disorder

Note in particular the following adverse events that occurred in at least 5% of the venlafaxine hydrochloride extended-release capsule patients and at a rate at least twice that of the placebo group for 4 placebo-controlled trials for the panic disorder indication (**Table 10**): gastrointestinal complaints (anorexia, constipation, dry mouth), CNS complaints (somnolence, tremor), abnormalities of sexual function (abnormal ejaculation), and sweating.

Table 6: Treatment-Emergent Adverse Event Incidence in Short-Term Placebo-Controlled Venlafaxine Hydrochloride Extended-Release Capsule Clinical Trials in Patients With Major Depressive Disorder[*†]

Body System	% Reporting Event	
	Venlafaxine Hydrochloride	Placebo

	Extended-Release Capsules	
Preferred Term	(n = 357)	(n = 285)
Body as a Whole		
Asthenia	8%	7%
Cardiovascular System		
Vasodilatation‡	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§	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¶	4%	< 1%
Urogenital System		
Abnormal Ejaculation (male)#,Þ	16%	< 1%
Impotence Þ	4%	< 1%
Anorgasmia (female)ß,à	3%	< 1%

* Incidence, rounded to the nearest %, for events reported by at least 2% of patients treated with venlafaxine hydrochloride extended-release capsules, 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.

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

‡ Mostly “hot flashes.”

§ Mostly “vivid dreams,” “nightmares,” and “increased dreaming.”
¶ Mostly “blurred vision” and “difficulty focusing eyes.”
# Mostly “delayed ejaculation.”
Þ Incidence is based on the number of male patients.
ß Mostly “delayed orgasm” or “anorgasmia.”
à Incidence is based on the number of female patients.

Table 7: Treatment-Emergent Adverse Event Incidence in Short-Term Placebo-Controlled Venlafaxine Hydrochloride Extended-Release Capsule Clinical Trials in Panic Disorder Patients*†

	% Reporting Event	
Body System Preferred Term	**Venlafaxine Hydrochloride Extended-Release Capsules** (n = 1001)	**Placebo** (n = 662)
Body as a Whole		
Asthenia	10%	8%
Cardiovascular System		
Hypertension	4%	3%
Vasodilatation‡	3%	2%
Digestive System		
Nausea	21%	14%
Dry Mouth	12%	6%
Constipation	9%	3%
Anorexia§	8%	3%
Nervous System		
Insomnia	17%	9%
Somnolence	12%	6%
Dizziness	11%	10%
Tremor	5%	2%
Libido Decreased	4%	2%
Skin		
Sweating	10%	2%
Urogenital System		
Abnormal Ejaculation¶,#	8%	< 1%
Impotence#	4%	< 1%
Orgasmic Dysfunction Þ,ß	2%	< 1%

* Adverse events for which the venlafaxine hydrochloride extended-release capsules reporting rate was less than or equal to the placebo rate are not included. These events are: abdominal pain, abnormal vision, accidental injury, anxiety, back pain, diarrhea, dysmenorrhea, dyspepsia, flu syndrome, headache, infection, nervousness, pain, paresthesia, pharyngitis, rash, rhinitis, and vomiting.
† < 1% means greater than zero but less than 1%.
‡ Mostly “hot flushes.”
§ Mostly “decreased appetite” and “loss of appetite.”
¶ Includes “delayed or retarded ejaculation” and “anorgasmia.”
# Percentage based on the number of males (venlafaxine hydrochloride extended-release capsules = 335, placebo = 238).
Þ Includes “anorgasmia” and “delayed orgasm.”

ß Percentage based on the number of females (venlafaxine hydrochloride extended-release capsules = 666, placebo = 424).

Vital Sign Changes

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. Venlafaxine hydrochloride extended-release capsules treatment for up to 12 weeks in premarketing placebo-controlled panic disorder trials was associated with a mean final on-therapy increase in pulse rate of approximately 1 beat per minute, compared with a decrease of less than 1 beat per minute for placebo (see **WARNINGS**, **Sustained Hypertension** and **Elevations in Systolic and Diastolic Blood Pressure** for effects on blood pressure).

In a flexible-dose study, with venlafaxine hydrochloride tablet (immediate release) 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

Serum Cholesterol

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. Venlafaxine hydrochloride extended-release capsules treatment for up to 12 weeks in premarketing placebo-controlled panic disorder trials was associated with mean final on-therapy increases in serum cholesterol concentration of approximately 5.8 mg/dL compared with a mean final decrease of 3.7 mg/dL for placebo.

Patients treated with venlafaxine hydrochloride tablets (immediate-release) 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*).

Serum Triglycerides

Venlafaxine hydrochloride extended-release capsules treatment for up to 12 weeks in pooled premarketing Panic Disorder trials was associated with a mean final on-therapy increase in fasting serum triglyceride concentration of approximately 5.9 mg/dL, compared with a mean final increase of 0.9 mg/dL for placebo. Venlafaxine hydrochloride extended-release capsules treatment for up to 6 months in a premarketing Panic Disorder trial was associated with a mean final on-therapy increase

in fasting serum triglyceride concentration of approximately 9.3 mg/dL, compared with a mean final on-therapy decrease of 0.3 mg/dL for placebo.

