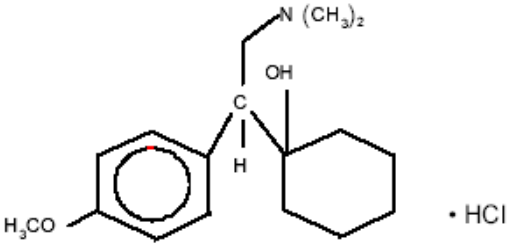
Efexor* XR

(venlafaxine hydrochloride)
Extended-Release Capsules

PHARMACOLOGICAL CLASSIFICATION
Antidepressant

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



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

Efexor XR is formulated as an extended-release capsule for once-a-day oral administration. Drug release is controlled by diffusion through the coating membrane on the spheroids and is not pH dependent. Capsules contain venlafaxine hydrochloride equivalent to 75 mg or 150 mg venlafaxine.

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 central nervous system (CNS). Preclinical studies have shown that venlafaxine and its major metabolite, O-desmethylvenlafaxine (ODV), are potent inhibitors of neuronal serotonin and norepinephrine reuptake, and weak inhibitors of dopamine reuptake. Animal studies indicate that tricyclic antidepressants may reduce β-adrenergic receptor responsiveness following chronic administration. In contrast, venlafaxine and ODV reduce β-adrenergic responsiveness after both acute (single dose) and chronic administration. These results may predict a more rapid onset of clinical activity for venlafaxine. Venlafaxine and its major metabolite appear to be equipotent with respect to their overall action on neurotransmitter reuptake and receptor binding.

Venlafaxine and ODV have virtually no affinity for rat brain muscarinic, histaminergic or α_1-adrenergic receptors *in vitro*. Pharmacologic activity at these receptors may be related to various side effects seen with other antidepressant drugs, such as anticholinergic, sedative, and cardiovascular effects. Venlafaxine does not possess monoamine oxidase (MAO) inhibitory activity.

In preclinical rodent models, venlafaxine demonstrated activity predictive of antidepressant and anxiolytic actions.

Venlafaxine also does not produce norepinephrine release from brain slices. It has no significant CNS stimulant activity in rodents.

Cardiac Electrophysiology
In a dedicated thorough QTc study in healthy subjects, venlafaxine did not prolong the QT interval to any clinically relevant extent at a dose of 450 mg/day (given as 225 mg twice a day).

Pharmacokinetics

Absorption: At least 92% of venlafaxine is absorbed following single oral doses of immediate-release venlafaxine. Absolute bioavailability is 40% to 45% due to pre-systemic metabolism. In single-dose studies with 25 mg to 150 mg of immediate-release venlafaxine, mean peak plasma concentrations (C_{max}) range, from 37 to 163 ng/mL, respectively, and are attained within 2.1 to 2.4 hours (t_{max}). Following the administration of venlafaxine extended-release capsules, peak plasma concentrations of venlafaxine and ODV are attained within 5.5 and 9 hours, respectively. Venlafaxine extended-release capsules and venlafaxine immediate-release tablets are associated with a similar extent of absorption.

Distribution: Steady-state concentrations of both venlafaxine and ODV in plasma are attained within 3 days of multiple-dose therapy of immediate-release venlafaxine. Both show linear kinetics over a dose range of 75 mg to 450 mg/day when administered every 8 hours. Venlafaxine and ODV are approximately 27% and 30% bound to human plasma proteins, respectively. Since this binding is independent of respective drug concentrations up to 2,215 and 500 mg/mL, both venlafaxine and ODV have low potential for involvement in significant drug-drug interactions involving drug displacement from serum proteins. The volume of distribution for venlafaxine at steady state is 4.4 ± 1.9 L/kg following intravenous administration.

Metabolism: Venlafaxine undergoes extensive hepatic metabolism. *In vitro* and *in vivo* studies indicate that venlafaxine is biotransformed to its major active metabolite, ODV, by the P450 isoenzyme CYP2D6. *In vitro* and *in vivo* studies indicate that venlafaxine is metabolized to a minor, less active metabolite, N-desmethylvenlafaxine, by CYP3A4. Although the relative activity of CYP2D6 may differ among patients, related modification of the venlafaxine dosage regimen is not required. Drug exposure (AUC) and fluctuation in plasma levels of venlafaxine and ODV were comparable following administration of equal daily doses of venlafaxine as twice daily or three times daily (t.i.d) regimens of immediate-release venlafaxine.

Elimination: Venlafaxine and its metabolites are excreted primarily through the kidneys. Approximately 87% of venlafaxine dose is recovered in the urine within 48 hours as either unchanged venlafaxine (5%), unconjugated ODV (29%), conjugated ODV (26%), or other minor inactive metabolites (27%).

Effects of Food: Food has no significant effect on the absorption of venlafaxine or the formation of ODV.

Patients with Hepatic Impairment: The pharmacokinetic disposition of venlafaxine and ODV are significantly altered in some patients with compensated hepatic cirrhosis (moderate hepatic impairment) following oral administration of single-dose venlafaxine. In patients with hepatic impairment, mean plasma clearance of venlafaxine and ODV are reduced by approximately 30% to 33% and mean elimination half-lives are prolonged by 2-fold or more compared to normal subjects.

In a second study, venlafaxine was administered orally and intravenously in normal subjects (n = 21), and in Child-Pugh A (n = 8) and Child-Pugh B (n = 11) subjects, mildly and moderately hepatically impaired, respectively. Oral bioavailability approximately doubled in patients with hepatic impairment compared to normal subjects. In patients with hepatic impairment, venlafaxine oral elimination half-life was approximately twice as long and oral clearance was reduced by more than half compared to normal subjects. In patients with hepatic impairment, 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.

Patients with Renal Impairment: Venlafaxine and ODV elimination half-lives increase with the degree of impairment in renal function. Elimination half-life increased by approximately 1.5-fold in patients with moderate renal impairment and by approximately 2.5-fold and 3-fold in patients with end-stage renal disease.

