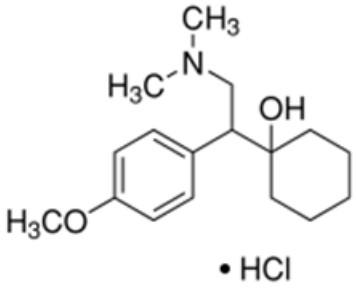
APO-VENLAFAXINE XR CAPSULES

NAME OF THE MEDICINE

Venlafaxine hydrochloride

Chemical name: 1-[(1*RS*)-2-(Dimethylamino)-1-(4-methoxyphenyl)ethyl] cyclohexanol hydrochloride

Structural Formula:



Molecular Formula: $C_{17}H_{27}NO_2.HCl$

Molecular Weight: 313.87

CAS Registry Number: 99300-78-4

DESCRIPTION

Each modified release capsule contains venlafaxine 75 mg (as 84.86 mg venlafaxine hydrochloride) as the active ingredient. In addition, each capsule contains the following inactive ingredients: Hypromellose, sodium lauryl sulfate, magnesium stearate, ammonio methacrylate copolymer and basic butylated methacrylate copolymer. The capsules contain titanium dioxide (E171, CI 77891), gelatin and red iron oxide (E172, CI77491).

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). APO-Venlafaxine XR capsules are a modified release formulation, which release the active constituent venlafaxine hydrochloride from a tablet or tablets within the capsule. Drug is released by a combination of swelling of the hydrophilic polymer (hypromellose), diffusion and erosion.

PHARMACOLOGY

Pharmacodynamics

Venlafaxine is a structurally novel antidepressant for oral administration; it is chemically unrelated to tricyclic, tetracyclic or other available antidepressant agents.

The antidepressant action of venlafaxine in humans is believed to be associated with its potentiation of neurotransmitter activity in the central nervous system.

Preclinical studies have shown that venlafaxine and its major metabolite, *O*-desmethylvenlafaxine (ODV), are potent inhibitors of serotonin and noradrenaline reuptake, and also weakly inhibit dopamine reuptake. Venlafaxine is a racemate. The *R*-enantiomer is relatively more potent than the *S*-enantiomer with regard to inhibition of noradrenaline reuptake; the *S*-enantiomer is more potent regarding inhibition of serotonin reuptake. Both enantiomers are more potent on serotonin compared to noradrenaline reuptake. The enantiomers of ODV also inhibit both noradrenaline and serotonin reuptake, with the *R*-enantiomer being more potent.

Venlafaxine and its major metabolite appear to be equipotent with respect to their overall action on neurotransmitter reuptake and receptor binding. Studies in animals show that tricyclic antidepressants may reduce beta-adrenergic receptor responsiveness following chronic administration. In contrast, venlafaxine and ODV reduce beta-adrenergic responsiveness after both acute (single dose) and chronic administration.

Venlafaxine has no significant affinity for rat brain muscarinic, H1-histaminergic or alpha1-adrenergic receptors in vitro. Pharmacological activity at these receptors is potentially associated with various sedative, cardiovascular and anticholinergic effects seen with other psychotropic drugs. Venlafaxine does not possess monoamine oxidase (MAO) inhibitory activity.

In vitro studies revealed that venlafaxine has virtually no affinity for opiate, benzodiazepine, phencyclidine (PCP) or *N*-methyl-D-aspartic acid (NMDA) receptors. Venlafaxine also does not produce noradrenaline release from brain slices. It has no significant central nervous system (CNS) stimulant activity in rodents. In primate drug discrimination studies, venlafaxine showed no significant stimulant or depressant abuse liability.

Pharmacokinetics
Steady-state concentrations of venlafaxine and ODV are attained within three 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 clearances of venlafaxine and ODV are 1.3 +/- 0.6 and 0.4 +/- 0.2 L/hour/kg, respectively; apparent elimination half-lives are 5 +/- 2 and 11 +/- 2 hours, respectively; and apparent (steady-state) volumes of distribution are 7.5 +/- 3.7 and 5.7 +/- 1.8 L/kg, respectively.

Absorption
On the basis of mass balance studies, at least 92% of a single oral dose of venlafaxine is absorbed, indicating that absorption of venlafaxine is nearly complete. However, the presystemic metabolism of venlafaxine (which primarily forms the active metabolite ODV) reduces the absolute bioavailability of venlafaxine to 42 +/- 15%.

After administration of modified release venlafaxine (150 mg daily), the peak plasma concentrations (Cmax) of venlafaxine (150 nanogram/mL) and ODV (260 nanogram/mL) are attained within 6.0 +/- 1.5 and 8.8 +/- 2.2 hours, respectively.

The rate of absorption of venlafaxine from the modified release venlafaxine capsule is slower than its rate of elimination.

Therefore, the apparent elimination half-life of venlafaxine following administration of modified release venlafaxine (15 +/- 6 hours) is actually the absorption half-life instead of the true disposition half-life (5 +/- 2 hours) observed following administration of an immediate release tablet.

When equal doses of venlafaxine, administered either as an immediate release tablet taken in divided doses or as a modified release capsule, were taken once a day, the exposure (AUC, area under the concentration curve) to both venlafaxine and ODV was similar for the two treatments, and the fluctuation in plasma concentrations was slightly lower following treatment with the modified release Venlafaxine capsule. Therefore, the modified release venlafaxine capsule provides a slower rate of absorption, but the same extent of absorption (i.e. AUC), as the venlafaxine immediate release tablet.

No accumulation of venlafaxine or ODV has been observed during chronic administration in healthy subjects.

Distribution
The degree of binding of venlafaxine to human plasma proteins is 27 +/- 2% at concentrations ranging from 2.5 to 2.215 nanogram/mL, and the degree of ODV binding to human plasma proteins is 30 +/- 12% at concentrations ranging from 100 to 500 nanogram/mL. Protein binding-induced drug interactions with concomitantly administered venlafaxine are not expected. Following intravenous administration, the steady state volume of distribution of venlafaxine is 4.4 +/- 1.9 L/kg, indicating that venlafaxine distributes well beyond the total body water.

Metabolism
Following absorption, venlafaxine undergoes extensive presystemic metabolism in the liver. The primary metabolite of venlafaxine is ODV, but venlafaxine is also metabolised to *N*-desmethylvenlafaxine, *N,O*-didesmethylvenlafaxine and other minor metabolites. In vitro studies indicate that the formation of ODV is catalysed by CYP2D6 and that the formation of *N*-desmethylvenlafaxine is catalysed by CYP3A3/4. The results of the in vitro studies have been confirmed in a clinical study with subjects who are CYP2D6 poor and CYP2D6 extensive metabolisers. However, despite the metabolic differences between the CYP2D6 poor and CYP2D6 extensive metabolisers, the total exposure to the sum of the two active species (venlafaxine and ODV) was similar in the two metaboliser groups. Therefore, CYP2D6 poor and CYP2D6 extensive metabolisers can be treated with the same regimen of venlafaxine XR (see **Interactions with other Medicines – CYP2D6 Inhibitors)**.

Excretion
Approximately 87% of a venlafaxine dose is recovered in the urine within 48 hours after a single radiolabelled dose as either unchanged venlafaxine (5%), unconjugated ODV (29%), conjugated ODV (26%) or other minor inactive metabolites (27%), and 92% of the radioactive dose is recovered within 72 hours. Therefore, renal elimination of venlafaxine and its metabolites is the primary route of excretion.