ECG Changes

In a flexible-dose study, with venlafaxine hydrochloride tablet (immediate release) 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**, *Use in Patients With Concomitant Illness*.)

Other Adverse Events Observed During the Premarketing Evaluation of Venlafaxine Hydrochloride Tablets and Venlafaxine Hydrochloride Extended-Release Capsules

During their premarketing assessment, multiple doses of venlafaxine hydrochloride extended-release capsules 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 1314 patients in Phase 3 panic disorder studies. In addition, in premarketing assessment of venlafaxine hydrochloride tablets, 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 (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 7212 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 7 and 10** 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, granuloma.

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

Digestive system - **Frequent:** increased appetite; **Infrequent:** bruxism, colitis, dysphagia, tongue edema, eructation, esophagitis, gastritis, gastroenteritis, gastrointestinal ulcer, gingivitis, glossitis, rectal hemorrhage, hemorrhoids, melena, oral moniliasis, stomatitis, mouth ulceration; **Rare:** abdominal distension, biliary pain, cheilitis, cholecystitis, cholelithiasis, esophageal spasms, duodenitis, hematemesis, gastroesophageal reflux disease, gastrointestinal hemorrhage, gum hemorrhage, hepatitis, ileitis, jaundice, intestinal obstruction, liver tenderness, parotitis, periodontitis, proctitis, rectal disorder, salivary gland enlargement, increased salivation, soft stools, tongue discoloration.

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

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

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

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

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

increased, torticollis.

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

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

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

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

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

Postmarketing Reports

Adverse Events

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, angioedema, aplastic anemia, catatonia, congenital anomalies, impaired coordination and balance, 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; toxic epidermal necrolysis/Stevens-Johnson syndrome, erythema multiforme, extrapyramidal symptoms (including dyskinesia and tardive dyskinesia), angle-closure glaucoma, 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), interstitial lung disease, involuntary movements, LDH increased, neutropenia, night sweats, pancreatitis, pancytopenia, panic, prolactin increased, renal failure,

rhabdomyolysis, 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).

Drug Interactions

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

Venlafaxine hydrochloride extended-release capsules are not a controlled substance.

Physical and Psychological Dependence

In vitro studies revealed that venlafaxine has virtually no affinity for opiate, benzodiazepine, phencyclidine (PCP), or N-methyl-D-aspartic acid (NMDA) receptors.

Venlafaxine was not found to have any significant CNS stimulant activity in rodents. In primate drug discrimination studies, venlafaxine showed no significant stimulant or depressant abuse liability.

Discontinuation effects have been reported in patients receiving venlafaxine (see **DOSAGE AND ADMINISTRATION**).

While venlafaxine has not been systematically studied in clinical trials for its potential for abuse, there was no indication of drug-seeking behavior in the clinical trials. However, it is not possible to predict on the basis of premarketing experience the extent to which a CNS active drug will be misused, diverted, and/or abused once marketed. Consequently, physicians should carefully evaluate patients for history of drug abuse and follow such patients closely, observing them for signs of misuse or abuse of venlafaxine (e.g., development of tolerance, incrementation of dose, drug-seeking behavior).

OVERDOSAGE

Human Experience

Among the patients included in the premarketing evaluation of venlafaxine hydrochloride extended-release capsules, there were 2 reports of acute overdosage with venlafaxine hydrochloride extended-release capsules in major depressive disorder trials, either alone or in combination with other drugs. One patient took a combination of 6 g of venlafaxine hydrochloride extended-release capsules 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 venlafaxine hydrochloride extended-release capsules. This patient reported paresthesia of all four limbs but recovered without sequelae.

There were 2 reports of acute overdose with venlafaxine hydrochloride extended-release capsules in panic disorder trials. One patient took 0.675 g of venlafaxine

hydrochloride extended-release capsules once, and the other patient took 0.45 g of venlafaxine hydrochloride extended-release capsules for 2 days. No signs or symptoms were associated with either overdose, and no actions were taken to treat them.

Among the patients included in the premarketing evaluation with venlafaxine hydrochloride tablets (immediate release), 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 mcg/mL, respectively, and the peak plasma levels of O-desmethylvenlafaxine were 3.37 and 1.30 mcg/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 QT_C 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. The most commonly reported events in overdosage include tachycardia, changes in level of consciousness (ranging from somnolence to coma), mydriasis, seizures, and vomiting. Electrocardiogram changes (e.g., prolongation of QT interval, bundle branch block, QRS prolongation), ventricular tachycardia, bradycardia, hypotension, rhabdomyolysis, vertigo, liver necrosis, serotonin syndrome, and death have been reported.

