For the use of a Registered Medical Practitioner or a Hospital or a Laboratory

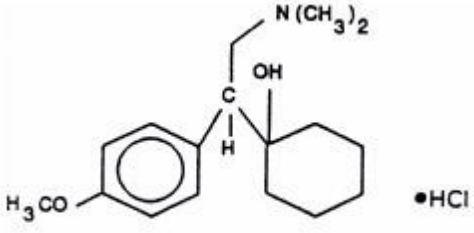
VENLIFT OD
Venlafaxine hydrochloride 37.5, 75 and 150mg Extended-Release Capsules

COMPOSITION
Venlift OD-37.5
Each hard gelatin capsule contains:
Venlafaxine Hydrochloride B.P. equivalent to Venlafaxine 37.5mg
(In the form of extended release pellets)
Approved colours used in hard gelatin capsule shells

Venlift OD-75
Each hard gelatin capsule contains:
Venlafaxine Hydrochloride B.P. equivalent to Venlafaxine 75mg
(In the form of extended-release pellets)
Approved colours used in hard gelatin capsule shells

Venlift OD-150
Each hard gelatin capsule contains:
Venlafaxine Hydrochloride B.P. equivalent to Venlafaxine 150mg
(In the form of extended release pellets)
Approved colours used in hard gelatin capsule shells

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



venlafaxine hydrochloride

CLINICAL PHARMACOLOGY
Pharmacodynamics
The mechanism of the antidepressant action of venlafaxine in humans is believed to be associated with its potentiation of neurotransmitter activity in the CNS. Preclinical studies have shown that venlafaxine and its active metabolite, O-desmethylvenlafaxine (ODV), are potent inhibitors of neuronal serotonin and norepinephrine reuptake and weak inhibitors of dopamine

reuptake. Venlafaxine and ODV have no significant affinity for muscarinic cholinergic, H1-histaminergic, or α1-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).

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 (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 (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 capsule. Venlafaxine Hydrochloride, therefore, provides a slower rate of absorption, but the same extent of absorption compared with the immediate release tablet.

Food did not affect the bioavailability of venlafaxine or its active metabolite, ODV. Time of administration (AM Vs PM) did not affect the pharmacokinetics of venlafaxine and ODV from the 75 mg Venlafaxine Hydrochloride capsule.

Metabolism and Excretion Following absorption, venlafaxine undergoes extensive pre systemic 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

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 2-3 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.

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.

INDICATIONS AND USAGE

Venlift OD-37.5 mg and 75 mg for Major depression
Venlift OD-150 mg for Generalised anxiety disorders

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.

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.

WARNINGS

Clinical Worsening and Suicide Risk

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

The pooled analyses of placebo-controlled trials in children and adolescents with MDD, obsessive compulsive disorder (OCD), or other psychiatric disorders included a total of 24 short-term trials of 9 antidepressant drugs in over 4400 patients. The pooled analyses of placebo-controlled trials in adults with MDD or other psychiatric disorders included a total of 295 short-term trials (median duration of 2 months) of 11 antidepressant drugs in over 77,000 patients. There was considerable variation in risk of suicidality among drugs, but a tendency toward an increase in 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 1

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

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

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

All patients being treated with antidepressants for any indication should be monitored appropriately and observed closely for clinical worsening, suicidality, 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.

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 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 is 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, 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 with MAOIs intended to treat psychiatric disorders is contraindicated. Venlafaxine hydrochloride 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. Venlafaxine hydrochloride should be discontinued before initiating treatment with the MAOI.

If concomitant use of Venlafaxine hydrochloride 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 for serotonin syndrome, particularly during treatment initiation and dose increases.

Treatment with Venlafaxine hydrochloride 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 may trigger an angle closure attack in a patient with anatomically narrow angles who does not have a patent iridectomy.

Sustained Hypertension
Venlafaxine hydrochloride 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 (immediate release) studies meeting criteria for sustained hypertension revealed a dose-dependent increase in the incidence of sustained hypertension for Venlafaxine hydrochloride (immediate release) (see Table 3).

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

Table 2 Number (%) of Sustained Elevations in SDBP in Venlafaxine Premarketing Studies by Indication

MDD (75-375 mg/day)	GAD (37.5-225 mg/day)	Social Anxiety Disorder (75-225 mg/day)	Panic Disorder (75-225 mg/day)
19/705 (3)	5/1011 (0.5)	5/771 (0.6)	9/973 (0.9)
MDD = major depressive disorder GAD = generalized anxiety disorder			

Table 3 Incidence (%) of Sustained Elevations in SDBP in Venlafaxine Immediate Release Studies

Venlafaxine 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 treated patients discontinued treatment because of elevated blood pressure. Among these patients, most of the blood pressure increases were in a modest range (12 to 16 mm Hg, SDBP). In premarketing GAD studies up to 8 weeks and up to 6 months, 0.7% (10/1381) and 1.3% (7/535) of the Venlafaxine hydrochloride treated patients, respectively, discontinued treatment because of elevated blood pressure. Among these patients, most of the blood pressure increases were in a modest range (12 to 25 mm Hg, SDBP up to 8 weeks; 8 to 28 mm Hg up to 6 months). In premarketing Social Anxiety Disorder studies up to 6 months, 0.6% (5/771) of the Venlafaxine hydrochloride treated patients discontinued treatment because of elevated blood pressure. In these patients, the blood pressure increases were modest (1-24 mm Hg, SDBP). In premarketing panic disorder studies up to 12 weeks, 0.5% (5/1001) of the Venlafaxine hydrochloride 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 post marketing experience. Pre-existing hypertension should be controlled before treatment with venlafaxine. It is recommended that patients receiving Venlafaxine hydrochloride 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 treated patients.