Age and Gender Studies: A population pharmacokinetic analysis of 404 immediate-release venlafaxine-treated patients from two studies involving both twice daily and three times daily regimens showed that dose-normalized trough plasma levels of either venlafaxine or ODV were unaltered by age or gender differences.

Preclinical safety data

Carcinogenicity

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 6 times (female rats) and 1 times (male rats) the plasma concentrations of patients receiving the maximum recommended human dose. Plasma levels of ODV were lower in rats than in patients receiving the maximum recommended dose. Tumors were not increased by venlafaxine treatment in mice or rats.

Mutagenicity

Venlafaxine and ODV were not mutagenic in the Ames reverse mutation assay in *Salmonella* bacteria or the Chinese hamster ovary/hypoxanthine guanine phosphoribosyl transferase (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, or in the *in vivo* chromosomal aberration assay in rat bone marrow.

Impairment of Fertility

Reproduction and fertility studies in rats showed no effect on male or female fertility at oral doses of up to 8 times the maximum recommended human daily dose, on a mg/kg basis, or of up to 2 times, on a mg/m^2 basis.

Reduced fertility was observed in a study in which both male and female rats were exposed to the major metabolite of venlafaxine (ODV). This ODV exposure was approximately 2 to 3 times that of a human venlafaxine dose of 225 mg/day. The human relevance of this finding is unknown.

Teratogenicity

Venlafaxine did not cause malformations in offspring of rats or rabbits given doses up to 11 times (rat) or 12 times (rabbit) the human dose of 375 mg/day of venlafaxine on a mg/kg basis, or 2.5 times (rat) and 4 times (rabbit) the human dose of 375 mg/day of venlafaxine, on a mg/m^2 basis.

CLINICAL EFFICACY

Depression

The efficacy of venlafaxine extended-release capsules as a treatment for depression, including depression with associated anxiety, was established in two placebo-controlled short-term studies. Populations in both trials consisted of outpatients meeting DSM-III-R or DSM-IV criteria for major depressive disorder.

The first study compared extended-release venlafaxine 75 to 150 mg/day, immediate-release venlafaxine 75 to 150 mg/day, and placebo for 12 weeks. Extended-release venlafaxine showed significant advantage over placebo starting at Week 2 of treatment on the Hamilton Rating Scale for Depression (HAM-D) Score and HAM-D Depressed Mood Item, at Week 3 on the Montgomery-Asberg Depression Rating Scale (MADRS) total, and at Week 4 on the Clinical Global Impressions (CGI) Severity of Illness Scale. All advantages were maintained through the end of treatment. Extended-release venlafaxine also showed significant advantage over immediate-release venlafaxine at Weeks 8 and 12 on the HAM-D total and CGI Severity of Illness Scale and at Week 12 for all efficacy variables.

The second study compared treatment with extended-release venlafaxine 75 to 225 mg/day and placebo for up to 8 weeks. Sustained statistical improvement over placebo was seen beginning at Week 2 for the CGI Severity of Illness Scale, beginning at Week 4 for the HAM-D total and MADRS total, and beginning at Week 3 for the HAM-D Depressed Mood Item.

A study of depressed outpatients who had responded to Efexor XR during an initial 8-week open-label treatment phase and were randomly assigned to continuation on Efexor XR or placebo for 6 months demonstrated a significantly lower relapse rate for patients taking Efexor XR compared with those on placebo.

A study of depressed outpatients who had responded to Efexor Tablet (the immediate-release form of venlafaxine) during an initial 6-month open-label treatment phase and were randomly assigned to maintenance therapy on Efexor Tablet or placebo for 12 months demonstrated a significantly lower recurrence rate for patients taking Efexor Tablet compared with those on placebo.

Generalized Anxiety Disorder
The efficacy of venlafaxine extended-release capsules as a treatment for generalized anxiety disorder (GAD) was established in two short-term (8-week), placebo-controlled, fixed-dose studies; one long-term (6-month), placebo-controlled, fixed-dose study; and one long-term (6-month), placebo-controlled, flexible-dose study in outpatients meeting DSM-IV criteria for GAD.

One short-term study evaluating extended-release venlafaxine doses of 75, 150 and 225 mg/day, and placebo showed that the 225 mg/day dose was more effective than placebo on the Hamilton Rating Scale for Anxiety (HAM-A) total score, both the HAM-A anxiety and tension items, and the CGI scale. While there was also evidence for superiority over placebo for the 75 and 150 mg/day doses, these doses were not as consistently effective as the highest dose.

A second short-term study evaluating extended-release venlafaxine doses of 75 and 150 mg/day, and placebo showed that both doses were more effective than placebo on some of these same outcomes; however, the 75 mg/day dose was more consistently effective than the 150 mg/day dose. Two long-term (6-month) studies, one with extended-release venlafaxine doses of 37.5, 75, and 150 mg/day and the other evaluating doses of 75 to 225 mg/day, showed that doses of 75 mg or higher were more effective than placebo on the HAM-A total, both the HAM-A anxiety and tension items, and the CGI scale after short-term (Week 8) and long-term (Month 6) treatment.

Social Anxiety Disorder (Social Phobia)
The efficacy of Efexor XR capsules as a treatment for social anxiety disorder (SAD) (also known as Social Phobia) was established in two double-blind, parallel group, 12-week, multicenter, placebo-controlled, flexible-dose studies in adult outpatients meeting DSM-IV criteria for SAD. Patients received doses in a range of 75 to 225 mg/day. Efficacy was assessed with the Liebowitz Social Anxiety Scale (LSAS). In these two trials, Efexor XR was significantly more effective than placebo on change from baseline to endpoint on the LSAS total score.

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

Panic Disorder
The efficacy of Efexor XR capsules as a treatment of panic disorder was established in two double-blind, 12-week, multicenter, placebo-controlled studies in adult outpatients meeting DSM-IV criteria for panic disorder, with or without agoraphobia. Patients received fixed doses of 75 or 150 mg/day in one study (Study 1) and 75 or 225 mg/day in other study (Study 2).

