

AUSTRALIAN PRODUCT INFORMATION

ENLAFAX-XR[®]

(Venlafaxine hydrochloride) modified release capsules



1 NAME OF THE MEDICINE

Venlafaxine Hydrochloride

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

ENLAFAX-XR modified release capsule contains either 75 mg or 150 mg of venlafaxine as the active ingredient.

Excipients with known effect: galactose and trace quantities of sulfites.

For the full list of excipients, see Section 6.1 LIST OF EXCIPIENTS.

3 PHARMACEUTICAL FORM

- ENLAFAX-XR 75mg : Presented as Flesh opaque-flesh opaque, No 0, capsules printed on cap with VEN and on the body with 75 containing two white, round, biconvex 37.5 mg film coated tablets
- ENLAFAX-XR 150mg : Presented as Scarlet opaque-scarlet opaque, No 00, printed on cap with VEN and on the body with 150, containing three white, round, biconvex 50 mg film coated tablets.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

ENLAFAX-XR is indicated for the treatment of:

- Major Depression, including prevention of relapse and recurrence where appropriate
- Social Anxiety Disorder

4.2 DOSE AND METHOD OF ADMINISTRATION

Usual Dose

The usual recommended dose for the treatment of major depression or social anxiety disorder is 75 mg per day given once daily. After two weeks, the dose may be increased to 150 mg per 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 2 weeks or more, but not less than 4 days.

The recommended dose is based on results of clinical trials in which ENLAFAX-XR was mostly given once daily in doses from 75 to 225 mg. Antidepressant activity with the 75 mg dose was observed after 2 weeks of treatment and anxiolytic activity was observed after one week.

It is recommended that ENLAFAX-XR be taken with food. Each capsule must be swallowed whole with fluid. ENLAFAX-XR should be administered once daily, at approximately the same time each day.

DO NOT DIVIDE, CRUSH, CHEW OR DISSOLVE. ENLAFAX-XR capsules are to be swallowed whole and are not to be divided, chewed or crushed. Taking divided, chewed or crushed ENLAFAX-XR capsules, in theory, could lead to the rapid release and absorption of venlafaxine.

Dosage Adjustment in Patients with Renal or Hepatic Impairment

Patients with renal and/or hepatic impairment should receive lower doses of ENLAFAX-XR. The total daily dose of venlafaxine should be reduced by 25% to 50% for patients with renal impairment with a glomerular filtration rate (GFR) of 10 to 70 mL/min. Haemodialysis clearances of both venlafaxine and ODV in humans are low. The total daily dose of venlafaxine should 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 Elderly Patients

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 physician should periodically re-evaluate the usefulness of long-term ENLAFAX-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 re-assessed in order to evaluate the benefit of long-term therapy.

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

Discontinuing ENLAFAX-XR

When ENLAFAX-XR at a dose of 75 mg/day or greater has been administered for more than 1 week is stopped, it is recommended that the dose be tapered gradually to minimise the risk of discontinuation symptoms. In clinical trials with modified release venlafaxine capsules, tapering was achieved by reducing the daily dose by 75 mg at 1 week intervals. To facilitate tapering below 75 mg of ENLAFAX-XR, physicians may consider prescribing the 37.5 mg of venlafaxine modified release capsules once daily (ENLAFAX-XR 37.5 mg capsules are not available). The time period required for tapering and the amount of dose reduction may depend on the dose, duration of therapy, and the individual patient. Patients should be advised to consult their physician before abruptly discontinuing ENLAFAX-XR. In some patients, discontinuation may need to occur very gradually over periods of months or longer.

4.3 CONTRAINDICATIONS

Hypersensitivity to venlafaxine or any excipients in the formulation.

Monoamine Oxidase Inhibitors (MAOIs)

Concomitant use of venlafaxine and any monoamine oxidase inhibitors (MAOIs) or reversible MAOIs (RIMA) (e.g. moclobemide, linezolid and intravenous methylene blue) is contraindicated. Modified release venlafaxine capsules must not be initiated for at least 14 days after discontinuation of treatment with a MAOI. Similarly, modified release venlafaxine capsules must be discontinued for at least 7 days before starting treatment with any 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 Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE and Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

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 behaviours (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 closely 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 18-24 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 4400 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 2 months) of 11 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 Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE - 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 co-morbid 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 non-psychiatric. 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 modified release venlafaxine capsules should be written for the smallest quantity of capsules consistent with good patient management in order to reduce the possibility of overdose. 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 torsade de pointes), convulsions, and death (see Section 4.9 OVERDOSE).