Food/drug interactions
Administration of Venlafaxine XR with food has no effect on the absorption of venlafaxine or on the subsequent formation of ODV.

Special Populations

Gender and Age
Subject age and sex do not significantly affect the pharmacokinetics of venlafaxine. A 20% reduction in clearance was noted for ODV in subjects over 60 years old; this was probably caused by the decrease in renal function that typically occurs with ageing.

Renal Impairment
In patients with moderate to severe impairment of renal function, the total clearance of both venlafaxine and ODV was reduced, and t1/2 was prolonged. The reduction in total clearance was most pronounced in subjects with creatinine clearance less than 30 mL/minute.

Hepatic Impairment
In some patients with compensated hepatic cirrhosis, the pharmacokinetic disposition of both venlafaxine and ODV was significantly altered. The reduction in both the metabolism of venlafaxine and elimination of ODV resulted in higher plasma concentrations of both venlafaxine and ODV.

CLINICAL TRIALS

Use in Major Depression

Three double blind, placebo controlled trials, of up to 12 weeks duration, have examined the clinical efficacy of modified release venlafaxine in the treatment of major depression. One of these studies also incorporated an active comparator, paroxetine. These studies showed modified release venlafaxine to have greater efficacy than both placebo and paroxetine in reducing depression.

Depression Relapse/Recurrence
A long-term study of depressed outpatients who had responded to modified release venlafaxine during an initial eight week open label treatment phase and were randomly assigned to continuation on venlafaxine or placebo for six months demonstrated a significantly lower relapse rate for patients taking venlafaxine compared with those on placebo.

In a second long-term study, outpatients with a history of recurrent depression who had responded to the immediate release form of venlafaxine by eight weeks and maintained improvement during an initial six month open label treatment phase were randomly assigned to maintenance therapy on immediate release venlafaxine or placebo for 12 months. Significantly fewer patients taking immediate release venlafaxine compared with those on placebo had a reappearance of depression.

INDICATIONS

- Treatment of major depression, including prevention of relapse and recurrence where appropriate.

CONTRAINDICATIONS

Hypersensitivity to venlafaxine or any excipients in the formulation.

Monoamine Oxidase Inhibitors (MAOIs)
Venlafaxine-XR should not be used in combination with monoamine oxidase inhibitors (MAOIs) or reversible MAOIs (RIMA) (e.g. moclobemide, linezolid and intravenous methylene blue), or within 14 days of discontinuing treatment with a MAOI. Similarly, at least 7 days should be allowed after stopping Venlafaxine-XR before starting a MAOI. Cases of serious reactions, such as potentially life-threatening serotonin syndrome (characterised by neuromuscular excitation, altered mental status and autonomic dysfunction) have been reported in patients receiving an SNRI in combination with MAOIs and RIMA, and in patients who have recently discontinued an SNRI and have been started on a MAOI (see also **PRECAUTIONS** and **INTERACTIONS WITH OTHER MEDICINES**).

PRECAUTIONS

Clinical Worsening and Suicide Risk
Patients with major depression, both adult and paediatric, may experience worsening of their depression and/or the emergence of suicidal ideation and behaviour (suicidality) or unusual changes in behaviour, 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. Antidepressants may have a role in inducing worsening of depression and the emergence of suicidality in certain patients during the early phases of treatment. As improvement may not occur during the first few weeks or more of treatment, patients should be monitored appropriately and observed closely for clinical worsening and suicidality, especially at the beginning of a course of treatment or at the time of dose changes, either increases or decreases.

Pooled analyses of short-term placebo controlled trials of antidepressant medicines (SSRIs and others) showed that these medicines increase the risk of suicidality in children, adolescents and young adults (ages 18 to 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 beyond the age of 24 years; there was a reduction in the risk of suicidality with antidepressants compared to placebo in adults aged 65 years and older.

The pooled analysis of placebo controlled trials in children and adolescents with major depression, obsessive compulsive disorder or other psychiatric disorders included a total of 24 short-term trials of nine antidepressant medicines in over 4,400 patients. The pooled analyses of placebo controlled trials in adults with major depression or other psychiatric disorders included a total of 295 short-term trials (median duration two months) of eleven antidepressant medicines in over 77,000 patients. There was considerable variation in risk of suicidality among medicines, but a tendency toward an increase in the younger patients for almost all medicines studied. There were differences in absolute risk of suicidality across the different indications, with the highest incidence with major depression.

No suicides occurred in any of the paediatric trials. There were suicides in the adult trials, but the number was not sufficient to reach any conclusion about the medicine 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.

Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients whose depression is persistently worse or whose emergent suicidality is severe, abrupt in onset or was not part of the patient's presenting symptoms (see **PRECAUTIONS, Discontinuation Effects**).

It is particularly important that appropriate monitoring be undertaken during the initial course of antidepressant treatment or at times of dose increase or decrease.

Patients with comorbid depression associated with other psychiatric or non-psychiatric disorders being treated with antidepressants should be similarly observed for clinical worsening and suicidality.

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

Prescriptions for Venlafaxine XR should be written for the smallest quantity of capsules consistent with good patient management in order to reduce the possibility of overdosage.
This is particularly so at the times of treatment initiation or dosage change. Events reported in overdose include electrocardiogram changes (QRS prolongation, QT prolongation), cardiac arrhythmias (ventricular fibrillation; ventricular tachycardia, including torsades de pointes), convulsions and death (see **OVERDOSAGE, Signs and Symptoms**).

Information for Patients and Caregivers
Patients, their families and their caregivers should be alerted about the need to monitor for the emergence of anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, mania, other unusual changes in behaviour, worsening of depression, and suicidal ideation, especially when initiating therapy or during any change in dose. Such symptoms should be reported to the patient's doctor, especially if they are severe, abrupt in onset, or were not part of the patient's presenting symptoms (see also **PRECAUTIONS, Paediatric Use).**

Akathisia/Psychomotor Restlessness
The use of venlafaxine has been associated with the development of akathisia, characterised by a subjectively unpleasant or distressing restlessness and need to move, often accompanied by an inability to sit or stand still. This is most likely to occur within the first few weeks of treatment. In patients who develop these symptoms, increasing the dose may be detrimental.

Serotonin Syndrome or Neuroleptic Malignant Syndrome (NMS)-Like Reactions
As with other serotonergic agents, the development of a potentially life threatening serotonin syndrome or neuroleptic malignant syndrome (NMS)-like reaction may occur with venlafaxine treatment, particularly with concomitant use of other serotonergic drugs (including SSRIs, SNRIs, triptans, fentanyl, dextromethorphan, tramadol, tapentadol, pethidine and methadone), and with drugs that impair metabolism of serotonin (e.g. MAOIs, including reversible MAOIs such as moclobemide, linezolid and intravenous methylene blue), or with antipsychotics or other dopamine antagonists (see **CONTRAINDICATIONS**). Serotonin syndrome symptoms may include mental status changes (e.g., agitation, confusion, hallucinations, and coma), autonomic instability (e.g., diaphoresis, tachycardia, labile blood pressure, and hyperthermia), neuromuscular aberrations (e.g., hyperreflexia, incoordination, myoclonus, tremor), and/or gastrointestinal symptoms (e.g., nausea, vomiting, and diarrhoea). 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 **INTERACTIONS WITH OTHER MEDICINES**).