Table 4 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 mg/day				Placebo	
	≤75		>75			
	SSBP[1]	SDBP[2]	SSBP	SDBP	SSBP	SDBP
Major Depressive Disorder						
8-12 weeks	-0.28	0.37	2.93	3.56	-1.08	-0.10
Generalized Anxiety Disorder						
8 weeks	-0.28	0.02	2.40	1.68	-1.26	-0.92
6 months	1.27	-0.69	2.06	1.28	-1.29	-0.74

Table 4 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 mg/day ≤75		>75		Placebo	
	SSBP[1]	SDBP[2]	SSBP	SDBP	SSBP	SDBP
Social Anxiety Disorder						
12 weeks	-0.29	-1.26	1.18	1.34	-1.96	-1.22
6 months	-0.98	-0.49	2.51	1.96	-1.84	-0.65
Panic Disorder						
10-12 weeks	-1.15	0.97	-0.36	0.16	-1.29	-0.99

[1]Supine Systolic Blood Pressure

[2]Supine Diastolic Blood Pressure

Across all clinical trials in MDD, GAD, Social Anxiety Disorder and panic disorder, 1.4% of patients in the Venlafaxine-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-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 Discontinuation symptoms have been systematically evaluated in patients taking venlafaxine, to include prospective analyses of clinical trials in Generalized Anxiety Disorder and retrospective surveys of trials in major depressive disorder, and Social Anxiety 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, 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. 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

Insomnia and Nervousness Treatment-emergent insomnia and nervousness were more commonly reported for patients treated with Venlafaxine (venlafaxine hydrochloride) extended-release capsules than with placebo in pooled analyses of short-term major depressive disorder, GAD, Social Anxiety Disorder, and panic disorder studies, as shown in Table 5.

Table 5 Incidence of Insomnia and Nervousness in Placebo-Controlled Major Depressive Disorder, GAD, Social Anxiety Disorder, and Panic Disorder Trials

Major Depressive Disorder			GAD		Social Anxiety Disorder		Panic Disorder	
Symptom	Venlafaxine n = 357	Placebo n = 285	Venlafaxine n = 381	Placebo n = 555	Venlafaxine n= 819	Placebo n = 695	Venlafaxine n=1001	Placebo = 662
Insomnia	17%	11%	15%	10%	24%	8%	17%	9%
Nervousness	10%	5%	6%	4%	10%	5%	4%	6%

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

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

In Social Anxiety Disorder trials, insomnia and nervousness led to drug discontinuation in 2% and 1%, respectively, of the patients treated with Venlafaxine up to 12 weeks and 2% and 3% respectively, of the patients treated with Venlafaxine up to 6 months.
In panic disorder trials, insomnia and nervousness led to drug discontinuation in 1% and 0.1%, respectively, of the patients treated with Venlafaxine up to 12 weeks.

Changes in Weight
Adult Patients: A loss of 5% or more of body weight occurred in 7% of Venlafaxine-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 was 0.1% in major depressive disorder studies. In placebo-controlled GAD studies, a loss of 7% or more of body weight occurred in 3% of Venlafaxine patients and 1% of placebo patients who received treatment for up to 6 months. The discontinuation rate for weight loss was 0.3% for patients receiving Venlafaxine in GAD studies for up to eight weeks. In placebo-controlled Social Anxiety Disorder trials, 4% of the Venlafaxine-treated and 1% of the placebo-treated patients sustained a loss of 7% or more of body weight during up to 6 months of treatment. None of the patients receiving Venlafaxine in Social Anxiety Disorder studies discontinued for weight loss. In placebo-controlled panic disorder trials, 3% of the Venlafaxine-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 in panic disorder studies discontinued for weight loss.