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 Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE – 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, serotonin syndrome, a potentially life threatening condition or neuroleptic malignant syndrome (NMS)-like reaction, may occur with venlafaxine treatment, particularly with concomitant use of other serotonergic drugs (including SSRIs, SNRIs, amphetamines, triptans, opioids [e.g. fentanyl, dextromethorphan, tramadol, tapentadol, pethidine, methadone and pentazocine]), 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 Section 4.3 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 Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF 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.

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.

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) should be closely monitored.

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.

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/min.

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.

Sustained Hypertension

Dose-related increases in blood pressure have been reported in some patients treated with venlafaxine.

Among patients treated with 75 to 375 mg per day of modified release venlafaxine capsules in pre-marketing depression studies, 3% (19/705) experienced sustained hypertension [defined as treatment-emergent supine diastolic blood pressure (SDBP) \geq 90 mm Hg and \geq 10 mm Hg above baseline for 3 consecutive on-therapy visits]. 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 modified release venlafaxine capsules over 300 mg per day to fully evaluate the incidence of sustained increases in blood pressure at these higher doses.

In placebo-controlled pre-marketing depression studies with modified release venlafaxine capsules 75 to 225 mg per day, a final on-drug mean increase in supine diastolic blood pressure (SDBP) of 1.2 mm Hg was observed for modified release venlafaxine capsules treated patients compared with a mean decrease of 0.2 mm Hg for placebo-treated patients. In pre-marketing Social Anxiety Disorder studies up to 12 weeks, the final on therapy mean change from baseline in SDBP was small - an increase of 0.78 mmHg, compared to a decrease of 1.41 mmHg in placebo-treated patients. In a 6-month study, the final on-therapy mean increase from baseline in SDBP with modified release venlafaxine capsules 150 to 225 mg was 1.49 mmHg. The increase was significantly different from the 0.6 mmHg decrease with placebo and the 0.2 mmHg decrease with modified release venlafaxine capsules 75 mg.

In pre-marketing depression studies, 0.7% (5/705) of the modified release venlafaxine capsules treated patients discontinued treatment because of elevated blood pressure. Among these patients, most of the blood pressure increases were in a modest range (12 to 16 mm Hg, SDBP).

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 modified release venlafaxine capsules have regular monitoring of blood pressure. For patients who experience a sustained increase in blood pressure while receiving venlafaxine, either dose reduction or discontinuation should be considered. 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 3 months in placebo-controlled clinical trials.

Treatment with modified release venlafaxine capsules for up to 12 weeks in pre-marketing 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).

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 modified-release-venlafaxine-capsules-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 (0.32mmol/L, 7%) in the modified release venlafaxine capsules 150 to 225 mg group; however the total cholesterol value was only slightly increased (0.01mmol/L) for the modified release venlafaxine capsules 75mg group.

There were also significant mean increases from baseline in LDL, but not HDL for the modified release venlafaxine capsules 150 to 225 mg group. The final on-therapy increase of 0.213 mmol/L from baseline in LDL with modified release venlafaxine capsules 150 to 225 mg was significantly different from the small decrease with placebo (0.079 mmol/L) and the negligible increase with modified release venlafaxine capsules 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 modified release venlafaxine capsules 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. ECG; serum electrolytes during diuretic treatment) should be considered during treatment with venlafaxine, particularly when the dose is increased beyond 150-200 mg daily.

Evaluation of the electrocardiograms for 769 patients who received immediate release Venlafaxine in 4 to 6-week double-blind, placebo-controlled trials showed that the incidence of trial-emergent conduction abnormalities did not differ from that with placebo.