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.

Treatment with venlafaxine should be discontinued if serotonin syndrome or NMS-like reactions occur and supportive symptomatic treatment initiated.

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

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.

Diabetes
In patients with diabetes treatment with an SSRI may alter glycaemic control. Insulin and/or hypoglycaemic dosage may need to be adjusted.

Mydriasis
Mydriasis may occur in association with venlafaxine. It is recommended that patients with raised intraocular pressure or patients at risk for acute narrow angle glaucoma (angle closure glaucoma) should be closely monitored.

Sustained Hypertension
Dose related increases in blood pressure have been reported in some patients treated with venlafaxine. Among patients treated with venlafaxine 75 to 375 mg/day in premarketing depression studies, 3% (19/705) experienced sustained hypertension (defined as treatment emergent supine diastolic blood pressure (SDBP) greater than or equal to 90 mmHg and greater than or equal to 10 mmHg above baseline for three consecutive on therapy visits). Among patients treated with 37.5 to 225 mg per day of venlafaxine XR in pre-marketing GAD studies, 0.5% (5/1011) experienced sustained hypertension. Experience with the immediate-release venlafaxine showed that sustained hypertension was dose-related, increasing from 3 to 7% at 100 to 300 mg per day to 13% at doses above 300 mg per day. An insufficient number

of patients received mean doses of venlafaxine XR over 300 mg per day to fully evaluate the incidence of sustained increases in blood pressure at these higher doses.

In placebo controlled premarketing depression studies with venlafaxine 75 to 225 mg/day, a final on drug mean increase in supine diastolic blood pressure (SDBP) of 1.2 mmHg was observed for venlafaxine treated patients compared with a mean decrease of 0.2 mmHg for placebo treated patients.

In premarketing depression studies, 0.7% (5/705) of the venlafaxine treated patients vdiscontinued treatment because of elevated blood pressure. Among these patients, most of the blood pressure increases were in a modest range (12 to 16 mmHg, SDBP). In pre-marketing GAD studies up to 8 weeks and up to 6 months, 0.7% (10/1381) and 1.3% (7/535) of the venlafaxine XR treated patients, respectively, discontinued treatment because of elevated blood pressure. Among these patients, most of the blood pressure increases were in a modest range (12 to 25 mm Hg, SDBP up to 8 weeks; 8 to 28 mm Hg up to 6 months).

Cases of elevated blood pressure requiring immediate treatment have been reported in post marketing experience.

Sustained increases of SDBP could have adverse consequences. Therefore, it is recommended that patients receiving venlafaxine have regular monitoring of blood pressure.

For patients who experience a sustained increase in blood pressure while receiving venlafaxine, either dose reduction or discontinuation should be considered. 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.

Increase in Serum Cholesterol
Clinically relevant increases in serum cholesterol were recorded in 5.3% of venlafaxine immediate release tablet treated patients and 0.0% of placebo treated patients for at least three months in placebo controlled clinical trials.

Treatment with venlafaxine for up to 12 weeks in premarketing placebo controlled depression trials was associated with a mean final on therapy increase in serum cholesterol concentration of approximately 0.039 mmol/L (1.5 mg/dL). Venlafaxine XR treatment for up to 8 weeks and up to 6 months in pre-marketing placebo-controlled GAD trials was associated with mean final on-therapy increases in serum cholesterol concentration of approximately 0.026 mmol/L (1.0 mg/dL) and 0.059 mmol/L (2.3 mg/dL), respectively.

In the 12 week Social Anxiety Disorder studies, small mean increases in fasting levels of total cholesterol (0.20 mmol/L, 4%) were seen in the venlafaxine XR-treated group at the final on- therapy evaluation; the increases were significantly different from the changes in the placebo group. In a 6-month study, the final on-therapy mean increase in total cholesterol was higher (0.32 mmol/L, 7%) in the venlafaxine XR 150 to 225 mg group; however the total cholesterol value was only slightly increased (0.01mmol/L) for the venlafaxine XR 75mg group.

There were also significant mean increases from baseline in LDL, but not HDL for the venlafaxine XR 150 to 225 mg group. The final on-therapy increase of 0.213 mmol/L from baseline in LDL with venlafaxine XR 150 to 225 mg was significantly different from the small decrease with placebo (0.079 mmol/L) and the negligible increase with venlafaxine XR 75mg (0.006 mmol/L).

Measurement of serum cholesterol levels should be considered during long-term treatment.

Hyponatraemia
Cases of hyponatraemia and/or the syndrome of inappropriate antidiuretic hormone secretion (SIADH) 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.

Caution is advised in administering Venlafaxine XR to patients with diseases or conditions that could affect haemodynamic responses or metabolism.

Use in Patients with Pre-Existing Heart Disease
Patients with a recent history of myocardial infarction or unstable heart disease were excluded from all venlafaxine clinical trials. However, patients with other pre-existing heart disease were not excluded, although they were neither separately analysed nor systematically studied.

Venlafaxine should be used with caution in patients with unstable heart disease (e.g. myocardial infarction; significant left ventricular dysfunction, ventricular arrhythmia). In these patients, assessment of the cardiovascular system (e.g. electrocardiogram (ECG); serum electrolytes during diuretic treatment) should be considered during treatment with venlafaxine, particularly when the dose is increased beyond 150 to 200 mg daily.

Evaluation of the electrocardiograms for 769 patients who received immediate release venlafaxine in four to six week double blind, placebo controlled trials showed that the incidence of trial emergent conduction abnormalities did not differ from that with placebo.

The electrocardiograms for patients who received venlafaxine XR or placebo in the depression GAD and Social Anxiety Disorder trials were analysed. The mean change from baseline in corrected QT interval (QTc) for venlafaxine XR treated patients in depression studies was increased relative to that for placebo-treated patients (increase of 4.7 msec for venlafaxine XR and decrease of 1.9 msec for placebo). The mean change from baseline QTc for venlafaxine XR treated patients in the GAD studies did not differ significantly from placebo. The final on- therapy mean increase from baseline in QTc (3 msec) was significant for venlafaxine XR treated patients in the Social Anxiety Disorder short-term studies. In the 6 month study, the final on- therapy mean increase from baseline in QTc with venlafaxine XR 150 to 225 mg (3 msec) was significant, but the increase was not significantly different from the small mean increase (0.5 msec) with placebo. The value for venlafaxine XR 75 mg was a 0.05 msec decrease.

Increases in heart rate may occur, particularly with higher doses. Therefore caution is advised in patients whose underlying conditions may be compromised by increases in heart rate.

The mean change from baseline in heart rate for venlafaxine XR treated patients in both the GAD and the depression studies was significantly higher than for placebo (a mean increase of 3-4 beats per minute for venlafaxine XR and 0-1 beat per minute for placebo in the GAD and depression studies respectively). In the pooled short-term Social Anxiety Disorder studies, the final on- therapy mean increase from baseline in heart rate with venlafaxine XR was 5 beats per minute.In the 6 month study, the final on-therapy mean increases from baseline in heart rate were significant with venlafaxine XR 75 (2 beats per minute) and venlafaxine XR 150 to 225 mg (6 beats per minute); however only the increase with the higher dose was significantly different from the small increase with placebo (0.4 beats per minute). The clinical significance of these changes is unknown.