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

Pediatric Patients: Weight loss has been observed in pediatric patients (ages 6-17) receiving Venlafaxine. In a pooled analysis of four eight-week, double-blind, placebo-controlled, flexible dose outpatient trials for major depressive disorder (MDD) and generalized anxiety disorder (GAD), Venlafaxine-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 than with placebo experienced a weight loss of at least 3.5% in both the MDD and the GAD studies (18% of Venlafaxine-treated patients vs. 3.6% of placebo-treated patients; $p<0.001$). In a 16-week, double-blind, placebo-controlled, flexible dose outpatient trial for Social Anxiety Disorder, Venlafaxine-treated patients lost an average of 0.75 kg (n = 137), while placebo-treated patients gained an average of 0.76 kg (n = 148). More patients treated with Venlafaxine than with placebo experienced a weight loss of at least 3.5% in the Social Anxiety Disorder study

(47% of Venlafaxine-treated patients vs. 14% of placebo-treated patients; p<0.001). Weight loss was not limited to patients with treatment-emergent anorexia

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

Changes in Height

Pediatric Patients: During the eight-week, placebo-controlled GAD studies, Venlafaxine-treated patients (ages 6-17) grew an average of 0.3 cm (n = 122), while placebo-treated patients grew an average of 1.0 cm (n = 132); p=0.041. This difference in height increase was most notable in patients younger than twelve. During the eight-week placebo-controlled MDD studies, Venlafaxine-treated patients grew an average of 0.8 cm (n = 146), while placebo-treated patients grew an average of 0.7 cm (n = 147). During the 16-week, placebo-controlled Social Anxiety Disorder study, both the Venlafaxine-treated (n = 109) and the placebo-treated (n = 112) patients each grew an average of 1.0 cm. 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-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 was 1.0% in major depressive disorder studies. Treatment-emergent anorexia was more commonly reported for Venlafaxine-treated (8%) than placebo-treated patients (2%) in the pool of short-term, double-blind, placebo-controlled GAD studies. The discontinuation rate for anorexia was 0.9% for patients receiving Venlafaxine for up to 8 weeks in GAD studies. Treatment-emergent anorexia was more commonly reported for Venlafaxine-treated (17%) than placebo-treated patients (2%) in the pool of short-term, double-blind, placebo-controlled Social Anxiety Disorder studies. The discontinuation rate for anorexia was 0.6% for patients receiving Venlafaxine for up to 12 weeks in Social Anxiety Disorder studies; no patients discontinued for anorexia between week 12 and month 6. Treatment-emergent anorexia was more commonly reported for Venlafaxine-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 for up to 12 weeks in panic disorder studies.

Pediatric Patients: Decreased appetite has been observed in pediatric patients receiving Venlafaxine. In the placebo-controlled trials for GAD and MDD, 10% of patients aged 6-17 treated with Venlafaxine for up to eight weeks and 3% of patients treated with placebo reported treatment-emergent anorexia (decreased appetite). None of the patients receiving Venlafaxine discontinued for anorexia or weight loss. In the placebo-controlled trial for Social Anxiety Disorder, 22% and 3% of patients aged 8-17 treated for up to 16 weeks with Venlafaxine and

placebo, respectively, reported treatment-emergent anorexia (decreased appetite). The discontinuation rates for anorexia were 0.7% and 0.0% for patients receiving Venlafaxine and placebo, respectively; the discontinuation rates for weight loss were 0.7% for patients receiving either Venlafaxine or placebo.

Activation of Mania/Hypomania
During premarketing major depressive disorder studies, mania or hypomania occurred in 0.3% of Venlafaxine-treated patients and no placebo patients. In premarketing GAD studies, no Venlafaxine-treated patients and 0.2% of placebo-treated patients experienced mania or hypomania. In premarketing Social Anxiety Disorder studies, 0.2% Venlafaxine-treated patients and no placebo-treated patients experienced mania or hypomania. In premarketing panic disorder studies, 0.1% of Venlafaxine-treated patients and no placebo-treated patients experienced mania or hypomania. In all premarketing major depressive disorder trials with Venlafaxine (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 should be used cautiously in patients with a history of mania.

Hyponatremia may occur as a result of treatment with SSRIs and SNRIs, including Venlafaxine. 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. Discontinuation of Venlafaxine 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-treated patients in the major depressive disorder studies, among 1381 Venlafaxine-treated patients in GAD studies, or among 819 Venlafaxine-treated patients in Social Anxiety Disorder studies. In panic disorder studies, 1 seizure occurred among 1,001 Venlafaxine-treated patients. In all premarketing major depressive disorder trials with Venlafaxine (immediate release), seizures were reported at various doses in 0.3% (8/3082) of venlafaxine-treated patients. Venlafaxine, 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, may increase the risk of bleeding events, ranging from ecchymoses, hematomas, epistaxis, petechiae, and gastrointestinal hemorrhage to life-threatening hemorrhage. Concomitant use of aspirin, nonsteroidal 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 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. 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 venlafaxinetreated 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 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 and 220 patients who received placebo in 8- to 12-week double-blind, placebo-controlled trials in major depressive disorder, for 610 patients who received Venlafaxine and 298 patients who received placebo in 8-week double-blind, placebo-controlled trials in GAD, for 593 patients who received Venlafaxine and 534 patients who received placebo in 12-week double-blind, placebo-controlled trials in Social Anxiety Disorder, and for 661 patients who received Venlafaxine and 395 patients who received placebo in three 10- to 12-week double-blind, placebo-controlled trials in panic disorder. The mean change from baseline in corrected QT interval (QTc) for Venlafaxine-treated patients in major depressive disorder studies was increased relative to that for placebo-treated patients (increase of 4.7 msec for Venlafaxine and decrease of 1.9 msec for placebo). The mean change from baseline in QTc interval for Venlafaxine-treated patients in the GAD studies did not differ significantly from that with placebo. The mean change from baseline in QTc interval for Venlafaxine-treated patients in the Social Anxiety Disorder studies was increased relative to that for placebo-treated patients (increase of 3.4 msec for Venlafaxine and decrease of 1.6 msec for placebo). The mean change from baseline in QTc interval for Venlafaxine-treated patients in the panic disorder studies was increased relative to that for placebo-treated patients (increase of 1.5 msec for Venlafaxine and decrease of 0.7 msec for placebo).