Published retrospective studies report that venlafaxine overdosage may be associated with an increased risk of fatal outcomes compared to that observed with SSRI antidepressant products, but lower than that for tricyclic antidepressants. Epidemiological studies have shown that venlafaxine-treated patients have a higher preexisting burden of suicide risk factors than SSRI-treated patients. The extent to which the finding of an increased risk of fatal outcomes can be attributed to the toxicity of venlafaxine in overdosage as opposed to some characteristic(s) of venlafaxine-treated patients is not clear. Prescriptions for venlafaxine hydrochloride extended-release capsules should be written for the smallest quantity of capsules consistent with good patient management, in order to reduce the risk of overdose.

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

Venlafaxine hydrochloride extended-release capsules 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 venlafaxine hydrochloride extended-release capsules is 75 mg/day, administered in a single dose. In the clinical trials establishing the efficacy of venlafaxine hydrochloride extended-release capsules 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 venlafaxine hydrochloride extended-release capsules 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 PHARMACOLOGY**, **Clinical Trials**).

It should be noted that, while the maximum recommended dose for moderately depressed outpatients is also 225 mg/day for venlafaxine hydrochloride tablets (immediate release), 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 venlafaxine hydrochloride extended-release capsules are needed for more severely depressed patients is unknown; however, the experience with venlafaxine hydrochloride extended-release capsule doses higher than 225 mg/day is very limited (see **PRECAUTIONS**, **General**, *Use in Patients With Concomitant Illness*).

Panic Disorder

It is recommended that initial single doses of 37.5 mg/day of venlafaxine hydrochloride extended-release capsules be used for 7 days. In clinical trials establishing the efficacy of venlafaxine hydrochloride extended-release capsules in outpatients with panic disorder, initial doses of 37.5 mg/day for 7 days were followed by doses of 75 mg/day

and subsequent weekly dose increases of 75 mg/day to a maximum dose of 225 mg/day. Although a dose-response relationship for effectiveness in patients with panic disorder was not clearly established in fixed-dose studies, certain patients not responding to 75 mg/day may benefit from dose increases to a maximum of approximately 225 mg/day. Dose increases should be in increments of up to 75 mg/day, as needed, and should be made at intervals of not less than 7 days (see **PRECAUTIONS**, *Use in Patients With Concomitant Illness*).

Switching Patients From Venlafaxine Hydrochloride Tablets

Depressed patients who are currently being treated at a therapeutic dose with venlafaxine hydrochloride tablets (immediate release) may be switched to venlafaxine hydrochloride extended-release capsules at the nearest equivalent dose (mg/day), e.g., 37.5 mg venlafaxine two-times-a-day to 75 mg venlafaxine hydrochloride extended-release capsules once daily. However, individual dosage adjustments may be necessary.

Switching a Patient To or From a Monoamine Oxidase Inhibitor (MAOI) Intended to Treat Psychiatric Disorders

At least 14 days should elapse between discontinuation of an MAOI intended to treat psychiatric disorders and initiation of therapy with venlafaxine hydrochloride extended-release capsules. Conversely, at least 7 days should be allowed after stopping venlafaxine hydrochloride extended-release capsules before starting an MAOI intended to treat psychiatric disorders (see **CONTRAINDICATIONS**).

Use of Venlafaxine Hydrochloride Extended-Release Capsules With Other MAOIs, Such as Linezolid or Methylene Blue

Do not start venlafaxine hydrochloride extended-release capsules in a patient who is being treated with linezolid or intravenous methylene blue because there is increased risk of serotonin syndrome. In a patient who requires more urgent treatment of a psychiatric condition, other interventions, including hospitalization, should be considered (see **CONTRAINDICATIONS**).

In some cases, a patient already receiving therapy with venlafaxine hydrochloride extended-release capsules may require urgent treatment with linezolid or intravenous methylene blue. If acceptable alternatives to linezolid or intravenous methylene blue treatment are not available and the potential benefits of linezolid or intravenous methylene blue treatment are judged to outweigh the risks of serotonin syndrome in a particular patient, venlafaxine hydrochloride extended-release capsules should be stopped promptly, and linezolid or intravenous methylene blue can be administered. The patient should be monitored for symptoms of serotonin syndrome for 7 days or until 24 hours after the last dose of linezolid or intravenous methylene blue, whichever comes first. Therapy with venlafaxine hydrochloride extended-release capsules may be resumed 24 hours after the last dose of linezolid or intravenous methylene blue (see **WARNINGS**).

The risk of administering methylene blue by non-intravenous routes (such as oral tablets or by local injection) or in intravenous doses much lower than 1 mg/kg with venlafaxine hydrochloride extended-release capsules is unclear. The clinician should, nevertheless, be aware of the possibility of emergent symptoms of serotonin syndrome with such use (see **WARNINGS**).

Special Populations

Treatment of Pregnant Women During the Third Trimester

Neonates exposed to venlafaxine hydrochloride extended-release capsules, 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 venlafaxine hydrochloride extended-release capsules during the third trimester, the physician should carefully consider the potential risks and benefits of treatment.