QTc Prolongation/Torsade de Pointes (TdP)
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.

Discontinuation Effects
Discontinuation effects are well known to occur with antidepressants. Discontinuation symptoms have been assessed both in patients with depression and in those with anxiety. Abrupt discontinuation, dose reduction or tapering 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.

Symptoms reported included agitation, anorexia, anxiety, confusion, dry mouth, fatigue, paraesthesiae, vertigo, hypomania, nausea, vomiting, dizziness, convulsion, headache, diarrhoea, sleep disturbance, insomnia, somnolence, sweating and nervousness. Where such symptoms occurred, they were usually self-limiting, but in a few patients lasted for several weeks.

Discontinuation effects were systematically studied in a long-term fixed-dose trial for generalised anxiety disorder; 24% and 11% of patients recorded the appearance of at least three withdrawal symptoms on abrupt discontinuation from 150 mg or 75 mg venlafaxine once daily, respectively, compared with 3% for placebo. The most commonly reported withdrawal symptoms on abrupt discontinuation were nausea, vomiting, dizziness, lightheadedness, and tinnitus from 150 mg venlafaxine once daily, and dizziness from 75 mg venlafaxine once daily.

In this study, severe withdrawal reactions were observed in 1.3% of patients discontinuing from 75 mg once daily (no patients requiring further drug treatment).

There is also a report of a withdrawal syndrome, confirmed by two challenges in a 32 year old woman who had received venlafaxine 300 mg daily for eight months. It is therefore recommended that the dosage of Venlafaxine XR be tapered gradually and the patient monitored. The period required for discontinuation may depend on the dose, duration of therapy and the individual patient (see **DOSAGE AND ADMINISTRATION and ADVERSE EFFECTS**).

Altered Weight
Weight changes, either losses or gains, do not appear to present a clinically important feature of venlafaxine treatment. Clinically significant weight gain or loss was seen in less than 1% of patients treated with venlafaxine during clinical trials. A dose dependent weight loss (mean loss < 1 kg) was noted in some patients treated with venlafaxine during the first few months of venlafaxine treatment. After month 9, the mean weight began to increase slightly but significantly, an effect often seen with tricyclic antidepressant therapy. Significant weight loss (> 7 kg) was seen in six (0.3%) of 2,181 patients, compared to no patients treated with placebo and 0.2% of patients treated with a comparative antidepressant.

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

Seizures
Seizures have been reported with venlafaxine therapy and in overdosage. Venlafaxine XR, as with all antidepressants, should be introduced with care in patients with a history of seizure disorders. Venlafaxine XR should be discontinued in any patient who develops seizures (see **OVERDOSAGE, Signs and Symptoms**).

Mania / Hypomania and Bipolar Disorder
Mania / hypomania may occur in a small proportion of patients with mood disorders treated with antidepressants, including venlafaxine.

Venlafaxine should be used cautiously in patients with a history or family history of 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 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 XR is not approved for use in treating bipolar depression.

Aggression may occur in a small proportion of patients who have received antidepressants, including venlafaxine treatment, dose reduction or discontinuation.

Venlafaxine should be used cautiously in patients with a history of aggression.

Skin / Allergic Reactions
Patients should be advised to notify their doctor if they develop a rash, hives or related allergic phenomena.

Abnormal Bleeding
Drugs that inhibit serotonin uptake may lead to abnormalities of platelet aggregation. Bleeding abnormalities have been reported with venlafaxine ranging from skin and mucous membrane bleeding and gastrointestinal haemorrhage, to life-threatening haemorrhages. The risk may be increased in patients predisposed to bleeding, including patients on anti-coagulants and platelet inhibitors, and venlafaxine should be used cautiously in these patients.

Physical and Psychological Dependence
Clinical studies have shown no evidence of drug seeking behaviour, development of tolerance or dose escalation over time among patients taking venlafaxine. Consequently, doctors should carefully evaluate patients for a history of drug abuse and follow such patients closely, observing them for signs of misuse or abuse of venlafaxine (e.g. development of tolerance, increase in dose, drug seeking behaviour) (see **PHARMACOLOGY**).

Electroconvulsive Therapy
There are no clinical data establishing the benefit of Venlafaxine XR combined with electroconvulsive therapy.

Use in Pregnancy (Category B2)
The safety of venlafaxine in human pregnancy has not been established. There are no adequate and well controlled studies in pregnant women. Venlafaxine must only be administered to pregnant women if the expected befits outweigh the possible risks. Patients should be advised to notify their doctor if they become pregnant or intend to become pregnant during therapy. If venlafaxine is used until or shortly before birth, discontinuation effects in the newborn infant should be considered.

Some neonates exposed to venlafaxine, other SNRIs (serotonin and noradrenaline reuptake inhibitors) or SSRIs (selective serotonin reuptake inhibitors) late in the third trimester have developed complications requiring prolonged hospitalisation, respiratory support and tube feeding. Such complications can arise immediately upon delivery. Reported clinical findings have included respiratory distress, cyanosis, apnoea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycaemia, hypotonia, hypertonia, hyper-reflexia, 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.

Epidemiological data have suggested that the use of SSRI's 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 reuptake of serotonin).

Use in Lactation
Venlafaxine and/or its metabolites are secreted in milk of lactating rats at concentrations higher than those found in the plasma of the dam. Venlafaxine and its metabolites have been shown to pass into human milk. The total dose of venlafaxine and *O*-desmethylvenlafaxine ingested by breastfed infants can be as high as 9.2% of maternal intake. Therefore, the use of Venlafaxine XR in breastfeeding women cannot be recommended. Exposed infants should be observed closely.

Paediatric Use
Venlafaxine XR is not indicated for use in children and adolescents below 18 years of age as safety and effectiveness have not been demonstrated. Therefore, Venlafaxine XR should not be used in this age group.

In paediatric clinical trials, the adverse reaction, suicidal ideation, was observed. There were also increased reports of hostility and, especially in major depressive disorder, self-harm (see **PRECAUTIONS, Clinical Worsening and Suicide Risk;** and **ADVERSE EFFECTS**).

As with adults, decreased appetite, weight loss, increased blood pressure and increased serum cholesterol have been observed in children and adolescents aged 6 to 17 years (see **ADVERSE EFFECTS**).

Use in the Elderly
No overall differences in effectiveness or safety were observed between elderly (aged 65 years and older) and younger patients. Venlafaxine XR does not appear to pose any exceptional safety problems for healthy elderly patients.

Use in Renal Impairment
The total daily dose of venlafaxine must be reduced by 25 to 50% for patients with renal impairment with a glomerular filtration rate (GFR) of 10 to 70 mL/minute.

The total daily dose of venlafaxine must be reduced by 50% in haemodialysis patients. Because of individual variability in clearance in these patients, individualisation of dosage may be desirable.

Use in Hepatic Impairment
The total daily dose of venlafaxine must 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, individualisation of dosage may be desirable.

Carcinogenesis, Genotoxicity, Effects on Fertility
Carcinogenicity
Venlafaxine was given by oral gavage to mice and rats for 18 and 24 months, respectively, at dosages up to 120 mg/kg/day. There were no clear drug related oncogenic effects in either species. In these studies, animal exposure to the main human metabolite ODV was less and exposure to venlafaxine was more than would be expected in humans taking the recommended therapeutic and maximum doses.