The electrocardiograms for patients who received modified release venlafaxine capsules or placebo in the depression and Social Anxiety Disorder trials were analysed. The mean change from baseline in corrected QT interval (QTc) for modified release venlafaxine capsules treated patients in depression studies was increased relative to that for placebo-treated patients (increase of 4.7 msec for modified release venlafaxine capsules and decrease of 1.9 msec for placebo). The final on-therapy mean increase from baseline in QTc (3 msec) was significant for modified release venlafaxine capsules 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 modified release venlafaxine capsules 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 modified release venlafaxine capsules 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 modified release venlafaxine capsules treated patients in the depression studies was significantly higher than for placebo (a mean increase of 3-4 beats per minute for modified release venlafaxine capsules and 0-1 beat per minute for placebo in the depression studies). In the pooled short-term Social Anxiety Disorder studies, the final on-therapy mean increase from baseline in heart rate with modified release venlafaxine capsules was 5 beats per minute. In the 6 month study, the final on-therapy mean increases from baseline in heart rate were significant with modified release venlafaxine capsules 75mg (2 beats per minute) and modified release venlafaxine capsules 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/Torsades de Pointes (TdP)

Case 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, and sometimes these effects can be protracted and severe (See Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)). Suicide/suicidal thoughts and aggression have been observed in patients during changes in venlafaxine dosing regimen, including during discontinuation (See Clinical Worsening and Suicide Risk above and Aggression below). 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, paraesthesias, 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.

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 8 months. It is, therefore, recommended that the dosage of modified release venlafaxine capsules be tapered gradually and individually and the patient monitored during discontinuation. The time period required for tapering and the amount of dose reduction may depend on the dose, duration of therapy and the individual patient (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION and Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)). In some patients, discontinuation could take months or longer.

Sexual Dysfunction

SNRIs may cause symptoms of sexual dysfunction (See Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)). There have been reports of long-lasting sexual dysfunction where the symptoms have continued despite discontinuation of SNRIs.

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 6 (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 modified release venlafaxine capsules and weight loss agents is not recommended. Modified release venlafaxine capsules is not indicated for weight loss alone or in combination with other products.

Seizures

Seizures have been reported with venlafaxine therapy and in overdose. Modified release venlafaxine capsules, as with all antidepressants, should be introduced with care, in patients with a history of seizure disorders. Modified release venlafaxine capsules should be discontinued in any patient who develops seizures (see Section 4.9 OVERDOSE).

Mania/Hypomania and Bipolar Disorder

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

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 both 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 modified release venlafaxine capsules 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 physician 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 anticoagulants 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, physicians 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 Section 5 PHARMACOLOGICAL PROPERTIES).

Electroconvulsive Therapy

There are no clinical data establishing the benefit of ENLAFAX-XR combined with electroconvulsive therapy

Use in the Elderly

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

Effectiveness in elderly patients with social anxiety disorder has not been established.

Paediatric Use

ENLAFAX-XR is not indicated for use in children and adolescents below 18 years of age as safety and effectiveness has not been demonstrated. Therefore, ENLAFAX-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 Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE – Clinical Worsening and Suicide Risk and Section 4.8 ADVERSE EFFECTS (UNDESIRABLE 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 Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)).

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.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Venlafaxine and ODV 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

Concomitant use of ENLAFAX-XR in patients taking monoamine oxidase inhibitors (MAOIs) or reversible MAOIs (e.g. moclobemide, linezolid and intravenous methylene blue) is contraindicated (see Section 4.3 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 ENLAFAX-XR in combination with a MAOI or reversible MAOI, or within at least 14 days of discontinuing MAOI treatment. Allow at least 7 days after stopping ENLAFAX-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.

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, opioids [e.g. fentanyl and its analogues, tramadol, dextromethorphan, tapentadol, pethidine, methadone, pentazocine], or St John's Wort [*Hypericum perforatum*]), with drugs which impair metabolism of serotonin (such as MAOIs, including moclobemide, linezolid [an antibiotic which is a reversible non-selective MAOI] and intravenous 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 Section 4.3 CONTRAINDICATIONS and Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

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 (such as tryptophan supplements) is not recommended (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

No information is available on the use of ENLAFAX-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.

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

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 Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE - QTc prolongation/TdP).

Indinavir

A pharmacokinetic study with Indinavir has shown a 28% decrease in 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.