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 and mild and moderate hepatic impairment compared with normal subjects (see **CLINICAL PHARMACOLOGY**), it is recommended that the total daily dose be reduced by 50% in patients with mild to moderate hepatic impairment. Since there was much individual variability in clearance between subjects with cirrhosis, it may be necessary to reduce the dose even more than 50%, and individualization of dosing 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%. 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 or panic disorder, however, caution should be exercised in treating the elderly. When individualizing the dosage, extra care should be taken when increasing the dose.

Maintenance Treatment

There is no body of evidence available from controlled trials to indicate how long patients with major depressive disorder or panic disorder, should be treated with venlafaxine hydrochloride extended-release capsules.

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 venlafaxine hydrochloride extended-release capsules were assigned randomly to placebo or to the same dose of venlafaxine hydrochloride extended-release capsules (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 venlafaxine hydrochloride tablets 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 venlafaxine hydrochloride tablets for periods of up to 52 weeks on the same dose (100 to 200 mg/day, on a b.i.d. schedule) (see **CLINICAL PHARMACOLOGY**, **Clinical Trials**). Based on these limited data, it is not known whether or not the dose of venlafaxine hydrochloride tablets/venlafaxine hydrochloride extended-release capsules 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 a study of panic disorder in which patients responding during 12 weeks of acute treatment with venlafaxine hydrochloride extended-release capsules were assigned randomly to placebo or to the same dose of venlafaxine hydrochloride extended-release capsules (75, 150, or 225 mg/day), patients continuing venlafaxine hydrochloride extended-release capsules experienced a significantly longer time to relapse than patients randomized to placebo. The need for continuing medication in patients with panic disorder who improve with venlafaxine hydrochloride extended-release capsules treatment should be periodically reassessed.

Discontinuing Venlafaxine Hydrochloride Extended-Release Capsules

Symptoms associated with discontinuation of venlafaxine hydrochloride extended-release capsules, 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 venlafaxine hydrochloride extended-release capsules, tapering was achieved by reducing the daily dose by 75 mg at 1 week intervals. Individualization of tapering may be necessary.

HOW SUPPLIED

Venlafaxine Hydrochloride Extended-Release Capsules USP are available as follows:

150 mg - light-orange opaque cap/light-orange opaque body with “93” and “7386” on both body and cap. They are available in bottles of 30, 60 and 90.

Store at 20º to 25ºC (68º to 77ºF) [See USP Controlled Room Temperature].

Dispense in a tight, light-resistant container as defined in the USP, with a child-resistant closure (as required).

KEEP THIS AND ALL MEDICATIONS OUT OF THE REACH OF CHILDREN.

Manufactured In Israel By:

TEVA PHARMACEUTICAL IND. LTD.

Jerusalem, 91010, Israel

Manufactured For:

TEVA PHARMACEUTICALS USA

Sellersville, PA 18960

Repackaged by:

PROFICIENT RX LP

Thousand Oaks, CA 91320

Rev. H 7/2014

MEDICATION GUIDE

Venlafaxine (ven la fax een) Hydrochloride Extended-Release Capsules USP

Read the Medication Guide that comes with **venlafaxine hydrochloride extended-release capsules** before you start taking them and each time you get a refill. There may be new information. This Medication Guide does not take the place of talking to your healthcare provider about your medical condition or treatment. Talk with your healthcare provider if there is something you do not understand or want to learn more about.

What is the most important information I should know about venlafaxine hydrochloride extended-release capsules?

Venlafaxine hydrochloride extended-release capsules and other antidepressant medicines may cause serious side effects, including:

1. Suicidal thoughts or actions:

- **Venlafaxine hydrochloride extended-release capsules and other antidepressant medicines may increase suicidal thoughts or actions** in some children, teenagers, or young adults **within the first few months of treatment or when the dose is changed.**
- Depression or other serious mental illnesses are the most important causes of suicidal thoughts or actions.
- Watch for these changes and call your healthcare provider right away if you notice:
    - New or sudden changes in mood, behavior, actions, thoughts, or feelings, especially if severe.
    - Pay particular attention to such changes when **venlafaxine hydrochloride extended-release capsules** are started or when the dose is changed.

Keep all follow-up visits with your healthcare provider and call between visits if you are worried about symptoms.

Call your healthcare provider right away if you have any of the following symptoms, or call 911 if an emergency, especially if they are new, worse, or worry you:

- attempts to commit suicide
- acting on dangerous impulses
- acting aggressive or violent
- thoughts about suicide or dying
- new or worse depression
- new or worse anxiety or panic attacks

- feeling agitated, restless, angry or irritable
- trouble sleeping
- an increase in activity or talking more than what is normal for you
- other unusual changes in behavior or mood
- **Visual Problems**
  ● eye pain
  ● changes in vision
  ● swelling or redness in or around the eye
  Only some people are at risk for these problems. You may want to undergo an eye examination to see if you are at risk and receive preventative treatment if you are.