Genotoxicity
There was no evidence of gene mutation or chromosomal change in a series of genotoxicity assays using venlafaxine and the main human metabolite ODV.

Effects on fertility
Reproduction and fertility studies in rats showed no effects on male or female fertility at oral doses of up to two times the maximum recommended human dose on a mg/m2 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 exposure was approximately two to three times that of a human dose of 225 mg/day. The human relevance of this finding is unknown.

Signs of pharmacological toxicity were seen in paternal and maternal rats given venlafaxine doses of 30 and 60 mg/kg/day, but no adverse effect was noted in fertility or general reproductive performance. Decreased foetal size and pup weight at birth with 60 mg/kg/day may be correlated with maternal toxicity.

Teratogenicity
In a rat teratology study, venlafaxine was given orally at dosages up to 80 mg/kg/day (approximately 11 times the maximum recommended human dose). Foetotoxicity evidenced by growth retardation was slightly increased at 80 mg/kg/day, an effect that may be related to maternal toxicity at this dose level. Foetal survival and morphologic development were not affected. In another teratology study, rabbits were given venlafaxine dosages up to 90 mg/kg/day. Foetotoxicity evidenced by resorption and foetal loss was slightly increased at 90 mg/kg/day (approximately 12 times the maximum recommended human dose). These effects could be correlated with maternal toxicity. No venlafaxine-associated teratogenic effect was noted in either species at any dosage, though there was an increased incidence of 'W'-shaped apex of the heart in the rabbit study. In these studies, animal exposure to the main human metabolite ODV was less, and estimated exposure to venlafaxine was approximately 6-fold more than would be expected in humans taking the recommended therapeutic and maximum doses. In rats, estimated exposure to venlafaxine was more than the expected human exposure. No teratogenic effect was seen.

In a perinatal toxicity study in rats after oral dosing of dams with 30 mg/kg or more, decreased pup survival following birth was observed. This effect is secondary to treatment-decreased maternal care, and is also seen with other antidepressants.

Effect on Ability to Drive or Operate Machinery
Although venlafaxine has been shown not to affect psychomotor, cognitive or complex behaviour performance in healthy volunteers, any psychoactive medication may impair judgment, thinking or motor skills, and patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that the treatment does not affect them adversely.

Effects on Laboratory Tests
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.

INTERACTIONS WITH OTHER MEDICINES

Venlafaxine and ODV (*O*-desmethylvenlafaxine) are 27 and 30% bound to plasma proteins respectively; therefore interactions due to protein binding of venlafaxine and the major metabolite are not expected.

Monoamine Oxidase Inhibitors (MAOI)
Concomitant use of Venlafaxine-XR in patients taking monoamine oxidase inhibitors (MAOIs) or reversible MAOIs (e.g. moclobemide, linezolid and intravenous methylene blue) is contraindicated (see **CONTRAINDICATIONS**).

Severe adverse reactions have been reported in patients who have recently been discontinued from a MAOI and started on venlafaxine, or have recently had venlafaxine therapy discontinued prior to initiation of a MAOI or when these two agents are co-administered. Reactions have included tremor, myoclonus, diaphoresis, nausea, vomiting, flushing, dizziness, hyperthermia with features resembling neuroleptic malignant syndrome and/or serotonergic syndrome, seizures, and death.

Do not use Venlafaxine-XR in combination with a MAOI or reversible MAOIs, or within at least

14 days of discontinuing MAOI treatment. Allow at least 7 days after stopping Venlafaxine-XR before starting a MAOI.

The appropriate washout period should take into account the pharmacological properties of venlafaxine, ODV and the MAOI and the clinician's assessment of the individual patient.

Central Nervous System 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, lithium, sibutramine, fentanyl and its analogues, tramadol, dextromethorphan, tapentadol, pethidine, methadone or St John's Wort (*Hypericum perforatum*), with drugs which impair metabolism of serotonin (including MAOIs including moclobemide), linezolid (an antibiotic which is a reversible non selective MAOI) and intravenous methylene blue , or with serotonin precursors (e.g. tryptophan supplements)). Serotonin syndrome symptoms may include mental status changes, autonomic instability, neuromuscular aberrations and/or gastrointestinal symptoms (see **CONTRAINDICATIONS** and **PRECAUTIONS**).

Serotonin syndrome has been reported in association with concomitant use with selective serotonin reuptake inhibitors (SSRIs). The decision to use venlafaxine in combination with SSRIs should include the advice of a psychiatrist.

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 (e.g. tryptophan supplements) is not recommended (see **PRECAUTIONS**).

As with other antidepressants, co administration of Venlafaxine XR and products containing St John's Wort *(Hypericum perforatum)* is not recommended due to possible pharmacodynamic interactions.

No information is available on the use of Venlafaxine XR in combination with opiates.

There have been reports of elevated clozapine levels in association with adverse events including seizures, following the administration of venlafaxine.

Drugs that Prolong the 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 **PRECAUTIONS**, **QTc Prolongation/Torsade de Pointes (TdP)**).

Ethanol
Venlafaxine has not been shown 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 XR.

Diazepam
The pharmacokinetic profiles of venlafaxine and ODV were not altered when venlafaxine and diazepam were administered together to healthy volunteers. Venlafaxine had no effect on the pharmacokinetics of diazepam nor did it affect the psychomotor and psychometric effects induced by diazepam.

Lithium
The steady-state pharmacokinetics of venlafaxine and ODV are not affected when lithium is co administered. Venlafaxine also has no effect on the pharmacokinetics of lithium. (See also **INTERACTIONS WITH OTHER MEDICINES, Central Nervous System Active Drugs**). However, there have been reports of venlafaxine interaction with lithium resulting in increased lithium levels.

Haloperidol
Venlafaxine administered under steady-state conditions (75 mg twice daily) to 24 healthy subjects decreased total oral clearance (Cl/F) of a single dose of haloperidol 2 mg by 42%, which resulted in a 70% increase in haloperidol AUC (area under the curve). In addition, the haloperidol Cmax increased 88% when co administered with venlafaxine, but the haloperidol elimination half-life (t1/2) was unchanged. The mechanism explaining this finding is unknown.

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.

Indinavir
A pharmacokinetic study with indinavir has shown a 28% decrease in AUC and a 36% decrease in Cmax for indinavir. Indinavir did not affect the pharmacokinetics of venlafaxine and ODV. The clinical significance of this interaction is unknown.

Cimetidine
At steady state cimetidine has been shown to inhibit the first-pass metabolism of venlafaxine but had no apparent effect on the formation or elimination of ODV, which is present in much greater quantity in the systemic circulation. The overall pharmacological activity of venlafaxine plus ODV is expected to increase only slightly in most patients. No dosage adjustment seems necessary when Venlafaxine XR is co administered with cimetidine. However, for elderly patients or patients with hepatic dysfunction, the interaction could potentially be more pronounced and for such patients clinical monitoring is indicated when Venlafaxine XR is administered with cimetidine.

Metoprolol
Concomitant administration of venlafaxine (50 mg every eight hours for five days) and metoprolol (100 mg every 24 hours for five days) to 18 healthy male subjects in a pharmacokinetic interaction study for both drugs resulted in an increase of plasma concentrations of metoprolol by approximately 30 to 40% without altering the plasma concentrations of its active metabolite, alpha-hydroxymetoprolol. Metoprolol did not alter the pharmacokinetic profile of venlafaxine or its active metabolite, ODV.