In one flexible-dose study (Study 3) (75 mg or 225 mg daily doses), the primary outcome, the percentage of patients free of full-symptom panic attacks, approached significance (p=0.056). In this study, Efexor XR was significantly more effective than placebo for the two key secondary outcomes, (1) mean change from baseline to endpoint on the panic disorder severity scale (PDSS) total score, and (2) percentage of patients rated as responders (much improved or very much improved) in the clinical global impressions (CGI) improvement scale.

In another flexible-dose study (Study 4) (dose range 75 mg to 225 mg per day), Efexor XR was not significantly more effective than placebo for the primary outcome, the percentage of patients free of full-symptom panic attacks, but it was significantly more effective than placebo for the secondary outcome, percentage of patients rated as responders (much improved or very much improved) in the clinical impressions (CGI) improvement global scale.

Efficacy was assessed on the basis of outcomes in three variables: (1) percentage of patients free of full-symptom panic attacks on the panic and anticipatory anxiety scale (PAAS), (2) mean change from baseline to endpoint on the panic disorder severity scale (PDSS) total score, and (3) percentage of patients rated as responders (much improved or very much improved) in the clinical global impression

(CGI) improvement scale. In Studies 1 and 2, Efexor XR was significantly more effective than placebo in all three variables.

Primary Efficacy Variable PAAS: Percent of Patients Free of Full-Symptom Panic Attacks, Final On-Therapy (12 weeks in Studies 1 and 2, 10 weeks in Studies 3 and 4), ITT Population				
Study	Treatment	n	Number (%) Panic Free	p-value vs. Placebo[a]
1	Placebo	154	53 (34.4)	
	Venlafaxine XR 75 mg	157	85 (54.1)	<0.001
	Venlafaxine XR 150 mg	158	97 (61.4)	<0.001
	Paroxetine	160	96 (60.0)	<0.001
2	Placebo	157	73 (46.5)	
	Venlafaxine XR 75 mg	156	100 (64.1)	<0.001
	Venlafaxine XR 225 mg	160	112 (70.0)	<0.001
	Paroxetine	151	89 (58.9)	0.008
3	Placebo	155	63 (40.6)	
	Venlafaxine XR 75-225 mg	155	79 (51.0)	0.056
4[b]	Placebo	168	88 (52.4)	
	Venlafaxine XR 75 mg	160	88 (55.0)	0.622

Abbreviations: PAAS=Panic and Anticipatory Anxiety Scale; ITT= Intent to treat.

a: Chi-square p-values obtained from logistic regression model logit (response) = treatment + center in studies 1, 3 and 4 and logistic regression model logit (response) = baseline + treatment + center in study 2.

b: Excluding site 39127.

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

In a longer-term study (Study 5) adult outpatients meeting DSM-IV criteria for panic disorder who had responded during a 12-week open phase with Efexor XR (75-225 mg/day) were randomly assigned to continue the same Efexor XR dose (75, 150 or 225 mg) or switch to placebo for observation for relapse during a 6-month double-blind phase. Response during the open phase was defined as ≥1 full symptom panic attack per week during the last 2 weeks of the open phase and a CGI Improvement score of 1 (very much improved) or 2 (much improved). Relapse during the double-blind phase was defined as having 2 or more full-symptom panic attacks per week for 2 consecutive weeks or having discontinued due to loss of effectiveness. Patients receiving continued Efexor XR treatment experienced significantly lower relapse rates over the subsequent 6 months compared with those receiving placebo.

Survival Analysis for Relapse of Panic Disorder, ITT Patients, Double-Blind Period				
Therapy Group	Number of Patients	Number of Relapse (%)	Cumulative Probability of Relapse	p-values[a]
Placebo	80	40 (50.0)	0.523	
Venlafaxine	89	20 (22.5)	0.239	<0.001

a: p-values obtained from log-ranked statistics of Kaplan-Meier survival model.

INDICATIONS

Efexor XR is indicated for the treatment of depression, including depression with associated anxiety, in hospitalized patients.

Treatment of anxiety or GAD, including long-term treatment.

The effectiveness of Efexor XR in long-term use for GAD has been evaluated for up to 6 months in controlled clinical trials.

For prevention of relapse of an episode of depression or for prevention of the recurrence of new depressive episodes.

Efexor XR is indicated for the treatment of SAD, also known as social phobia, as defined in DSM-IV.

SAD (DSM-IV) is characterized by a marked and persistent fear of 1 or more social or performance situations in which the person is exposed to unfamiliar people or to possible scrutiny by others. Exposure to the feared situation almost invariably provokes anxiety, which may approach the intensity of a panic attack. The feared situations are avoided or endured with intense anxiety or distress. The avoidance, anxious anticipation, or distress in the feared situation(s) interferes significantly with the person's normal routine, occupational or academic functioning, or social activities or relationships, or there is a marked distress about having the phobias. Lesser degrees of performance anxiety or shyness generally do not require psychopharmacological treatment.

Efexor XR is indicated for the treatment of panic disorder, including prevention of relapse.

CONTRAINDICATIONS
Hypersensitivity to venlafaxine or any excipients in the formulation.

Concomitant use of venlafaxine and any monoamine oxidase inhibitor (MAOI).

Venlafaxine must not be initiated for at least 14 days after discontinuation of treatment with an MAOI; a shorter interval may be justified in the case of a reversible MAOI (see prescribing information of the reversible MAOI). Venlafaxine must be discontinued for at least 7 days before starting treatment with any MAOI (see section **DRUG INTERACTIONS**).

SPECIAL WARNINGS AND PRECAUTIONS
Suicide/Suicidal Thoughts or Clinical Worsening
All patients treated with venlafaxine should be monitored appropriately and observed closely for clinical worsening and suicidality. 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 when initiating therapy or during any change in dose or dosage regimen. The risk of suicide attempt must be considered, especially in patients with depression, and the smallest quantity of drug, consistent with good patient management, should be provided to reduce the risk of overdose (see also sections **PEDIATRIC USE** and **ADVERSE REACTIONS**).