Call your healthcare provider right away if you have any of the following symptoms, or call 911 if an emergency. Venlafaxine hydrochloride extended-release capsules may be associated with these serious side effects:

2. Serotonin Syndrome.

This condition can be life-threatening and may include:

- agitation, hallucinations, coma or other changes in mental status
- coordination problems or muscle twitching (overactive reflexes)
- racing heartbeat, high or low blood pressure
- sweating or fever
- nausea, vomiting, or diarrhea
- muscle rigidity

3. Changes in blood pressure. Venlafaxine hydrochloride extended-release capsules may:

- increase your blood pressure. Control high blood pressure before starting treatment and monitor blood pressure regularly

4. Enlarged pupils (mydriasis).

5. Anxiety and insomnia.

6. Changes in appetite or weight.

7. Manic/hypomanic episodes:

- greatly increased energy
- severe trouble sleeping
- racing thoughts
- reckless behavior
- unusually grand ideas
- excessive happiness or irritability
- talking more or faster than usual

8. Low salt (sodium) levels in the blood.

Elderly people may be at greater risk for this. Symptoms may include:

- headache
- weakness or feeling unsteady

- confusion, problems concentrating or thinking or memory problems

9. Seizures or convulsions.

10. Abnormal bleeding: **Venlafaxine hydrochloride extended-release capsules** and other antidepressant medicines may increase your risk of bleeding or bruising, especially if you take the blood thinner warfarin (Coumadin®, Jantoven®), a non-steroidal anti-inflammatory drug (NSAIDs, like ibuprofen or naproxen), or aspirin.

11. Elevated cholesterol.

12. Lung disease and pneumonia: **Venlafaxine hydrochloride extended-release capsules** may cause rare lung problems. Symptoms include:

- worsening shortness of breath
- cough
- chest discomfort

13. Severe allergic reactions:

- trouble breathing
- swelling of the face, tongue, eyes or mouth
- rash, itchy welts (hives) or blisters, alone or with fever or joint pain.

Do not stop venlafaxine hydrochloride extended-release capsules without first talking to your healthcare provider. Stopping **venlafaxine hydrochloride extended-release capsules** too quickly or changing from another antidepressant too quickly may cause serious symptoms including:

- anxiety, irritability
- feeling tired, restless or problems sleeping
- headache, sweating, dizziness
- electric shock-like sensations, shaking, confusion, nightmares
- vomiting, nausea, diarrhea

What are venlafaxine hydrochloride extended-release capsules?

Venlafaxine hydrochloride extended-release capsules are a prescription medicine used to treat depression. It is important to talk with your healthcare provider about the risks of treating depression and also the risks of not treating it. You should discuss all treatment choices with your healthcare provider. **Venlafaxine hydrochloride extended-release capsules** are also used to treat:

- Panic Disorder (PD)

Talk to your healthcare provider if you do not think that your condition is getting better with **venlafaxine hydrochloride extended-release capsule** treatment.

Who should not take venlafaxine hydrochloride extended-release capsules?

Do not take **venlafaxine hydrochloride extended-release capsules** if you:

- are allergic to **venlafaxine hydrochloride extended-release capsules** or any of the ingredients in **venlafaxine hydrochloride extended-release capsules**.

See the end of this Medication Guide for a complete list of ingredients in **venlafaxine hydrochloride extended-release capsules**.
- have uncontrolled angle-closure glaucoma.
- take a Monoamine Oxidase Inhibitor (MAOI). Ask your healthcare provider or pharmacist if you are not sure if you take an MAOI, including the antibiotic linezolid.
- Do not take an MAOI within 7 days of stopping **venlafaxine hydrochloride extended-release capsules** unless directed to do so by your physician.
- Do not start **venlafaxine hydrochloride extended-release capsules** if you stopped taking an MAOI in the last 2 weeks unless directed to do so by your physician.

People who take venlafaxine hydrochloride extended-release capsules close in time to an MAOI may have serious or even life-threatening side effects. Get medical help right away if you have any of these symptoms:

- high fever
- uncontrolled muscle spasms
- stiff muscles
- rapid changes in heart rate or blood pressure
- confusion
- loss of consciousness (pass out)

What should I tell my healthcare provider before taking venlafaxine hydrochloride extended-release capsules? Ask if you are not sure.

Before starting **venlafaxine hydrochloride extended-release capsules**, tell your healthcare provider if you:

- Are taking certain drugs such as:
- Medicines used to treat migraine headaches such as:
    - triptans
- Medicines used to treat mood, anxiety, psychotic or thought disorders, such as:
    - tricyclic antidepressants
    - lithium
    - SSRIs
    - SNRIs
    - antipsychotic drugs
- Medicines used to treat pain such as:
    - tramadol
- Medicines used to thin your blood such as:
    - warfarin
- Medicines used to treat heartburn such as:
    - Cimetidine

- Over-the-counter medicines or supplements such as:
    - Aspirin or other NSAIDs
    - Tryptophan
    - St. John’s Wort
- have heart problems
- have diabetes
- have liver problems
- have kidney problems
- have thyroid problems
- have or had seizures or convulsions
- have bipolar disorder or mania
- have low sodium levels in your blood
- have high blood pressure
- have high cholesterol
- have or had bleeding problems
- are pregnant or plan to become pregnant. It is not known if **venlafaxine hydrochloride extended-release capsules** will harm your unborn baby. Talk to your healthcare provider about the benefits and risks of treating depression during pregnancy
- are breastfeeding or plan to breastfeed. Some **venlafaxine hydrochloride** may pass into your breast milk. Talk to your healthcare provider about the best way to feed your baby while taking **venlafaxine hydrochloride extended-release capsules**.