Warfarin

There have been reports of increases in prothrombin time, partial thromboplastin time, or INR when venlafaxine was given to patients receiving warfarin therapy.

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 ENLAFAX-XR.

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 ENLAFAX-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 ENLAFAX-XR is administered with cimetidine.

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 or 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 Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS - CNS 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 2 mg dose of haloperidol by 42%, which resulted in a 70% increase in haloperidol AUC. In addition, the haloperidol C_{max} increased 88% when co-administered with venlafaxine, but the haloperidol elimination half-life (t_{1/2}) was unchanged. The mechanism explaining this finding is unknown.

Metoprolol

Concomitant administration of venlafaxine (50 mg every 8 hours for 5 days) and metoprolol (100 mg every 24 hours for 5 days) to 18 healthy male subjects in a pharmacokinetic interaction study for both drugs resulted in an increase of plasma concentrations of metoprolol by approximately 30-40% without altering the plasma concentrations of its active metabolite, 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 ENLAFAX-XR have regular monitoring of blood pressure (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE – Sustained Hypertension).

Risperidone

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

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, ENLAFAX-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 venlafaxine does 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 –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, 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. 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 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 (such as amiodarone and quinidine) and venlafaxine. CYP3A4 is a minor pathway relative to CYP2D6 in the metabolism of venlafaxine.

CYP2D6 Inhibitors

The concomitant use of CYP2D6 inhibitors and venlafaxine may reduce the metabolism of venlafaxine to ODV, resulting in increased the 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 (such as erythromycin, fluconazole, ketoconazole and grapefruit juice) and venlafaxine may increase levels of venlafaxine and ODV. Therefore, caution is advised when combining venlafaxine with a CYP3A4 inhibitor.

In vitro studies indicate that venlafaxine is likely metabolised to a minor, less active metabolite, Ndesmethylvenlafaxine, 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 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

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 Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE - Use in Patients with Pre-Existing Heart Disease).

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.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on Fertility

Reproduction and fertility studies in rats showed no effects on male or female fertility at oral doses of up to 2 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 2 to 3 times that of a human dose of 225 mg/day. The human relevance of this finding is unknown.

Signs of pharmacologic 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.

Use in Pregnancy

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 benefits outweigh the possible risks. Patients should be advised to notify their physician 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 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, or 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, hyperreflexia, tremor, jitteriness, irritability and constant crying. These features are consistent with either a direct toxic effect of SSRIs and SNRIs or, possibly, a drug discontinuation syndrome.

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 re-uptake of serotonin).

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. During pregnancy both Major Depression and antidepressant medications may present risks to the mother and the neonate. The benefits and choice of specific therapy must be weighed against the risks.

Epidemiological studies suggest that exposure to SNRIs in mid to late pregnancy may increase the risk for preeclampsia. Exposure to SNRIs near delivery may increase the risk for postpartum haemorrhage.

Australian Categorisation Definition of Category B2: Drugs which have been taken by only limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human foetus having been observed. Studies in animals are inadequate or may be lacking, but available data show no evidence of an increased occurrence of foetal damage.

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 breast fed infants can be as high as 9.2% of maternal intake. Therefore, the use of ENLAFAX-XR in nursing women cannot be recommended. Exposed infants should be observed closely.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

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.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Clinical Trials

The information included in the Adverse Effects clinical trials subsection are those that were observed in short-term, placebo-controlled studies with modified release venlafaxine capsules 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 – 225mg/day) and 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). The adverse events occurring at an incidence $\geq 2\%$ among modified release venlafaxine capsules treated patients or at an incidence greater than the placebo treated patients are provided in Table 1.

Table 1 shows the percentage of patients in each group 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.