Suicide is a known risk of depression and certain other psychiatric disorders, and these disorders themselves are strong predictors of suicide. Pooled analyses of short-term placebo-controlled trials of antidepressant medicines (selective serotonin reuptake inhibitors [SSRIs] and others) showed that these medicines increase the risk of suicidality in children, adolescents, and young adults (ages 18-24 years) with major depression and other psychiatric disorders. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults older than 24 years of age; there was a reduction in the risk of suicidality with antidepressants compared to placebo in adults aged 65 years and older.

Aggression
Aggression may occur in some patients who have received antidepressants, including venlafaxine treatment, dose reduction, or discontinuation. As with other antidepressants, venlafaxine should be used cautiously in patients with a history of aggression.

Discontinuation
Discontinuation effects are well known to occur with antidepressants, and sometimes these effects can be protracted and severe (see section **ADVERSE REACTIONS**). Suicide/suicidal thoughts and aggression have been observed in patients during changes in venlafaxine dosing regimen, including during discontinuation (see above in section **SPECIAL WARNINGS AND PRECAUTIONS** - Suicide/Suicidal Thoughts or Clinical Worsening and Aggression). It is therefore recommended that the dosage of venlafaxine be tapered gradually and individually and the patients be closely monitored during discontinuation (see section **DOSAGE AND ADMINISTRATION**). In some patients, discontinuation could take months or longer.

Sexual Dysfunction

Serotonin-norepinephrine reuptake inhibitors (SNRIs) may cause symptoms of sexual dysfunction (see section **ADVERSE REACTIONS**). There have been reports of long-lasting sexual dysfunction where the symptoms have continued despite discontinuation of SNRIs.

Bone Fractures
Epidemiological studies show an increased risk of bone fractures in patients receiving serotonin reuptake inhibitors (SRIs) including venlafaxine. The mechanism leading to this risk is not fully understood.

NMS-like Reactions
As with other serotonergic agents, serotonin syndrome, a potentially life-threatening condition or neuroleptic malignant syndrome (NMS)-like reactions may occur with venlafaxine treatment, particularly with concomitant use of other serotonergic drugs including SSRIs, SNRIs, amphetamines, and triptans, fentanyl, dextromethorphan, tramadol, tapentadol, meperidine, methadone, pentazocine, with drugs that impair metabolism of serotonin including MAOIs, e.g. methylene blue, or with antipsychotics or other dopamine antagonists. Symptoms of serotonin syndrome may include mental status changes (e.g. agitation, hallucinations and coma), autonomic instability (e.g. tachycardia, labile blood pressure and hyperthermia), neuromuscular aberrations (e.g. hyperreflexia, incoordination), and/or gastrointestinal symptoms (e.g. nausea, vomiting and diarrhea). Serotonin syndrome, in its most severe form, can resemble NMS, which includes hyperthermia, muscle rigidity, autonomic instability with possible rapid fluctuation of vital signs, and mental status changes (see section **DRUG INTERACTIONS**).

If concomitant treatment with venlafaxine and other agents that may affect the serotonergic and/or dopaminergic neurotransmitter systems is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases.

The concomitant use of venlafaxine with serotonin precursors, such as tryptophan supplements is not recommended.

Angle Closure Glaucoma
Mydriasis may occur in association with venlafaxine. It is recommended that patients with raised intra-ocular pressure or patients at risk for acute narrow angle glaucoma (angle closure glaucoma) be closely monitored.

Cardiovascular System
Venlafaxine has not been evaluated in patients with a recent history of myocardial infarction or unstable heart disease. Therefore, it should be used with caution in these patients. In these patients, assessment of the cardiovascular system (e.g. ECG, serum electrolytes during diuretic treatment) should be considered during treatment with venlafaxine, particularly when the dose is increased beyond 150 - 200 mg daily.

Dose-related increases in blood pressure have been reported in some patients treated with venlafaxine. Cases of elevated blood pressure requiring immediate treatment have been reported in post-marketing experience. Measurement of blood pressure is recommended for patients receiving venlafaxine. For patients who experience a sustained increase in blood pressure while receiving venlafaxine, either dose reduction or discontinuation should be considered. Pre-existing hypertension should be controlled before treatment with venlafaxine. Caution should be exercised in patients whose underlying conditions might be compromised by increases in blood pressure.

Increases in heart rate can occur, particularly with higher doses. Caution should be exercised in patients whose underlying conditions might be compromised by increases in heart rate. The electrocardiograms for 357 patients who received Efexor XR and 285 patients who received placebo in 8- to 12-week double-blind, placebo-controlled trials were analysed. The mean change from baseline in corrected QT interval for Efexor XR-treated patients was increased relative to that for placebo-treated patients (increase of 4.7 msec for Efexor XR and decrease of 1.9 msec for placebo).

Cases of QTc prolongation, Torsade de Pointes (TdP), ventricular tachycardia, and sudden death have been reported during the post-marketing use of venlafaxine. The majority of reports occurred in

association with overdose or in patients with other risk factors for QTc prolongation/TdP. Therefore, venlafaxine should be used with caution in patients with risk factors for QTc prolongation.

Convulsions
Convulsions may occur with venlafaxine therapy. As with all antidepressants, venlafaxine should be introduced with caution in patients with a history of convulsions.

Mania/Hypomania
Mania/hypomania may occur in a small proportion of patients with mood disorders who have received antidepressants, including venlafaxine. As with other antidepressants, venlafaxine should be used cautiously in patients with a history or family history of bipolar disorder.

Hyponatremia
Cases of hyponatremia and/or the syndrome of inappropriate antidiuretic hormone (SIADH) secretion may occur with venlafaxine, usually in volume-depleted or dehydrated patients. Elderly patients, patients taking diuretics, and patients who are otherwise volume depleted may be at greater risk for this event.