Tell your healthcare provider about all the medicines that you take, including prescription and non-prescription medicines, vitamins, and herbal supplements. **Venlafaxine hydrochloride extended-release capsules** and some medicines may interact with each other, may not work as well, or may cause serious side effects.

Your healthcare provider or pharmacist can tell you if it is safe to take **venlafaxine hydrochloride extended-release capsules** with your other medicines. Do not start or stop any medicine while taking **venlafaxine hydrochloride extended-release capsules** without talking to your healthcare provider first.

If you take **venlafaxine hydrochloride extended-release capsules**, you should not take any other medicines that contain (venlafaxine) including: venlafaxine HCl.

How should I take venlafaxine hydrochloride extended-release capsules?

- Take **venlafaxine hydrochloride extended-release capsules** exactly as prescribed. Your healthcare provider may need to change the dose of **venlafaxine hydrochloride extended-release capsules** until it is the right dose for you.
- **Venlafaxine hydrochloride extended-release capsules** are to be taken with food.
- If you miss a dose of **venlafaxine hydrochloride extended-release capsules**, take the missed dose as soon as you remember. If it is almost time for the next dose, skip the missed dose and take your next dose at the regular time. Do not take two doses of **venlafaxine hydrochloride extended-release capsules** at the same time.
- If you take too many **venlafaxine hydrochloride extended-release capsules**,

call your healthcare provider or poison control center right away, or get emergency treatment.
- When switching from another antidepressant to **venlafaxine hydrochloride extended-release capsules** your doctor may want to lower the dose of the initial antidepressant first to avoid side effects

What should I avoid while taking venlafaxine hydrochloride extended-release capsules?

Venlafaxine hydrochloride extended-release capsules can cause sleepiness or may affect your ability to make decisions, think clearly, or react quickly. You should not drive, operate heavy machinery, or do other dangerous activities until you know how **venlafaxine hydrochloride extended-release capsules** affect you. Do not drink alcohol while using **venlafaxine hydrochloride extended-release capsules**.

What are the possible side effects of venlafaxine hydrochloride extended-release capsules? Venlafaxine hydrochloride extended-release capsules may cause serious side effects, including:

- See "**What is the most important information I should know about venlafaxine hydrochloride extended-release capsules**?"
- Increased cholesterol- have your cholesterol checked regularly
- Newborns whose mothers take **venlafaxine hydrochloride extended-release capsules** in the third trimester may have problems right after birth including:
    - problems feeding and breathing
    - seizures
    - shaking, jitteriness or constant crying
- Angle-closure glaucoma

Common possible side effects in people who take **venlafaxine hydrochloride extended-release capsules** include**:**

- unusual dreams
- sexual problems
- loss of appetite, constipation, diarrhea, nausea or vomiting, or dry mouth
- feeling tired, fatigued or overly sleepy
- change in sleep habits, problems sleeping
- yawning
- tremor or shaking
- dizziness, blurred vision
- sweating
- feeling anxious, nervous or jittery
- headache
- increase in heart rate

Tell your healthcare provider if you have any side effect that bothers you or that does not go away. These are not all the possible side effects of **venlafaxine hydrochloride extended-release capsules**. For more information, ask your healthcare provider or pharmacist.

CALL YOUR DOCTOR FOR MEDICAL ADVICE ABOUT SIDE EFFECTS. YOU MAY

REPORT SIDE EFFECTS TO THE FDA AT 1-800-FDA-1088.

How should I store venlafaxine hydrochloride extended-release capsules?

- Store **venlafaxine hydrochloride extended-release capsules** at room temperature between 68°F and 77°F (20°C to 25°C).
- Keep **venlafaxine hydrochloride extended-release capsules** in a dry place.

Keep venlafaxine hydrochloride extended-release capsules and all medicines out of the reach of children.

General information about venlafaxine hydrochloride extended-release capsules

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use **venlafaxine hydrochloride extended-release capsules** for a condition for which they were not prescribed. Do not give **venlafaxine hydrochloride extended-release capsules** to other people, even if they have the same condition. They may harm them.

This Medication Guide summarizes the most important information about **venlafaxine hydrochloride extended-release capsules**. If you would like more information, talk with your healthcare provider. You may ask your healthcare provider or pharmacist for information about **venlafaxine hydrochloride extended-release capsules** that is written for healthcare professionals.

For more information about **venlafaxine hydrochloride extended-release capsules** call 1-888-838-2872.

What are the ingredients in venlafaxine hydrochloride extended-release capsules?

Active ingredient: venlafaxine hydrochloride, USP.