Table 1

Body System	Adverse event incidence in Clinical Trials			
	Major Depressive Disorder ^{1,3}		Social Anxiety Disorder ²	
	Modified release venlafaxine capsules	Placebo	Modified release venlafaxine capsules	Placebo
	n=357	n=285	n=819	n=695
	%	%	%	%
Body as a whole				
Headache	-	-	38	34
Asthenia	8	7	19	9
Abdominal pain	-	-	6	4
Accidental injury	-	-	4	3
Cardiovascular				
Hypertension	4	1	5	3
Vasodilation ⁴	4	2	3	2
Palpitation	-	-	3	1

Digestive				
Nausea	31	12	31	9
Constipation	8	5	9	3
Anorexia ⁵	8	4	17	2
Vomiting	4	2	3	2
Diarrhoea	-	-	8	6
Dyspepsia	-	-	7	6
Flatulence	4	3	-	-
Metabolic/Nutritional				
Weight loss	3	0	2	<1
Nervous				
Dizziness	20	9	16	8
Somnolence	17	8	20	8
Insomnia	17	11	24	8
Dry mouth	12	6	17	4
Nervousness	10	5	10	5
Abnormal dreams ⁶	7	2	3	<1
Tremor	5	2	5	2
Depression	3	<1	-	-
Paresthesia	3	1	-	-
Libido decreased	3	<1	8	2
Agitation	3	1	3	1
Hypertonia	-	-	-	-
Anxiety	-	-	5	4
Twitching	-	-	3	<1
Respiratory				
Pharyngitis	7	6	-	-
Yawning	3	0	5	<1
Skin				
Sweating	14	3	13	4
Special Senses				
Abnormal vision ⁷	4	<1	4	2

Urogenital				
Abnormal ejaculation ⁸	16	<1	19	<1
Impotence ⁹	4	<1	6	<1
Orgasmic Dysfunction ¹⁰	3	<1	5	<1
1. Incidence, rounded to the nearest %, for events reported by at least 2% of patients treated with modified release venlafaxine capsules, 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 modified-release venlafaxine capsules 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				
3. <1% indicates an incidence greater than zero but less than 1%.				
4. Mostly “hot flashes”				
5. Mostly “decreased appetite” and “loss of appetite”				
6. Mostly “vivid dreams”, “nightmare” and “increased dreaming”				
7. Mostly “blurred vision” and “difficulty focusing eyes”				
8. Males only – Mostly “delayed ejaculation”				
9. Incidence is based on number of male patients				
10. Females only – Mostly “delayed orgasm”, “abnormal orgasm” or “anorgasmia”				

Adverse effects are listed in Table 2 in CIOMS frequency categories:

Common: $\geq 1\%$; Uncommon: $\geq 0.1\%$ and $<1\%$; Rare: $\geq 0.01\%$ and $<0.1\%$; Very rare: $<0.01\%$.

Table 2

System Organ Class	Adverse Drug Reactions
General Disorders and Administration Site Conditions	
Common:	Asthenia, fatigue
Uncommon:	Mucosal haemorrhage
Immune System Disorders	
Rare:	Anaphylactic reaction
Cardiac Disorders	
Common:	Tachycardia
Vascular Disorders	
Common:	Hypertension, hot flush
Uncommon:	Hypotension, orthostatic hypotension

Gastrointestinal Disorders	
Very common:	Constipation, nausea, dry mouth
Common:	Vomiting
Hepatobiliary Disorders	
Uncommon:	Liver function test abnormal
Blood and Lymphatic System Disorders	
Rare:	Thrombocytopenia
Endocrine Disorders	
Rare:	Inappropriate antidiuretic hormone secretion
Metabolism and Nutrition Disorders	
Common:	Decreased appetite
Uncommon:	Hyponatraemia
Investigations	
Common:	Blood cholesterol increased, weight decreased, weight increased
Rare:	Bleeding time prolonged
Musculoskeletal and Connective Tissue Disorders	
Common:	Hypertonia
Psychiatric Disorders	
Very common:	Insomnia
Common:	Abnormal dreams, libido decreased, anorgasmia, nervousness
Uncommon:	Mania, hypomania, hallucination, abnormal orgasm, bruxism, apathy
Nervous System Disorders	
Very common:	Dizziness, sedation
Common:	Paraesthesia, tremor, dysgeusia
Uncommon:	Syncope. Myoclonus
Rare:	Convulsion, neuroleptic malignant syndrome, serotonin syndrome
Respiratory, Thoracic and Mediastinal Disorders	
Common:	Yawning
Skin and Subcutaneous Tissue Disorders	
Very common:	Hyperhidrosis
Common:	Rash
Uncommon:	Ecchymosis, photosensitivity reaction
Eye Disorders	
Common:	Accommodation disorder, mydriasis, visual impairment
Renal and Urinary Disorders	
Common:	Urinary hesitation, urinary retention
Reproductive System and Breast Disorders	
Common:	Ejaculation disorder, erectile dysfunction