Bleeding
Drugs that inhibit serotonin uptake may lead to abnormalities of platelet aggregation. There have been reports of bleeding abnormalities with venlafaxine ranging from skin and mucous membrane bleeding and gastrointestinal hemorrhage to life-threatening hemorrhage. As with other SRIs, venlafaxine should be used cautiously in patients predisposed to bleeding, including patients on anticoagulants and platelet inhibitors.

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 hydrochloride and weight loss agents is not recommended. Venlafaxine hydrochloride is not indicated for weight loss, alone or in combination with other products.

Serum Cholesterol
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 clinical trials. Measurement of serum cholesterol levels should be considered during long-term treatment.

PREGNANCY
The safety of venlafaxine in human pregnancy has not been established. Venlafaxine must be administered to pregnant women only if the expected benefits outweigh the possible risks. If venlafaxine is used until or shortly before birth, discontinuation effects in the newborn should be considered. Some neonates exposed to venlafaxine late in the third trimester have developed complications requiring tube feeding, respiratory support, or prolonged hospitalization. Such complications can arise immediately upon delivery.

When venlafaxine was administered orally to pregnant rats throughout gestation and lactation, there was a decrease in pup weight, an increase in stillborn pups, and an increase in pup deaths during the first 5 days of lactation, when dosing began during pregnancy and continued until weaning. The cause of these deaths is not known. These effects occurred at 10 times the human daily dose (on a mg/kg basis) or 2.5 times (on a mg/m^2 basis) the human daily dose of 375 mg of venlafaxine. The no-effect dose for rat pup mortality was 1.4 times the human dose, on a mg/kg basis, or 0.25 times the human dose, on a mg/m^2 basis.

A prospective longitudinal study of 201 women with a history of major depression who were euthymic at the beginning of pregnancy showed that women who discontinued antidepressant medication during pregnancy were more likely to experience a relapse of major depression than women who continued antidepressant medication.

Exposure to SNRIs in mid to late pregnancy may increase the risk for preeclampsia, and exposure to SNRIs near delivery may increase the risk for postpartum haemorrhage.

Epidemiological data have suggested that the use of SSRIs in pregnancy, particularly in late pregnancy, may increase the risk of persistent pulmonary hypertension in the newborn (PPHN). Although no studies have investigated an association of PPHN to SNRI treatment, this potential risk cannot be ruled out with venlafaxine taking into account the related mechanism of action (inhibition of the re-uptake of serotonin).

LACTATION
Venlafaxine and ODV are excreted in human milk; therefore, a decision should be made whether to breast-feed or to discontinue venlafaxine.

PEDIATRIC USE
Efficacy in patients younger than 18 years of age has not been established.

Regular measurement of weight and blood pressure is recommended if venlafaxine is used in children and adolescents. Discontinuation of venlafaxine treatment should be considered in children and adolescents who experience a sustained increase in blood pressure. Measurement of serum cholesterol levels should be considered during long-term treatment of children and adolescents (see sections **DOSAGE AND ADMINISTRATION** and **ADVERSE REACTIONS**). Safety in children younger than 6 years of age has not been evaluated.

DRUG INTERACTIONS

- ***Monoamine Oxidase Inhibitors***

Severe adverse reactions have been reported in patients who have recently been discontinued from an MAOI and started on venlafaxine, or have recently had venlafaxine therapy discontinued prior to initiation of an MAOI (see section **CONTRAINDICATIONS**). These reactions have included tremor, myoclonus, diaphoresis, nausea, vomiting, flushing, dizziness and hyperthermia with features resembling NMS, seizures, and death.

- ***CNS-Active Drugs***

The risk of using venlafaxine in combination with other CNS-active drugs has not been systematically evaluated. Consequently, caution is advised when venlafaxine is taken in combination with other CNS-active drugs.

- ***Serotonin Syndrome***

As with other serotonergic agents, serotonin syndrome, a potentially life-threatening condition, may occur with venlafaxine treatment, particularly with concomitant use of other agents that may affect the serotonergic neurotransmitter system including triptans, SSRIs, other SNRIs, amphetamines, lithium, sibutramine, fentanyl and its analogues, tramadol, dextromethorphan, tapentadol, meperidine, methadone, pentazocine, or St. John's wort (*Hypericum perforatum*), with drugs which impair the metabolism of serotonin, such as MAOIs, including linezolid (an antibiotic, which is a reversible non-selective MAOI) and methylene blue; or with serotonin precursors, such as tryptophan supplements. Serotonin syndrome symptoms may include mental status changes, autonomic instability, neuromuscular aberrations and/or gastrointestinal symptoms (see sections **CONTRAINDICATIONS** and **SPECIAL WARNINGS AND PRECAUTIONS**).

If concomitant treatment of venlafaxine with an SSRI, an SNRI, or a 5-hydroxytryptamine receptor agonist (triptan) is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases. The concomitant use of venlafaxine with serotonin precursors, such as tryptophan supplements is not recommended (see section **SPECIAL WARNINGS AND PRECAUTIONS**).

- ***Drugs that Prolong QT Interval***

The risk of QTc prolongation and/or ventricular arrhythmias (e.g. TdP) is increased with concomitant use of other drugs, which prolong the QTc interval (e.g. some antipsychotics and antibiotics) (see section **SPECIAL WARNINGS AND PRECAUTIONS**).

- ***Indinavir***

A pharmacokinetic study with indinavir has shown a 28% decrease in area under the concentration versus time curve (AUC) and a 36% decrease in C_{max} for indinavir. Indinavir did not affect the pharmacokinetics of venlafaxine and ODV. The clinical significance of this interaction is unknown.

- ***Ethanol***

Venlafaxine has been shown not to increase the impairment of mental and motor skills caused by ethanol. However, as with all CNS-active drugs, patients should be advised to avoid alcohol consumption while taking venlafaxine.