Inactive ingredients: black iron oxide, dibutyl sebacate, ethylcellulose, gelatin, polyethylene glycol, povidone, propylene glycol, shellac, sugar spheres (which contain sucrose and corn starch), sunset yellow FCF FD&C yellow 6, talc, and titanium dioxide. The 37.5 mg capsules also contain D&C yellow 10 and potassium hydroxide, the 75 mg capsules also contain D&C yellow 10 and may contain potassium hydroxide, and the 150 mg capsules also contain potassium hydroxide.

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

Manufactured In Israel By:

TEVA PHARMACEUTICAL IND. LTD.

Jerusalem, 91010, Israel

Manufactured For:

TEVA PHARMACEUTICALS USA

Sellersville, PA 18960

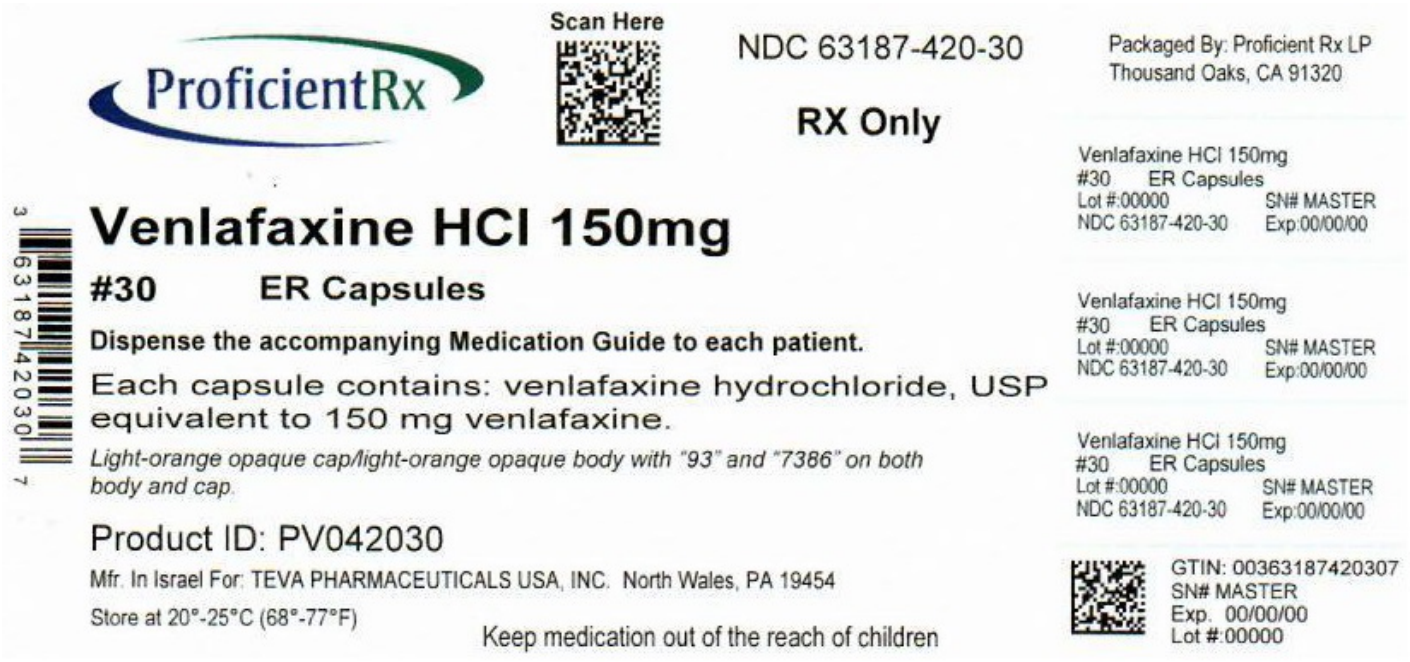
Rev. C 7/2014

Repackaged by:

PROFICIENT RX LP

Thousand Oaks, CA 91320

Package/Label Display Panel



VENLAFAXINE HYDROCHLORIDE

venlafaxine hydrochloride capsule, extended release

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:63187-420(NDC:0093-7386)
Route of Administration	ORAL		

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
VENLAFAXINE HYDROCHLORIDE (UNII: 7D7RX5A8MO) (VENLAFAXINE - UNII:GRZ5RCB1QG)	VENLAFAXINE	150 mg

Inactive Ingredients	
Ingredient Name	**Strength**
FERROSOFERRIC OXIDE (UNII: XM0M87F357)	