Venlafaxine appeared to reduce the blood pressure lowering effect of metoprolol in this study. 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 XR have regular monitoring of blood pressure (see **PRECAUTIONS, Sustained Hypertension**).

Antihypertensive and Hypoglycaemic Agents
Retrospective analysis of study events occurring in patients taking venlafaxine concurrently with antihypertensive or hypoglycaemic agents in clinical trials provided no evidence suggesting incompatibility between treatment with venlafaxine and treatment with either antihypertensive or hypoglycaemic agents.

Drugs Metabolised by Cytochrome P450 Isoenzymes
In vitro studies indicate that venlafaxine is a relatively weak inhibitor of CYP2D6 and that venlafaxine does not inhibit CYP1A2, CYP2C9 or CYP3A4. Some of these findings have been confirmed with drug interaction studies between venlafaxine and imipramine

(metabolised by CYP2D6) and diazepam (metabolised by CYP2C19). Therefore, Venlafaxine XR is not expected to interact with other drugs metabolised by these isoenzymes.

Imipramine
Venlafaxine did not affect the CYP2D6 mediated 2-hydroxylation of imipramine or its active metabolite desimipramine, which indicates that venlafaxinedoes not inhibit the CYP2D6 isoenzyme. However, the renal clearance of 2-hydroxydesimipramine was reduced with co administration of venlafaxine.

Imipramine partially inhibited the CYP2D6 mediated formation of ODV, however, the total concentrations of active compounds (venlafaxine plus ODV) was not affected with imipramine administration. Additionally, in a clinical study involving CYP2D6 poor and CYP2D6 extensive metabolisers, the total sum of the two active species (venlafaxine and ODV) was similar in the two metaboliser groups. Therefore, no dosage adjustment is expected when venlafaxine is co administered with a CYP2D6 inhibitor. However, desipramine AUC, Cmax and Cmin 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. The clinical significance of this finding is unknown.

Potential for Other Drugs to Affect Venlafaxine
The metabolic pathways for venlafaxine include CYP2D6 and CYP3A4.

In vitro and *in vivo* studies
In vitro and *in vivo* studies indicate that venlafaxine is metabolised predominantly to its active metabolite ODV by the cytochrome P450 enzyme 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 (e.g. amiodarone and quinidine) and venlafaxine. 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 decrease concentrations of ODV. As venlafaxine and ODV are both pharmacologically active, no dosage adjustment is required when venlafaxine is co administered with CYP2D6 inhibitor.

CYP3A4 inhibitors
Concomitant use of CYP3A4 inhibitors (such as erythromycin, fluconazole, ketoconazole and grape fruit juice) and venlafaxine may increase levels of venlafaxine and ODV. Therefore, caution is advised when combining venlafaxine and CYP3A4 inhibitor.

*In vitr*o studies indicate that venlafaxine is likely metabolised to a minor, less active metabolite, *N*-desmethylvenlafaxine, by CYP3A4. A pharmacokinetic study with ketoconazole (a CYP3A4 inhibitor) in extensive metabolisers (EM) and poor metabolisers (PM) of CYP2D6 resulted in higher plasma concentrations of both venlafaxine and ODV in most subjects following administration of ketoconazole. Venlafaxine Cmax 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. AUC values for ODV increased by 23 and 33% in EM and PM subjects, respectively.

CYP2D6 and CYP3A4 inhibitors
The concomitant use of venlafaxine with drug treatment(s) that potentially inhibits both CYP2D6 and CYP3A4, the primary metabolising enzymes for venlafaxine, has not been studied. However, this concomitant use would be expected to increase venlafaxine plasma concentrations. Therefore, caution is advised if a patient's therapy includes venlafaxine and any agent(s) that produces simultaneous inhibition of these two enzyme systems. In patients with unstable heart disease receiving these combinations, assessment of the cardiovascular system (e.g. ECG; serum electrolytes during diuretic treatment) should be considered during

treatment with venlafaxine (see **PRECAUTIONS, Use in Patients with Pre-Existing Heart Disease**).

ADVERSE EFFECTS

Clinical Trials

The information included in the Adverse Reactions clinical trials subsection are those that were observed in short term, placebo controlled studies with modified release venlafaxine. and has been based on data from a pool of three 8 and 12 week controlled clinical trials in Major Depressive Disorder (dose range of 75 - 225 mg/day), on data up to 8 weeks from a pool of five controlled clinical trials in Generalised Anxiety Disorder with-venlafaxine XR (dose range 37.5– 225 mg/day), on data up to 12 weeks from a pool of five controlled clinical trials in Social Anxiety Disorder (dose range of 75 – 225 mg/day), and on data up to 12 weeks from a pool of four controlled clinical trials in Panic Disorder (dose range of 75 – 225 mg/day).

The adverse events occurring at an incidence greater than or equal to 2% among modified release venlafaxine treated patients or at an incidence greater than the placebo treated patients are provided in the table below. The table shows the percentage of patients who had at least one episode of an event at some time during the treatment. 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.

Adverse Event Incidence in Clinical Trials

Body System Preferred Term	**Major Depressive Disorder [1,5]**		**Generalised Anxiety Disorder[2]**		**Social Anxiety Disorder[3]**		**Panic Disorder[4]**	
	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								
Headache	-	-	-	-	38%	34%	-	-
Asthenia	8%	7%	12%	8%	19%	9%	10%	8%
Abdominal Pain	-	-	-	-	6%	4%	-	-
Accidental Injury	-	-	-	-	4%	3%	-	-
Cardiovascular								
Hypertension	4%	1%	-	-	5%	3%	4%	3%
Vasodilatation[6]	4%	2%	4%	2%	3%	2%	3%	2%
Palpitation	-	-	-	-	3%	1%	-	-
Digestive								
Nausea	31%	12%	35%	12%	31%	9%	21%	14%
Constipation	8%	5%	10%	4%	9%	3%	9%	3%
Anorexia[7]	8%	4%	8%	2%	17%	2%	8%	3%
Vomiting	4%	2%	5%	3%	3%	2%	-	-
Diarrhoea	-	-	-	-	8%	6%	-	-
Dyspepsia	-	-	-	-	7%	6%	-	-

Flatulence	4%	3%	-	-	-	-	-	-
Metabolic /Nutritional								
Weight Loss	3%	0%	-	-	2%	<1%	-	-
Nervous								
Dizziness	20%	9%	16%	11%	16%	8%	11%	10%
Somnolence	17%	8%	14%	8%	20%	8%	12%	6%
Insomnia	17%	11%	15%	10%	24%	8%	17%	9%
Dry Mouth	12%	6%	16%	6%	17%	4%	12%	6%
Nervousness	10%	5%	6%	4%	10%	5%	-	-
Abnormal Dreams[8]	7%	2%	3%	2%	3%	<1%	-	-
Tremor	5%	2%	4%	<1%	5%	2%	5%	2%
Depression	3%	<1%	-	-	-	-	-	-
Paresthesia	3%	1%	2%	1%	-	-	-	-
Libido Decreased	3%	<1%	4%	2%	8%	2%	4%	2%
Agitation	3%	1%	-	-	3%	1%	-	-
Hypertonia	-	-	3%	2%	-	-	-	-
Anxiety	-	-	-	-	5%	4%	-	-
Twitching	-	-	-	-	3%	<1%	-	-
Respiratory								
Pharyngitis	7%	6%	-	-	-	-	- -	-
Yawning	3%	0%	3%	<1%	5%	<1%	- -	3%
Skin								
Sweating	14%	3%	10%	3%	13%	4%	10%	2%
Special Senses								
Abnormal Vision[9]	4%	<1%	5%	<1%	4%	2%	-	-
Urogenital								
Abnormal Ejaculation[10]	16%	<1%	11%	<1%	19%	<1%	8%	<1%
Impotence[11]	4%	<1%	5%	<1%	6%	<1%	4%	<1%
Orgasmic Dysfunction[12]	3%	<1%	2%	0%	5%	<1%	2%	<1%