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

In a flexible-dose study, with Venlafaxine (immediate release) doses in the range of 200 to 375 mg/day and mean dose greater than 300 mg/day, Venlafaxine -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 (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. Venlafaxine, 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 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. 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.

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 and triptans, tramadol, tryptophan supplements or other serotonergic agents. Patients should be advised that taking Venlafaxine can cause mild pupillary dilation, which in susceptible individuals, can lead to an episode of angle closure glaucoma. Pre-existing 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 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.

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 (Cmax) of the drug were increased by about 60%. However, coadministration of cimetidine had no apparent effect on the pharmacokinetics of ODV, which is present in much greater quantity in the circulation than venlafaxine. The overall pharmacological activity of venlafaxine plus ODV is expected to increase only slightly, and no dosage adjustment should be necessary for most normal adults. However, for patients with pre-existing hypertension, and for elderly patients or patients with hepatic dysfunction, the interaction associated with the concomitant use of venlafaxine and cimetidine is not known and potentially could be more pronounced. Therefore, caution is advised with such patients.

Diazepam
Under steady-state conditions for venlafaxine administered at 150 mg/day, a single 10 mg dose of diazepam did not appear to affect the pharmacokinetics of either venlafaxine or ODV in 18 healthy male subjects. Venlafaxine also did not have any effect on the pharmacokinetics of diazepam or its active metabolite, 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 (t1/2) was unchanged. The mechanism explaining this finding is unknown.

Lithium
The steady-state pharmacokinetics of venlafaxine administered at 150 mg/day were not affected when a single 600 mg oral dose of lithium was administered to 12 healthy male subjects. ODV also was unaffected. Venlafaxine had no effect on the pharmacokinetics of lithium.

Drugs Highly Bound to Plasma Proteins
Venlafaxine is not highly bound to plasma proteins; therefore, administration of Venlafaxine 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, havebeen reported when SSRIs and SNRIs are coadministered with warfarin. Patients receiving warfarin therapy should be carefully monitored when Venlafaxine is initiated or discontinued.

Drugs that Inhibit Cytochrome P450 Isoenzymes
CYP2D6 Inhibitors: In vitro and in vivo studies indicate that venlafaxine is metabolized to its active metabolite, ODV, by CYP2D6, the isoenzyme that is responsible for the genetic polymorphism seen in the metabolism of many antidepressants. Therefore, the potential exists for a drug interaction between drugs that inhibit CYP2D6-mediated metabolism 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. 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. Cmax 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, Cmax, and Cmin increased by about 35% in the presence of venlafaxine. The 2-OH-desipramine AUC's increased by at least 2.5 fold (with venlafaxine 37.5 mg q12h) and by 4.5 fold (with venlafaxine 75 mg q12h). Imipramine did not affect the pharmacokinetics of venlafaxine and ODV. The clinical significance of elevated 2-OH-desipramine levels is unknown.

Metoprolol - Concomitant administration of venlafaxine (50 mg every 8 hours for 5 days) and metoprolol (100 mg every 24 hours for 5 days) to 18 healthy male subjects in a pharmacokinetic interaction study for both drugs resulted in an increase of plasma concentrations of metoprolol by approximately 30-40% without altering the plasma concentrations of its active metabolite, 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 co-administration 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 have regular monitoring of blood pressure.

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).

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.

Triptans: There have been rare postmarketing reports of serotonin syndrome with use of an SSRI and a triptan. If concomitant treatment of Venlafaxine with a triptan is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases.

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 (venlafaxine hydrochloride) extended-release capsules treatment. Postmarketing Spontaneous Drug Interaction 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^2basis.

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.

Non-teratogenic Effects Neonates exposed to Venlafaxine, 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. When treating a pregnant woman with Venlafaxine during the third trimester, the physician should carefully consider the potential risks and benefits of treatment.

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, 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. Two placebo-controlled trials in 766 pediatric patients with MDD and two placebo-controlled trials in 793 pediatric patients with GAD have been conducted with Venlafaxine, and the data were not sufficient to support a claim for use in pediatric patients.

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

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

In the studies conducted in pediatric patients (ages 6-17), the occurrence of blood pressure and cholesterol increases considered to be clinically relevant in pediatric patients was similar to that observed in adult patients. Consequently, the precautions for adults apply to pediatric patients.