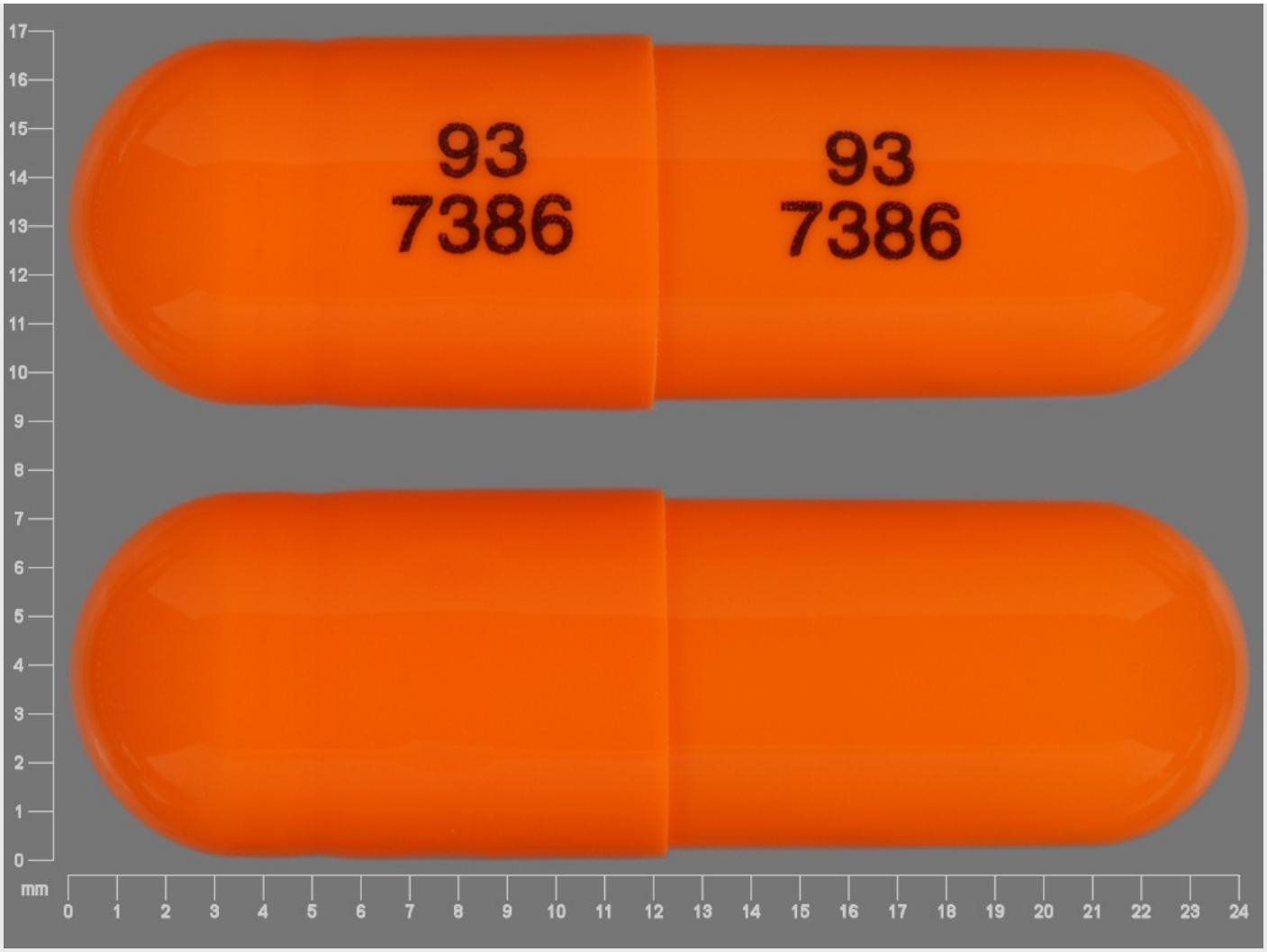
DIBUTYL SEBACATE (UNII: 4W5IH7FLNY)	
ETHYLCELLULOSE (7 MPA.S) (UNII: H3UP11403C)	
GELATIN, UNSPECIFIED (UNII: 2G86QN327L)	
POLYETHYLENE GLYCOL 400 (UNII: B697894SGQ)	
POVIDONE K30 (UNII: U725QWY32X)	
PROPYLENE GLYCOL (UNII: 6DC9Q167V3)	
SHELLAC (UNII: 46N107B71O)	
SUCROSE (UNII: C151H8M554)	
STARCH, CORN (UNII: O8232NY3SJ)	
FD&C YELLOW NO. 6 (UNII: H77VEI93A8)	
TALC (UNII: 7SEV7J4R1U)	
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)	
POTASSIUM HYDROXIDE (UNII: WZH3C48M4T)	
AMMONIA (UNII: 5138Q19F1X)	

Product Characteristics

Color	ORANGE (light-orange)	**Score**	no score
Shape	CAPSULE	**Size**	23mm
Flavor		**Imprint Code**	93;7386;93;7386
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:63187-420-30	30 in 1 BOTTLE; Type 0: Not a Combination Product	03/02/2015	
2	NDC:63187-420-60	60 in 1 BOTTLE; Type 0: Not a Combination Product	03/02/2015	
3	NDC:63187-420-90	90 in 1 BOTTLE; Type 0: Not a Combination Product	03/02/2015	



Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA076565	07/01/2010	

Labeler - Proficient Rx LP (079196022)

Establishment

Name	Address	ID/FEI	Business Operations
Proficient Rx LP		079196022	REPACK(63187-420) , RELABEL(63187-420)

Revised: 10/2024 Proficient Rx LP