Uncommon:	Menorrhagia
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Post-Marketing Reports

Table 3 lists adverse reactions derived from post-marketing spontaneous reports. Adverse reactions are shown in CIOMS frequency categories: Common: >1%; Uncommon: >0.1% and <1%; Rare: >0.01% and <0.1%; Very rare: <0.01%; Not known: cannot be estimated from the available data.

Table 3

System Organ Class	Adverse Drug Reactions
General Disorders and Administration	
Site Conditions	
Common:	Chills
Cardiac Disorders	
Common:	Palpitations
Rare:	Electrocardiogram QT prolonged, ventricular fibrillation, ventricular tachycardia, torsade de pointes, stress cardiomyopathy (takosubo cardiomyopathy)
Gastrointestinal Disorders	
Common:	Diarrhoea
Uncommon	Gastrointestinal haemorrhage
Rare:	Pancreatitis
Hepatobiliary Disorders	
Rare:	Hepatitis
Blood and Lymphatic System Disorders	
Rare:	Agranulocytosis, aplastic anemia, neutropenia, pancytopenia
Endocrine Disorders	
Very rare:	Blood prolactin increased
Musculoskeletal and Connective Tissue Disorders	
Rare:	Rhabdomyolysis
Psychiatric Disorders	
Common:	Agitation, confusional state, depersonalisation
Rare:	Delirium
Nervous System Disorders	
Very common:	Headache
Common:	Akathisia
Uncommon:	Balance disorder, coordination abnormal, dyskinesia
Rare:	Dystonia
Very rare:	Tardive dyskinesia
Not known:	Psychotic disorder, paranoia, aggression
Respiratory, Thoracic and Mediastinal Disorders	
Common:	Dyspnoea

Rare:	Interstitial lung disease, pulmonary eosinophilia
Skin and Subcutaneous Tissue Disorders	
Common:	Pruritus, night sweats
Uncommon:	Angioedema, urticaria, alopecia
Rare:	Erythema multiforme, toxic epidermal necrolysis, Stevens-Johnson syndrome
Eye Disorders	
Rare:	Angle closure glaucoma
Ear and Labyrinth Disorders	
Common:	Tinnitus
Renal and Urinary Disorders	
Common:	Pollakiuria
Uncommon:	Proteinuria, urinary incontinence
Reproductive System and Breast Disorders	
Common	Metrorrhagia
Injury, Poisoning and Procedural Complications	
Uncommon	Bone fracture

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 Section 4.2 DOSE AND METHOD OF 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, vomiting, visual impairment, and hypertension. In pre-marketing studies, the majority of discontinuation reactions were mild and resolved without treatment. (See Section 4.2 DOSE AND METHOD OF ADMINISTRATION AND Section 4.4 – SPECIAL WARNINGS AND PRECAUTIONS FOR USE). There have been reports of serious discontinuation symptoms and sometimes these effects can be protracted and severe.

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 modified release venlafaxine capsules 75 mg and modified release venlafaxine capsules 150-225 mg, respectively.

Paediatric Patients (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE – Clinical Worsening and Suicide Risk and Paediatric Use)

In general, the Adverse effect 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 effects 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.

Reporting Suspected Adverse Effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

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 Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

Signs and Symptoms

During pre-marketing 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 patient in an on-going study who ingested an estimated 2.75g 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.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

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 Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE - 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 are not considered dialyzable because haemodialysis clearance of both compounds is low.

For information on the management of overdose, contact the Poison Information Centre on 131126 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of Action

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

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 noradrenaline reuptake and weak inhibitors of dopamine reuptake. In vitro, venlafaxine has no significant affinity for rat brain muscarinic, H1-histaminergic or alpha1-adrenergic receptors. Pharmacological activity at these receptors is hypothesized to be associated with various anticholinergic, cardiovascular, and sedative effects seen with other psychotropic drugs. Venlafaxine does not possess monoamine oxidase (MAO) inhibitory activity.