Geriatric Use
Approximately 4% (14/357), 6% (77/1381), 1% (10/819), and 2% (16/1001) of Venlafaxine-treated patients in placebo-controlled premarketing major depressive disorder, GAD, Social Anxiety Disorder trials, and panic disorder trials, respectively, were 65 years of age or over. Of 2,897 Venlafaxine -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 have been associated with cases of clinically significant hyponatremia in elderly patients, who may be at greater risk for this adverse event.

The pharmacokinetics of venlafaxine and ODV are not substantially altered in the elderly. 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.

ADVERSE REACTIONS

The information included in the Adverse Findings Observed in Short-Term, Placebo-Controlled Studies with Venlafaxine subsection is based on data from a pool of three 8- and 12-week controlled clinical trials in major depressive disorder (includes two U.S. trials and one European trial), on data up to 8 weeks from a pool of five controlled clinical trials in GAD with Venlafaxine, on data up to 12 weeks from a pool of five controlled clinical trials in Social Anxiety Disorder, and on data up to 12 weeks from a pool of four controlled clinical trials in panic disorder.

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

Adverse Events Associated with Discontinuation of Treatment Approximately 11% of the 357 patients who received Venlafaxine (venlafaxine hydrochloride) extended-release capsules in placebo-controlled clinical trials for major depressive disorder discontinued treatment due to an adverse experience, compared with 6% of the 285 placebo-treated patients in those studies. Approximately 18% of the 1381 patients who received Venlafaxine capsules in placebo-controlled clinical trials for GAD discontinued treatment due to an adverse experience, compared with 12% of the 555 placebo-treated patients in those studies. Approximately 15% of the 819 patients who received Venlafaxine capsules in placebo-controlled clinical trials for Social Anxiety Disorder discontinued treatment due to an adverse experience, compared with 5% of the 695 placebo-treated patients in those studies. Approximately 7% of the 1,001 patients who received Venlafaxine capsules in placebo-controlled clinical trials for panic disorder discontinued treatment due to an adverse experience, compared with 6% of the 662 placebo-treated patients in those studies. The most common events leading to discontinuation and considered to be drug-related (ie, leading to discontinuation in at least 1% of the Venlafaxine-treated patients at a rate at least twice that of placebo for any indication) are shown in Table 6.

Table 6 Common Adverse Events Leading to Discontinuation of Treatment in Placebo-Controlled

Trials[1] Percentage of Patients Discontinuing Due to Adverse Event								
Adverse Event	**MajorDepressive Disorder Indication[2]**		**GAD Indication[3,4]**		**SocialAnxiety Disorder Indication[5]**		**Panic Disorder Indication**	
	Venlafaxine n=357	**Placebo n = 285**	**Venlafaxine n=1381**	**Placebo n = 555**	Venlafaxine n = 819	**Placebo n = 695**	**Venlafaxine n=1001**	**Placebo n = 662**
Body as a Whole								
Asthenia	--	--	3%	<1%	2%	<1%	1%	0%
Headache	--	--	--	--	1%	<1%	--	--
Digestive System								
Nausea	4%	<1%	8%	<1%	3%	<1%	2%	<1%
Anorexia	1%	<1%	--	--	--	--	--	--

Dry Mouth	1%	0%	2%	<1%	--	--	--	--
Vomiting	--	--	1%	<1%	--	--	--	--
Nervous system	--	--	--	--	--	--	--	--
Dizziness	2%	1%	--	--	--	<1%	--	--
Insomnia	1%	<1%	3%	<1%	2%	<1%	1%	<1%
Somnolence	2%	<1%	3%	<1%	2%	<1%	--	--
Nervousness	--	--	2%	<1%	2%	--	--	--
Tremor Skin	--	--	1%	0%	--	--	--	--
Sweating	--	--	2%	<1%	--	--	--	--
Urogenital System	--	--	--	--	--	--	--	--
Impotence[6]	--	--	--	--	2%	0%	--	--

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

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

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

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

[5]In a 6-month placebo-controlled trial for Social Anxiety Disorder, the following was also a common event leading to discontinuation and was considered to be drug-related for Venlafaxine-treated patients (% Venlafaxine [n = 257], % Placebo [n = 129]: depression (5%, 0%), libido decrease (1%, 0%), and nervousness (3%, 0%).

[6] Incidence is based on the number of men (Venlafaxine = 454, placebo = 357).

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

Tables 7, 8, 9, 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), of GAD (up to 8 weeks; dose range of 37.5 to 225 mg/day), of Social Anxiety Disorder (up to 12 weeks; dose range of 75 to 225 mg/day), and of panic disorder (up to 12 weeks; dose range of 37.5 to 225 mg/day), respectively, in 2% or more of patients treated with Venlafaxine (venlafaxine hydrochloride) where the incidence in patients treated with Venlafaxine 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, 8, 9, and 10:

Major Depressive Disorder

Note in particular the following adverse events that occurred in at least 5% of the Venlafaxine 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-treated patients (n = 192) and at a rate at least twice that of the placebo group: Abnormalities of sexual function (impotence in men, anorgasmia in women, and libido decreased), gastrointestinal complaints (constipation and flatulence), CNS complaints (insomnia, nervousness, and tremor), problems of special senses (abnormal vision), cardiovascular effects (hypertension and vasodilatation), and yawning.