[1] Incidence, rounded to the nearest %, for events reported by at least 2% of patients treated with venlafaxine modified release, except the following events which had an incidence equal to or less than placebo: abdominal pain, accidental injury, anxiety, back pain, bronchitis, diarrhoea, dysmenorrhoea, dyspepsia, flu syndrome, headache, infection, pain palpitation, rhinitis, and sinusitis.
[2] Adverse events for which the venlafaxine XR reporting rate was less than or equal to the placebo rate are not included. These events are: abdominal pain, accidental injury, anxiety, back pain, diarrhoea, dysmenorrhoea, dyspepsia, flu syndrome, headache, infection, myalgia, pain, palpitation, pharyngitis, rhinitis, tinnitus, and urinary frequency.

[3] Adverse events for which the venlafaxine XR reporting rate was less than or equal to the placebo rate are not included. These events are: arthralgia, back pain, dysmenorrhoea, flu syndrome, infection, pain, pharyngitis, rhinitis, and upper respiratory infection.
[4] Adverse events for which the venlafaxine XR 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, diarrhoea, dysmenorrhoea, dyspepsia, flu syndrome, headache, infection, nervousness, pain, paraesthesia, pharyngitis, rash, rhinitis, and vomiting.
[5] <1% indicates an incidence greater than zero but less than 1%.
[6] Mostly "hot flashes".
[7] Mostly "decreased appetite" and "loss of appetite".
[8] Mostly "vivid dreams", "nightmare" and "increased dreaming".
[9] Mostly "blurred vision" and "difficulty focusing eyes".
[10] Males only – Mostly "delayed ejaculation".
[11] Incidence is based on number of male patients.
[12] Females only – Mostly "delayed orgasm", "abnormal orgasm" or "anorgasmia".

The following text lists adverse reactions from combined analyses of the clinical studies for Major Depression, Generalised Anxiety Disorder, Social Anxiety Disorder, and Panic Disorder. The adverse reactions have been presented using the CIOMS frequency categories: common: greater than or equal to 1%; uncommon: greater than or equal to 0.1% and < 1%; rare: greater than or equal to 0.01% and < 0.1%; very rare: < 0.01%.

Body as a Whole
Common: Asthenia/ fatigue.
Uncommon: Photosensitivity reaction.
Very rare: Anaphylaxis.

Cardiovascular
Common: Hypertension, vasodilatation (mostly hot flashes/flushes).
Uncommon: Hypotension, postural hypotension, syncope, tachycardia.

Digestive
Common: Appetite decreased, constipation, nausea, vomiting.
Uncommon: Bruxism.

Haematological/Lymphatic
Uncommon: Ecchymosis, mucous membrane bleeding, gastrointestinal bleeding.
Rare: Prolonged bleeding time, thrombocytopenia.

Metabolic/Nutritional
Common: Serum cholesterol increased (particularly with prolonged administration and with higher doses), weight loss.
Uncommon: Abnormal liver function tests, hyponatraemia, weight gain.
Rare: Syndrome of inappropriate antidiuretic hormone secretion (SIADH).

Nervous
Common: Abnormal dreams, decreased libido, dizziness, dry mouth, increased muscle tonus, insomnia, nervousness, paraesthesia, sedation, tremor.
Uncommon: Apathy, hallucinations, myoclonus.
Rare: Convulsion, manic reaction, neuroleptic malignant syndrome (NMS), serotonergic syndrome.

Respiratory
Common: Yawning.

Skin
Common: Sweating.
Uncommon: Rash.

Special senses
Common: Abnormality of accommodation, mydriasis, visual disturbance.
Uncommon: Altered taste sensation.

Urogenital:
Common: Abnormal ejaculation/ orgasm (males), anorgasmia, erectile dysfunction, urination impaired (mostly hesitancy).
Uncommon: Abnormal orgasm (females), menorrhagia, urinary retention.

Post-Marketing Reports
The following lists adverse reactions derived from post-marketing spontaneous reports in patients with major depression, generalised anxiety disorder, social anxiety disorder and panic disorder. Adverse reactions are shown in CIOMS frequency categories: greater than or equal to 1%; uncommon: greater than or equal to 0.1% and < 1%; rare: greater than or equal to 0.01% and < 0.1%; very rare: < 0.01%.

Body as a Whole
Common: Chills.
Uncommon: Angioedema.

Cardiovascular
Common: Palpitations.
Very rare: QT prolongation, ventricular fibrillation, ventricular tachycardia (including torsade de pointes).
Unknown: Stress cardiomyopathy.

Digestive
Uncommon: Diarrhoea.
Very rare: Pancreatitis.

Haematological/Lymphatic
Uncommon: Gastrointestinal bleeding.
Very rare: Blood dyscrasias (including agranulocytosis, aplastic anaemia, neutropenia and pancytopenia).

Metabolic/Nutritional
Rare: Hepatitis.
Very rare: Prolactin increased.

Musculoskeletal
Very rare: Rhabdomyolysis.

Nervous
Very common: Headache.
Common: Confusion, depersonalisation.
Uncommon: Agitation, impaired coordination and balance.
Rare: Akathisia/psychomotor restlessness.
Very rare: Delirium, extrapyramidal reactions (including dystonia and dyskinesia), tardive dyskinesia.
Unknown: Psychotic disorder, paranoia, aggression.

Respiratory
Uncommon: Dyspnoea
Very rare: Pulmonary eosinophilia.

Skin
Common: Night sweats.
Uncommon: Alopecia.
Very rare: Erythema multiforme, Steven-Johnsons syndrome, pruritus, urticaria.

Unknown: Toxic epidermal necrolysis.

Special Senses
Uncommon: Tinnitus.
Very rare: Angle closure glaucoma.

Urogenital
Common: Menstrual disorders associated with increased bleeding or increased irregular bleeding (e.g. menorrhagia, metrorrhagia), urinary frequency increased.
Uncommon: Proteinuria.
Rare: Urinary incontinence.

Discontinuation Symptoms
Discontinuation effects are well known to occur with antidepressants and it is therefore recommended that the dosage is tapered gradually and the patient monitored **(**see **DOSAGE AND ADMINISTRATION)**. 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, paraesthesia, dizziness, convulsion, vertigo, headache, flu like symptoms, tinnitus, impaired coordination, and balance, tremor, sweating, dry mouth, anorexia, diarrhoea, nausea and vomiting. In pre-marketing studies, the majority of discontinuation reactions were mild and resolved without treatment.