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

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

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 capsules in the treatment of major depression. One of these studies also incorporated an active comparator, paroxetine. These studies showed modified release venlafaxine capsules 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 capsules during an initial 8-week open-label treatment phase and were randomly assigned to continuation on modified release venlafaxine capsules or placebo for 6 months demonstrated a significantly lower relapse rate for patients taking modified release venlafaxine capsules compared with those on placebo.

In a second long-term study, outpatients with a history of recurrent depression who had responded to venlafaxine (the immediate-release form of venlafaxine) by 8 weeks and maintained improvement during an initial 6-month open-label treatment phase were randomly assigned to maintenance therapy on venlafaxine or placebo for 12 months. Significantly fewer patients taking venlafaxine compared with those on placebo had a reappearance of depression.

Social Anxiety Disorder

The efficacy of modified release venlafaxine capsules as a treatment for social anxiety disorder (also known as social phobia) was established in four double-blind, parallel-group, 12-week, multi-centre, placebo-controlled, flexible-dose studies and one double-blind, parallel-group, 6-month, fixed/flexible dose study in

adult outpatients meeting DSM-IV criteria for Social Anxiety Disorder. Patients received doses in a range of 75-225 mg/day. Efficacy was assessed with the Liebowitz Social Anxiety Scale (LSAS). The LSAS measures the relationship of impairment because of social anxiety disorder symptoms by evaluating a patient's fear and avoidance in a broad range of situations (i.e., 13 performance and 11 social interaction situations). Psychometric studies have shown the LSAS to be a valid and reliable measure of social anxiety.¹ The LSAS scale has also been shown to be sensitive to differences between active and placebo treatments.²

The results of these trials are presented in Table 4 below. In these five trials, modified release venlafaxine capsules were significantly more effective than placebo on change from baseline to endpoint on the LSAS total score.

Table 4 - Summary of Results for Primary Efficacy Variable in ITT Patients at final On-Therapy Visit: 12 week

Variable Study Number Treatment group	Number of Patients	Raw baseline Score	Adjusted Final On-therapy Score	Adjusted Mean Change from Baseline	p-value Placebo	vs.
Short-term (12 week) studies						
LSAS						
Study 1						
Placebo	138	86.7	69.0	-19.9		
Venlafaxine XR ^a	133	91.1	57.8	-31.0	< 0.001	
Study 2 ^b						
Placebo	135	87.4	66.9	-22.1		
Venlafaxine XR ^a	126	90.8	56.3	-32.8	0.003	
Study 3						
Placebo	132	83.6	64.5	-19.1		
Venlafaxine XR ^a	129	83.2	47.6	-36.0	< 0.001	
Paroxetine ^c	128	83.9	48.1	-35.4	< 0.001	
Study 4						
Placebo	144	86.1	64.3	-22.2		
Venlafaxine XR ^a	133	86.2	51.5	-35.0	< 0.001	
Paroxetine	136	87.2	47.3	-39.2	< 0.001	

1 Clark DB, et al. Systematic assessment of social phobia in clinical practice. *Depress and Anxiety* 1997;6:47-61.

2 Davidson JRT, et al. Treatment of social phobia with clonazepam and placebo. *J Clin Psychopharmacol.* 1993;13:423-428.

a: Flexible dose range for venlafaxine XR was 75-225mg/day; b: Data shown are for ITT population; c: Flexible dose range for paroxetine was 20-50mg/day

Table 5 - Summary of Results for Primary Efficacy Variable in ITT Patients at final On-Therapy Visit: 6 Month

Variable	Number of Patients	Raw baseline Score	Adjusted Final On-therapy Score	Adjusted Mean Change from Baseline	p-value vs. Placebo
Long-term (6 month) Study					
LSAS					
Study 5					
Placebo	126	89.3	65.6	-23.5	
Venlafaxine XR (total) ^d	238	89.0	51.2	-37.8	< 0.001
Venlafaxine XR 75mg	119	91.8	51.0	-38.1	< 0.001
Venlafaxine 150-225mg	119	86.2	51.5	-37.6	< 0.001

a: Flexible dose range for venlafaxine XR was 75-225mg/day; b: Data shown are for ITT population; c: Flexible dose range for paroxetine was 20-50mg/day; d: Primary treatment group. Abbreviations: ITT = intent to treat; LSAS = Liebowitz Social Anxiety Scale