Generalized Anxiety Disorder

Note in particular the following adverse events that occurred in at least 5% of the Venlafaxine patients and at a rate at least twice that of the placebo group for all placebo-controlled trials for the GAD indication (Table 8): Abnormalities of sexual function (abnormal ejaculation and impotence), gastrointestinal complaints (nausea, dry mouth, anorexia, and constipation), problems of special senses (abnormal vision), and sweating.

Social Anxiety Disorder

Note in particular the following adverse events that occurred in at least 5% of the Venlafaxine patients and at a rate at least twice that of the placebo group for the 5 placebo-controlled trials for the Social Anxiety Disorder indication (Table 9): Asthenia, gastrointestinal complaints (anorexia, constipation, dry mouth, nausea), CNS complaints (insomnia, libido decreased, nervousness, somnolence, tremor), abnormalities of sexual function (abnormal ejaculation, impotence), yawn, and sweating.

In the 6-month trial, the following adverse events occurred twice as often in the 150-225 mg/day Venlafaxine group compared to the 75 mg/day Venlafaxine group and placebo: vasodilation, libido decreased, tremor, yawn, abnormal vision, and impotence.

Panic Disorder

Note in particular the following adverse events that occurred in at least 5% of the Venlafaxine 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 7 Treatment-Emergent Adverse Event Incidence in Short-Term Placebo-Controlled Venlafaxine Clinical Trials in Patients with Major Depressive Disorder[1,2]

	% Reporting Event	
Body System Preferred Term	**Venlafaxine** (n = 357)	**Placebo** n = 285)
Body as a Whole		
Asthenia	8%	7%
Cardiovascular System		
Vasodilatation[3]	4%	2%
Hypertension	4%	1%
Digestive System		
Nausea	31%	12%
Constipation	8%	5%
Anorexia	8%	4%
Vomiting	4%	2%
Flatulence	4%	3%
Metabolic/Nutritional		
Weight Loss	3%	0%
Nervous System		
Dizziness	20%	9%
Somnolence	17%	8%
Insomnia	17%	11%
Dry Mouth	12%	6%
Nervousness	10%	5%
Abnormal Dreams[4]	7%	2%
Tremor	5%	2%
Depression	3%	<1%
Paresthesia	3%	1%
Libido Decreased	3%	<1%
Agitation	3%	1%
Respiratory System		
Pharyngitis	7%	6%
Yawn	3%	0%
Skin		
Sweating	14%	3%
Abnormal Vision[5]	4%	<1%
Urogenital System		
Abnormal Ejaculation	16%	<1%
(male)[6,7]		
Impotence[7]	4%	<1%

Anorgasmia (female)[8,9]	3%	<1%

[1] Incidence, rounded to the nearest %, for events reported by at least 2% of patients treated with Venlafaxine, except the following events which had an incidence equal to or less than placebo: abdominal pain, accidental injury, anxiety, back pain, bronchitis, diarrhea, dysmenorrhea, dyspepsia, flu syndrome, headache, infection, pain, palpitation, rhinitis, and sinusitis.
[2] <1% indicates an incidence greater than zero but less than 1%.
[3] Mostly "hot flashes." [4] Mostly "vivid dreams," "nightmares," and "increased dreaming."
[5] Mostly "blurred vision" and "difficulty focusing eyes."
[6] Mostly "delayed ejaculation."
[7] Incidence is based on the number of male patients.
[8] Mostly "delayed orgasm" or "anorgasmia."
[9] Incidence is based on the number of female patients.

Table 8 Treatment-Emergent Adverse Event Incidence in Short-Term Placebo-Controlled Venlafaxine Clinical Trials in GAD Patients[1,2]

	% Reporting Event	
Body System Preferred Term	Venlafaxine (n = 1381)	Placebo (n = 555)
Body as a Whole		
Asthenia	12%	8%
Cardiovascular System		
Vasodilatation[3]	4%	2%
Digestive System		
Nausea	35%	12%
Constipation	10%	4%
Anorexia	8%	2%
Vomiting	5%	3%
Nervous System		
Dizziness	16%	11%
Dry Mouth	16%	6%
Insomnia	15%	10%
Somnolence	14%	8%
Nervousness	6%	4%
Libido Decreased	4%	2%
Tremor	4%	<1%
Abnormal Dreams[4]	3%	2%
Hypertonia	3%	2%
Paresthesia	2%	1%
Respiratory System		
Yawn	10%	3%
Special Senses		
Abnormal Vision[5]	5%	<1%
Urogenital System		
Abnormal Ejaculation[6,7]	11%	<1%
Impotence[7]	5%	<1%