- ***Haloperidol***

A pharmacokinetic study with haloperidol has shown a 42% decrease in total oral clearance, a 70% increase in AUC, an 88% increase in C_{max}, but no change in half-life. This should be taken into account in patients treated with haloperidol and venlafaxine concomitantly.

- ***Cimetidine***

At steady state, cimetidine has been shown to inhibit first-pass metabolism of venlafaxine; however, cimetidine had no effect on the pharmacokinetics of ODV. The overall pharmacological activity of venlafaxine plus ODV is expected to increase only slightly in most patients. In the elderly and in patients with hepatic dysfunction, this interaction may be more pronounced.

- ***Imipramine***

Venlafaxine did not affect the pharmacokinetics of imipramine and 2-OH-imipramine. However, desipramine AUC, C_{max}, and C_{min} increased by about 35% in the presence of venlafaxine. There was an increase of 2-OH-desipramine AUC by 2.5- to 4.5-fold. Imipramine did not affect the pharmacokinetics of venlafaxine and ODV. This should be taken into account in patients treated with imipramine and venlafaxine concomitantly.

- ***Ketoconazole***

A pharmacokinetic study with ketoconazole in extensive metabolizers (EM) and poor metabolizers (PM) of CYP2D6 resulted in higher plasma concentrations of both venlafaxine and ODV in subjects following administration of ketoconazole. Venlafaxine C_{max} increased by 26% in EM subjects, and 48% in PM subjects. C_{max} values for ODV increased by 14% and 29% in EM and PM subjects, respectively. Venlafaxine AUC increased by 21% in EM subjects and 70% in PM subjects. AUC values for ODV increased by 23% and 33% in EM and PM subjects, respectively (see **Potential for Other Drugs to Affect Venlafaxine**).

- ***Metoprolol***

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

- ***Risperidone***

Venlafaxine increased risperidone AUC by 32% but did not significantly alter the pharmacokinetic profile of the total active moiety (risperidone plus 9-hydroxyrisperidone). The clinical significance of this interaction is unknown.

- ***Diazepam***

Diazepam does not appear to affect the pharmacokinetics of either venlafaxine or ODV. Venlafaxine has no effects on the pharmacokinetics and pharmacodynamics of diazepam and its active metabolite, desmethyldiazepam.

- ***Lithium***

The steady-state pharmacokinetics of venlafaxine and ODV are not affected when lithium is co-administered. Venlafaxine has no effect on the pharmacokinetics of lithium (see also subheading above, **CNS-Active Drugs**).

- ***Drugs Highly Bound to Plasma Proteins***

Venlafaxine is not highly bound to plasma proteins (27% bound); therefore, administration of venlafaxine to a patient taking another drug that is highly protein bound is not expected to cause increased free concentrations of the other drug.

- ***Drugs Metabolized by Cytochrome P450 Isoenzymes***

Studies indicate that venlafaxine is a relatively weak inhibitor of CYP2D6. Venlafaxine did not inhibit CYP3A4, CYP1A2, and CYP2C9 *in vitro*. This was confirmed by *in vivo* studies with the following drugs: alprazolam (CYP3A4), caffeine (CYP1A2), carbamazepine (CYP3A4), diazepam (CYP3A4 and CYP2C19) and tolbutamide (CYP2C9).

- ***Potential for Other Drugs to Affect Venlafaxine***

The metabolic pathways for venlafaxine include CYP2D6 and CYP3A4. Venlafaxine is primarily metabolized to its active metabolite, ODV, by the cytochrome P450 enzyme, CYP2D6. CYP3A4 is a minor pathway relative to CYP2D6 in the metabolism of venlafaxine.

CYP2D6 Inhibitors:
Concomitant use of CYP2D6 inhibitors and venlafaxine may reduce the metabolism of venlafaxine to ODV, resulting in increased plasma concentrations of venlafaxine and decreased concentrations of ODV. As venlafaxine and ODV are both pharmacologically active, no dosage adjustment is required when venlafaxine is co-administered with a CYP2D6 inhibitor.

CYP3A4 Inhibitors:
Concomitant use of CYP3A4 inhibitors and venlafaxine may increase the levels of venlafaxine and ODV (see ***Ketoconazole*** above). Therefore, caution is advised when combining venlafaxine with a CYP3A4 inhibitor.

CYP2D6 and CYP3A4 Inhibitors:
The concomitant use of venlafaxine with drug treatment(s) that potentially inhibits both CYP2D6 and CYP3A4, the primary metabolizing enzymes for venlafaxine, has not been studied. However, this concomitant use would be expected to increase venlafaxine plasma concentrations. Therefore, caution is advised when combining venlafaxine with any agent(s) that produces simultaneous inhibition of these two enzyme systems.

- ***Electroconvulsive Therapy***

There are no clinical data establishing the benefit of electroconvulsive therapy combined with venlafaxine treatment.

- ***Drug-Laboratory Test Interactions***

False-positive urine immunoassay screening tests for 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.

EFFECTS ON ACTIVITIES REQUIRING CONCENTRATION AND PERFORMANCE

Venlafaxine did not affect psychomotor, cognitive, or complex behavior performance in healthy volunteers. However, any psychoactive drug may impair judgement, thinking, and motor skills. Therefore, patients should be cautioned about their ability to drive or operate hazardous machinery.

ABUSE AND DEPENDENCE

Clinical studies did not show evidence of drug-seeking behavior, development of tolerance, or dose escalation over time.

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.