In the Social Anxiety Disorder pooled short-term studies, the most common taper/post-study- emergent adverse events were dizziness (13%), nausea (7%), insomnia (3%), nervousness (3%) and asthenia (2%). In the 6-month study, the most common taper/post-study treatment emergent adverse events were dizziness (21% and 16%) and nausea (7% and 10%) for venlafaxine XR 75 mg and venlafaxine XR 150-225 mg, respectively.

Paediatric patients
(See **PRECAUTIONS, Clinical worsening and Suicide Risk; and Paediatric Use**)

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 for adults.

As with adults, decreased appetite, weight loss, increased blood pressure and increased serum cholesterol were observed. Additionally, the following adverse reactions were observed: abdominal pain, agitation, dyspepsia, ecchymosis, epistaxis and myalgia.

In paediatric clinical trials, there were increased reports of hostility and, especially in major depression, suicide related adverse events such as suicidal ideation and self-harm.

DOSAGE AND ADMINISTRATION

Usual Dosage
The usual recommended dose for the treatment of major depression is 75 mg/day given once daily. After two weeks the dose may be increased to 150 mg/day given once daily if further clinical improvement is required. If needed, this can be increased up to 225 mg given once daily. Dose increments should be made at intervals of approximately two weeks or more, but not less than four days.

The recommended dose is based on results of clinical trials in which modified release venlafaxine was mostly given once daily in doses from 75 to 225 mg. Antidepressant activity with the 75 mg dose was observed after two weeks of treatment and anxiolytic activity was observed after one week.

It is recommended that Venlafaxine XR be taken with food. Each capsule should be swallowed whole with fluid. Do not divide, crush, chew or dissolve Venlafaxine XR should be administered once daily.

Dosage Adjustment in Renal or Hepatic Impairment
Patients with renal and/or hepatic impairment should receive lower doses of Venlafaxine XR. The total daily dose of venlafaxine must be reduced by 25 to 50% for patients with renal impairment with a glomerular filtration rate (GFR) of 10 to 70 mL/minute. Haemodialysis clearances of both venlafaxine and ODV in humans are low. The total daily dose of venlafaxine must be reduced by 50% in haemodialysis patients.

Patients with mild to moderate hepatic impairment should also have their dosage reduced by 50%. Further reductions in dosage should be considered for patients with more severe degrees of hepatic impairment. Because of individual variability in clearance in these patients, individualisation of dosage may be desirable.

Dosage Adjustment in the Elderly
No adjustment in the usual dose is recommended for elderly patients solely because of their age. As with any antidepressant, however, caution should be exercised in treating the elderly. When individualising the dosage, extra care should be taken when increasing the dose.
Maintenance / Continuation / Extended Treatment
The doctor should periodically re-evaluate the usefulness of long-term Venlafaxine XR treatment for the individual patient. It is generally agreed that acute episodes of major depression require several months or longer of sustained pharmacological therapy. Whether the dose of antidepressant needed to induce remission is identical to the dose needed to maintain and/or sustain euthymia is unknown.

Usually, the dosage for prevention of relapse or for 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.

Discontinuing Venlafaxine XR
When Venlafaxine XR at a dose of 75 mg/day or greater which has been administered for more than one week is stopped, it is recommended that the dose be tapered gradually to minimise the risk of discontinuation symptoms.

In clinical trials with venlafaxine XR, tapering was achieved by reducing the daily dose by 75mg at one week intervals. To facilitate tapering below Venlafaxine XR 75 mg, doctors may consider prescribing venlafaxine 37.5 mg capsules once daily (see **Usual dosage**, above, as Venlafaxine XR 37.5mg capsules are not available, alternative venlafaxine products should be used if a 37.5mg dose is required).

The period required for tapering may depend on the dose, duration of therapy and the individual patient. Patients should be advised to consult their doctor before abruptly discontinuing Venlafaxine XR.

OVERDOSAGE
In managing overdosage, consider the possibility of multiple medication involvement. The physician should consider contacting the Poison Information Centre on the treatment of any overdose (see **INTERACTIONS WITH OTHER MEDICINES**).

Signs and Symptoms
During premarketing trials, most patients who have overdosed with venlafaxine were asymptomatic. Of the remainder, somnolence was the most commonly reported symptom. Mild sinus tachycardia and mydriasis have also been reported.

There were no reports of seizures, respiratory distress, significant cardiac disturbances or significant laboratory test result abnormalities among any of the cases reported to date. However, seizures and respiratory distress occurred in one additional patient in an ongoing study who ingested an estimated 2.75 g of venlafaxine with naproxen and thyroxine. Generalised convulsions and coma resulted and emergency resuscitation was required. Recovery was good without sequelae.

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, vomiting and seizures. Other events reported included electrocardiogram changes (e.g. prolongation of QT interval, bundle branch block, QRS prolongation), ventricular fibrillation, ventricular tachycardia (including torsades de pointes), bradycardia, hypotension, vertigo and death. Serotonin toxicity has been reported in association with venlafaxine overdose.

Fatal Overdoses
Published retrospective analyses from the United Kingdom (UK) report the rate of antidepressant overdose deaths per million prescriptions. In these analyses, the rate for venlafaxine is higher than that for SSRIs, but lower than that for tricyclic antidepressants. These analyses did not adjust for suicide risk factors.

Epidemiological studies have shown that venlafaxine is prescribed to patients with a higher pre-existing burden of suicide risk factors than patients prescribed SSRIs. 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 of venlafaxine should be written for the smallest quantity of drug consistent with good patient management, in order to reduce the risk of overdose (see **PRECAUTIONS - Clinical Worsening and Suicide Risk**).

Management of Overdosage
General supportive and symptomatic measures are recommended. Ensure an adequate airway, oxygenation and ventilation. Cardiac rhythm and vital signs must be monitored. Administration of activated charcoal may also limit drug absorption.

Where there is a risk of aspiration, induction of emesis is not recommended. No specific antidotes for venlafaxine are known. Forced diuresis, dialysis, haemoperfusion and exchange transfusion are unlikely to be of benefit.

Venlafaxine and ODV (*O*-desmethylvenlafaxine) are not considered dialysable because haemodialysis clearance of both compounds is low.

Contact the Poisons Information Centre on 13 11 26 (Australia) for advice on the management of overdosage

PRESENTATION AND STORAGE CONDITIONS

APO-Venlafaxine XR 75 mg Modified Release Capsules
Flesh-coloured, opaque size 0 hard gelatin capsules
Blister (PVC/PE/PVDC/Al) packs of 28 capsules
AUST R Number 151878

APO-Venlafaxine XR 75 mg Modified Release Capsules are intended for oral administration.

Each modified release capsule contains venlafaxine 75 mg (as 84.86 mg venlafaxine hydrochloride).

APO-Venlafaxine XR 150 mg Modified Release Capsules
Scarlet coloured, opaque size 00 hard gelatin capsules.
Blister (PVC/PE/PVDC/Al) packs of 28 capsules
AUST R 151877

APO-Venlafaxine XR 150 mg Modified Release Capsules are intended for oral administration.

Each modified release capsule contains venlafaxine 150 mg (as 169.71 mg venlafaxine hydrochloride).

Storage
Store below 25°C.

NAME AND ADDRESS OF THE SPONSOR

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POISONS SCHEDULE OF THE MEDICINE
S4: Prescription Only Medicine

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