Orgasmic Dysfunction (female)[8,9]	2%	0%

[1] Adverse events for which the Venlafaxine reporting rate was less than or equal to the placebo rate are not included. These events are: abdominal pain, accidental injury, anxiety, back pain, diarrhea, dysmenorrhea, dyspepsia, flu syndrome, headache, infection, myalgia, pain, palpitation, pharyngitis, rhinitis, tinnitus, and urinary frequency.
[2] <1% means greater than zero but less than 1%.
[3] Mostly "hot flashes."
[4] Mostly "vivid dreams," "nightmares," and "increased dreaming."
[5] Mostly "blurred vision" and "difficulty focusing eyes."
[6] Includes "delayed ejaculation" and "anorgasmia."
[7] Percentage based on the number of males (Venlafaxine = 525, placebo = 220).
[8] Includes "delayed orgasm," "abnormal orgasm," and "anorgasmia."
[9] Percentage based on the number of females (Venlafaxine = 856, placebo = 335).

Table 9 Treatment-Emergent Adverse Event Incidence in Short-Term Placebo-Controlled Venlafaxine Clinical Trials in Social Anxiety Disorder Patients[1,2]

	% Reporting Event	
Body System Preferred Term	**Venlafaxine** (n = 819)	**Placebo** (n = 695)
Body as a Whole		
Headache	38%	34%
Asthenia	19%	9%
Abdominal Pain	6%	4%
Accidental Injury	4%	3%
Cardiovascular System		
Hypertension	5%	3%
Vasodilatation[3]	3%	2%
Palpitation	3%	1%
Digestive System		
Nausea	31%	9%
Anorexia[4]	17%	2%
Constipation	9%	3%
Diarrhea	8%	6%
Dyspepsia	7%	6%
Vomiting	3%	2%
Metabolic/Nutritional		
Weight Loss	2%	<1%
Nervous System		
Insomnia	24%	8%
Somnolence	20%	8%
Dry Mouth	17%	4%
Dizziness	16%	8%
Nervousness	10%	5%
Libido Decreased	8%	2%
Anxiety	5%	4%

Tremor	5%	2%
Agitation	3%	1%
Abnormal Dreams[5]	3%	<1%
Twitching	3%	<1%
Respiratory System		
Yawn	5%	<1%
Skin		
Sweating	13%	4%
Special Senses		
Abnormal Vision[6]	4%	2%
Urogenital System		
Abnormal Ejaculation[7,8]	19%	<1%
Impotence[8]	6%	<1%
Orgasmic Dysfunction[9,10]	5%	<1%

[1] Adverse events for which the Venlafaxine reporting rate was less than or equal to the placebo rate are not included. These events are: arthralgia, back pain, dysmenorrhea, flu syndrome, infection, pain, pharyngitis, rhinitis, and upper respiratory infection.
[2] <1% means greater than zero but less than 1%.
[3] Mostly "hot flashes."
[4] Mostly "decreased appetite" and "loss of appetite."
[5] Mostly "vivid dreams," "nightmares," and "increased dreaming."
[6] Mostly "blurred vision."
[7] Includes "delayed ejaculation" and "anorgasmia."
[8] Percentage based on the number of males (Venlafaxine = 454, placebo = 357).
[9] Includes "abnormal orgasm" and "anorgasmia."
[10] Percentage based on the number of females (Venlafaxine = 365, placebo = 338).

Table 10 Treatment-Emergent Adverse Event Incidence in Short-Term Placebo-Controlled Venlafaxine Clinical Trials in Panic Disorder Patients[1,2]

	% Reporting Event	
Body System Preferred Term	**Venlafaxine** (n = 1001)	**Placebo** (n = 662)
Body as a Whole		
Asthenia	10%	8%
Cardiovascular System		
Hypertension	4%	3%
Vasodilatation[3]	3%	2%
Digestive System		
Nausea	21%	14%
Dry mouth	12%	6%
Constipation	9%	3%
Anorexia[4]	8%	3%
Nervous System		
Insomnia	17%	9%
Somnolence	12%	6%

Dizziness	11%	10%
Tremor	5%	2%
Libido Decreased	4%	2%
Skin		
Sweating	10%	2%
Urogenital System		
Abnormal Ejaculation[5,6]	8%	<1%
Impotence[6]	4%	<1%
Orgasmic Dysfunction[7,8]	2%	<1%

[1] Adverse events for which the Venlafaxine reporting rate was less than or equal to the placebo rate are not included. These events are: abdominal pain, abnormal vision, accidental injury, anxiety, back pain, diarrhea, dysmenorrhea, dyspepsia, flu syndrome, headache, infection, nervousness, pain, paresthesia, pharyngitis, rash, rhinitis, and vomiting.
[2] <1% means greater than zero but less than 1%.
[3] Mostly "hot flushes."
[4] Mostly "decreased appetite" and "loss of appetite."
[5] Includes "delayed or retarded ejaculation" and "anorgasmia."
[6] Percentage based on the number of males (Venlafaxine = 335, placebo = 238).
[7] Includes "anorgasmia" and "delayed orgasm."
[8] Percentage based on the number of females (Venlafaxine = 666, placebo = 424).