ADVERSE REACTIONS

Adverse Drug Reaction Table

Adverse Drug Reactions (ADRs) by System Organ Class (SOC) and Council for International Organizations of Medical Sciences (CIOMS) frequency category listed in order of decreasing medical seriousness within each frequency category and SOC

System Organ Class	Very Common ≥1/10	Common ≥1/100 to <1/10	Uncommon ≥1/1,000 to < 1/100	Rare ≥1/10,000 to < 1/1,000	Very Rare <1/10,000	Frequency Not Known (cannot be estimated from the available data)
Blood and lymphatic system disorders				Agranulocytosis[*§], Aplastic anaemia[*§], Pancytopenia[*§], Neutropenia[*§]	Thrombocytopenia[*]	
Immune system disorders				Anaphylactic reaction[*§]		
Endocrine disorders				Inappropriate antidiuretic hormone secretion[*§]	Blood prolactin increased[*]	
Metabolism and nutrition disorders		Decreased appetite		Hyponatraemia[*]		
Psychiatric disorders	Insomnia	Abnormal dreams, Nervousness, Libido decreased, Agitation[*], Anorgasmia	Confusional state[*], Mania, Hypomania, Depersonalisation, Hallucination, Abnormal orgasm, Bruxism[*], Apathy	Delirium[*§]		
Nervous system disorders	Headache[*], Dizziness, Sedation	Akathisia[*], Tremor, Paraesthesia, Dysgeusia	Syncope, Myoclonus, Balance disorder[*], Coordination abnormal[*], Dyskinesia[*]	Neuroleptic malignant syndrome[*§], Serotonin syndrome[*§], Convulsion, Dystonia[*]	Tardive dyskinesia[*]	
Eye disorders		Visual impairment, Accommodation disorder, Mydriasis		Angle closure glaucoma[*§]		
Ear and labyrinth disorders		Tinnitus[*]				

System Organ Class	Very Common ≥1/10	Common ≥1/100 to <1/10	Uncommon ≥1/1,000 to < 1/100	Rare ≥1/10,000 to < 1/1,000	Very Rare <1/10,000	Frequency Not Known (cannot be estimated from the available data)
Cardiac disorders		Tachycardia, Palpitations		Torsade de pointes*§, Ventricular tachycardia*§, Ventricular fibrillation*§, Electrocardiogram QT prolonged*, Stress cardiomyopathy (takotsubo cardiomyopathy)*§		
Vascular disorders		Hypertension, Hot flush	Orthostatic hypotension, Hypotension*			
Respiratory, thoracic and mediastinal disorders		Dyspnoea*, Yawning		Interstitial lung disease*§, Pulmonary eosinophilia*§		
Gastrointestinal disorders	Nausea, Dry mouth, Constipation	Diarrhoea*, Vomiting	Gastrointestinal haemorrhage*	Pancreatitis*		
Hepatobiliary disorders			Liver function test abnormal*	Hepatitis*§		
Skin and subcutaneous tissue disorders	Hyperhidrosis*	Rash, Pruritus*, Night sweats*	Urticaria*, Alopecia*, Ecchymosis, Photosensitivity reaction	Stevens-Johnson syndrome*§, Toxic epidermal necrolysis*§, Angioedema*§, Erythema multiforme*§		
Musculoskeletal and connective tissue disorders		Hypertonia		Rhabdomyolysis*§		
Renal and urinary disorders		Urinary hesitation, Urinary retention, Pollakiuria*	Urinary incontinence*			
Reproductive system and breast disorders		Erectile dysfunction, Ejaculation disorder	Metrorrhagia*, Menorrhagia*			

System Organ Class	Very Common ≥1/10	Common ≥1/100 to <1/10	Uncommon ≥1/1,000 to < 1/100	Rare ≥1/10,000 to < 1/1,000	Very Rare <1/10,000	Frequency Not Known (cannot be estimated from the available data)
General disorders and administration site conditions		Fatigue, Asthenia, Chills*			Mucosal Haemorrhage*	
Investigations		Weight decreased, Weight increased	Blood cholesterol increased		Bleeding time prolonged*	
Injury, poisoning and procedural complications			Bone fracture			

*ADR identified post-marketing
§ADR frequency estimated using "The Rule of 3"
ADR = Adverse Drug Reaction

Discontinuation Effects
The following symptoms have been reported in association with abrupt discontinuation or dose reduction, or tapering of treatment: hypomania, anxiety, agitation, nervousness, confusion, insomnia or other sleep disturbances, fatigue, somnolence, paresthaesia, dizziness, convulsion, vertigo, headache, flu-like symptoms, tinnitus, impaired coordination and balance, tremor, sweating, dry mouth, anorexia, diarrhoea, nausea, vomiting, visual impairment and hypertension. In pre-marketing studies, the majority of discontinuation reactions were mild and resolved without treatment (see sections **DOSAGE AND ADMINISTRATION** and **SPECIAL WARNINGS AND PRECAUTIONS**). While these events are generally self-limiting, there have been reports of serious discontinuation symptoms, and sometimes these effects can be protracted and severe.

Pediatric Patients
In general, the adverse reaction profile of venlafaxine (in placebo-controlled clinical trials) in children and adolescents (aged 6 to 17) was similar to that seen in adults. As with adults, decreased appetite, weight loss, increased blood pressure, and increased serum cholesterol were observed (see sections **SPECIAL WARNINGS AND PRECAUTIONS** and **PEDIATRIC USE**).

In pediatric clinical trials, the adverse reaction suicidal ideation was observed. There were also increased reports of hostility and, especially in major depressive disorder, self-harm.

Particularly, the following adverse reactions were observed in pediatric patients: abdominal pain, agitation, dyspepsia, ecchymosis, epistaxis, and myalgia.

DOSAGE AND ADMINISTRATION
It is recommended that venlafaxine extended-release capsules be taken with food, at approximately the same time each day. Capsules must be swallowed whole with fluid and not divided, crushed, chewed, or dissolved, or it may be administered by carefully opening the capsule and sprinkling the entire contents on a spoonful of applesauce. This drug/food mixture should be swallowed immediately without chewing and should be followed with a glass of water to ensure complete swallowing of the pellets.

Depression
The recommended dose for Efexor XR is 75 mg/day given once daily.

When required, the venlafaxine dosage can be increased in increments of 75 mg/day, at intervals of no less than 4 days. The venlafaxine dose can be titrated up to 225 mg/day in moderately depressed patients and 375 mg/day for severely depressed patients.

Extended-release venlafaxine dosage increases can be made at intervals of approximately 2 weeks or more, but not less than 4 days.

Usually, the dosage for prevention of relapse or for the prevention of recurrence of a new episode is similar to that used during initial treatment. Patients should be regularly reassessed in order to evaluate the benefit of long-term therapy.

Generalized Anxiety Disorder
The recommended dose for Efexor XR is 75 mg per day given once daily.

When required, the venlafaxine dosage can be increased in increments of 75 mg/day, up to a maximum dose of 225 mg/day, at intervals of no less than 4 days.

Extended-release venlafaxine dosage increases can be made at intervals of approximately 2 weeks or more, but not less than 4 days. Patients should be regularly reassessed in order to evaluate the benefit of long-term therapy.

Social Anxiety Disorder (Social Phobia)
For most patients with SAD (social phobia), the recommended starting dose for Efexor XR is 75 mg/day, administered in a single dose. In clinical trials establishing the efficacy of Efexor XR in outpatients with SAD, the initial dose of Efexor XR was 75 mg/day and the maximum dose was 225 mg/day. Although a dose-response relationship for effectiveness in patients with SAD was not clearly established in fixed-dose studies, certain patients not responding to the initial 75 mg/day dose may benefit from dose increases to a maximum of approximately 225 mg/day. Dose increases should be in increments of up to 75 mg/day, as needed, and should be made at intervals of not less than 4 days.

In SAD, continuing therapeutic benefit has been established for periods of up to 6 months. The need for continuing medication in patients with SAD who improve with Efexor XR treatment should be periodically assessed.

Panic Disorder
The recommended dose is 75 mg of Efexor XR once daily. Treatment should be started with a dose of 37.5 mg per day of Efexor XR for the first 4 to 7 days, after which the dose should be increased to 75 mg once daily.

Patient not responding to the 75 mg/day dose may benefit from dose increases to a maximum of 225 mg/day although there is no direct clinical trial evidence of any significant increase in efficacy with increased dose. Dosage increases can be made in increments of 75 mg per day at intervals of approximately 2 weeks or more, but not less than 4 days.

Discontinuing Efexor XR
Gradual dose tapering is recommended when discontinuing venlafaxine therapy (see sections **SPECIAL WARNINGS AND PRECAUTIONS** and **ADVERSE REACTIONS**). Tapering over at least a two-week period is recommended if venlafaxine has been used for more than 6 weeks. In clinical trials with venlafaxine extended-release capsules, tapering was achieved by reducing the daily dose by 75 mg at 1-week intervals. However, the time period required for tapering and the amount of dose reduction may depend on the dose, duration of therapy, and the individual patient. In some patients, discontinuation may need to occur very gradually over periods of months or longer.

It is recommended that venlafaxine extended-release capsules to be taken with food, at approximately the same time each day. Capsules must be swallowed whole with fluid and not divided, crushed, chewed, or dissolved.

Use in Patients with Renal Impairment

The total daily dose of venlafaxine should be reduced by 25% to 50% in patients with renal impairment with a glomerular filtration rate (GFR) of 10-70 mL/min.

The total daily dose of venlafaxine should be reduced by 50% in hemodialysis patients. Administration must be withheld until the dialysis session is completed.

Because of individual variability in clearance in these patients, individualization of dosage may be desirable.

Use in Patients with Hepatic Impairment
The total daily dose of venlafaxine should be reduced by 50% in patients with mild to moderate hepatic impairment. Reductions of more than 50% may be appropriate for some patients.

Because of individual variability in clearance in these patients, individualization of dosage may be desirable.

Use in Children
There is insufficient experience with the use of venlafaxine in patients younger than 18 years of age (see sections **PEDIATRIC USE** and **ADVERSE REACTIONS**).

Use in Elderly Patients
No specific dose adjustments of venlafaxine are recommended based on patient age.

OVERDOSAGE
In post-marketing experience, overdose with venlafaxine was reported predominantly in combination with alcohol and/or other drugs. The most commonly reported events in overdose include tachycardia, changes in level of consciousness (ranging from somnolence to coma), mydriasis, convulsion, and vomiting. Other events reported include electrocardiographic changes (e.g., prolongation of QT interval, bundle branch block, QRS prolongation), ventricular tachycardia, bradycardia, hypotension, vertigo, and death.

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 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 characteristics of venlafaxine-treated patients is not clear. Prescriptions for venlafaxine should be written for the smallest quantity of drug consistent with good patient management, in order to reduce the risk of overdose.

RECOMMENDED TREATMENT
General supportive and symptomatic measures are recommended; cardiac rhythm and vital signs must be monitored.

When there is a risk of aspiration, induction of emesis is not recommended.

Gastric lavage may be indicated if performed soon after ingestion or in symptomatic patients. Administration of activated charcoal may also limit drug absorption.

Forced diuresis, dialysis, hemoperfusion, and exchange transfusion are unlikely to be of benefit.

No specific antidotes for venlafaxine are known.

HOW SUPPLIED

Efexor XR 75 mg:	Packages of 2 x 14 capsules
	Packages of 1 x 14 capsules
Efexor XR 150 mg:	Packages of 2 x 14 capsules
	Packages of 1 x 14 capsules

Not all pack sizes or presentation is available locally.

STORAGE CONDITION
Store below 30°C.
Keep out of reach of children.
Shelf-life is 36 months from the date of manufacture.

OTHER INFORMATION
The extended-release formulation of venlafaxine capsules contains spheroids, which release the drug slowly into the digestive tract. The insoluble portion of these spheroids is eliminated and may be seen in stools.

PRODUCT COMPOSITION
Active Ingredient: Venlafaxine hydrochloride
Inactive Ingredients: Microcrystalline cellulose, hydroxypropylmethylcellulose, ethylcellulose, gelatin, red and yellow iron oxides (E172), titanium dioxide (E171) and printing ink.

PRODUCT OWNER
Pfizer Inc.
235 East 42nd Street
New York 10017
United States

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