Vital Sign Changes
Venlafaxine (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 treatment for up to 8 weeks in premarketing placebo-controlled GAD trials was associated with a mean final on-therapy increase in pulse rate of approximately 2 beats per minute, compared with less than 1 beat per minute for placebo. Venlafaxine treatment for up to 12 weeks in premarketing placebo-controlled Social Anxiety Disorder trials was associated with a mean final on-therapy increase in pulse rate of approximately 3 beats per minute, compared with an increase of 1 beat per minute for placebo. Venlafaxine 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.

In a flexible-dose study, with Venlafaxine (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 (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 treatment for up to 8 weeks and up to 6 months in premarketing placebo-controlled GAD trials was associated with

mean final on-therapy increases in serum cholesterol concentration of approximately 1.0 mg/dL and 2.3 mg/dL, respectively while placebo subjects experienced mean final decreases of 4.9 mg/dL and 7.7 mg/dL, respectively. Venlafaxine treatment for up to 12 weeks and up to 6 months in premarketing placebo-controlled Social Anxiety Disorder trials was associated with mean final on-therapy increases in serum cholesterol concentration of approximately 7.9 mg/dL and 5.6 mg/dL, respectively, compared with mean final decreases of 2.9 and 4.2 mg/dL, respectively, for placebo. Venlafaxine 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 (immediate release) for at least 3 months in placebo-controlled 12month 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.

Serum Triglycerides

Venlafaxine treatment for up to 12 weeks in pooled premarketing Social Anxiety Disorder trials was associated with a mean final on-therapy increase in fasting serum triglyceride concentration of approximately 8.2 mg/dL, compared with a mean final increase of 0.4 mg/dL for placebo. Venlafaxine treatment for up to 6 months in a premarketing Social Anxiety Disorder trial was associated with a mean final on-therapy increase in fasting serum triglyceride concentration of approximately 11.8 mg/dL, compared with a mean final on-therapy increase of 1.8 mg/dL for placebo.

Venlafaxine 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 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 (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.

Other Adverse Events Observed During the Premarketing Evaluation of Venlafaxine and Venlafaxine

During its premarketing assessment, multiple doses of Venlafaxine were administered to 705 patients in Phase 3 major depressive disorder studies and Venlafaxine was administered to 96

patients. During its premarketing assessment, multiple doses of Venlafaxine were also administered to 1381 patients in Phase 3 GAD studies, 819 patients in Phase 3 Social Anxiety Disorder studies, and 1314 patients in Phase 3 panic disorder studies. In addition, in premarketing assessment of Venlafaxine, 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 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, 8, 9, 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 (venlafaxine hydrochloride) extended-release capsules is not a controlled substance.

Physical and Psychological Dependence

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

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

Discontinuation effects have been reported in patients receiving venlafaxine.

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

OVERDOSAGE

Human Experience

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

There were 2 reports of acute overdose with Venlafaxine in GAD trials. One patient took a combination of 0.75 g of Venlafaxine and 200 mg of paroxetine and 50 mg of zolpidem. This patient was described as being alert, able to communicate, and a little sleepy. This patient was hospitalized, treated with activated charcoal, and recovered without any untoward effects. The other patient took 1.2 g of Venlafaxine. This patient recovered and no other specific problems were found. The patient had moderate dizziness, nausea, numb hands and feet, and hot-cold spells 5 days after the overdose. These symptoms resolved over the next week.

There were no reports of acute overdose with Venlafaxine in Social Anxiety Disorder trials.

There were 2 reports of acute overdose with Venlafaxine in panic disorder trials. One patient took 0.675 g of Venlafaxine once, and the other patient took 0.45 g of Venlafaxine for 2 days. o 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 (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 μg/mL, respectively, and the peak plasma levels of O-desmethylvenlafaxine were 3.37 and 1.30 μg/mL, respectively. Plasma venlafaxine levels were not obtained for the patient who ingested 6.75 g of venlafaxine. All 14 patients recovered without sequelae. Most patients reported no symptoms. Among the remaining patients, somnolence was the most commonly reported symptom. The patient who ingested 2.75 g of venlafaxine was observed to have 2 generalized convulsions and a prolongation of QTc to 500 msec, compared with 405 msec at baseline. Mild sinus tachycardia was reported in 2 of the other patients.

In postmarketing experience, overdose with venlafaxine has occurred predominantly in combination with alcohol and/or other drugs. 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 (eg, 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 pre-existing 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 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.

EXPIRAY DATE
Do not use later than the date of expiry.

STORAGE
Store in a dry place at a temparature not exceeding 30°c

PRESENTATION
VENLIFT OD-37.5, VENLIFTOD -75 & VENLIFT OD-150 is available in blister strip of 10 capsules.

MARKETED BY:

TORRENT PHARMACEUTICALS LTD.
Torrent House, Off Ashram Road,
Ahmedabad-380 009, INDIA

VEOD/AUG 2014/Ver 01