5.2 PHARMACOKINETIC PROPERTIES

Steady-state concentrations of venlafaxine and ODV are attained within 3 days of oral multiple-dose therapy. Venlafaxine and ODV exhibited linear kinetics over the dose range of 75 to 450mg/day. Mean \pm SD steady-state plasma clearance of venlafaxine and ODV is 1.3 ± 0.6 and 0.4 ± 0.2 L/h/kg, respectively; apparent elimination half-life is 5 ± 2 and 11 ± 2 hours, respectively; and apparent (steady-state) volume of distribution is 7.5 ± 3.7 and 5.7 ± 1.8 L/kg, respectively.

Absorption

Venlafaxine is well absorbed. On the basis of mass balance studies, at least 92% of a single oral dose of venlafaxine is absorbed. However, the presystemic metabolism of venlafaxine (which primarily forms the active metabolite, ODV) reduces the absolute bioavailability of venlafaxine to $42\% \pm 15\%$.

After administration of venlafaxine 75 mg at steady state, the peak plasma concentrations (C_{max}) of venlafaxine (69.8 ± 37.8 ng/mL) and ODV (151.0 ± 36.8 ng/mL) were attained within 5.38 ± 1.37 and 7.64 ± 2.24 hours, respectively. After the administration of venlafaxine (150mg) under the fasting conditions, the peak plasma concentration (C_{max}) of venlafaxine (95.1 ± 44.5 ng/mL) and ODV (208 ± 63.2 ng/mL) were attained within 5.32 ± 1.48 and 8.08 ± 3.03 hours, respectively. After the administration of venlafaxine (150 mg) under the fed condition, the peak plasma concentration (C_{max}) of venlafaxine (103.0 ± 49.2 ng/mL) and ODV (220.9 ± 59.3 ng/mL) were attained within 6.11 ± 1.66 and 8.27 ± 2.54 hours respectively. The apparent elimination half-life of venlafaxine following administration of venlafaxine modified release capsules is 9.26 ± 2.00 and 8.56 ± 2.32 hours under fasting and fed conditions respectively.

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 venlafaxine modified release capsule. Therefore, the venlafaxine modified release 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 $27\% \pm 2\%$ at concentrations ranging from 2.5 to 2215 ng/mL, and the degree of ODV binding to human plasma proteins is $30\% \pm 12\%$ at concentrations ranging from 100 to 500 ng/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 -extensive metabolisers. However, despite the metabolic differences between the CYP2D6-poor and -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 -extensive metabolisers can be treated with the same regimen of venlafaxine modified release capsules (see Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS - CYP2D6 Inhibitors).

Excretion

Approximately 87% of a venlafaxine dose is recovered in the urine within 48 hours after a single radio-labelled 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

There is no evidence to suggest that administration of ENLAFAX-XR with food affects the absorption of venlafaxine or on the subsequent formation of ODV.

Special Populations

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 aging.

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.

Renal Impairment

In patients with moderate to severe impairment of renal function, the total clearance of both venlafaxine and ODV was reduced, and $t_{1/2}$ was prolonged. The reduction in total clearance was most pronounced in subjects with creatinine clearance less than 30 mL/min.

5.3 PRECLINICAL SAFETY DATA

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.

Carcinogenicity

Venlafaxine was given by oral gavage to mice and rats for 18 months 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.

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 which 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.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

sodium lauryl sulphate, ammonio methacrylate copolymer, magnesium stearate, hypromellose and basic butylated methacrylate copolymer. The capsule shells contain gelatin, and titanium dioxide. In addition to these, the 75 mg capsule shells also contain iron oxide red and TekPrint SW-1102 Red Ink (ARTG PI No:107015), whilst 150 mg capsule shells contain erythrosine, indigo carmine and TekPrint SB-0007P White Ink (ARTG PI No: 2216).

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C.

6.5 NATURE AND CONTENTS OF CONTAINER

Container type: [PVC/PE/PVDC/Al] blister pack

Pack sizes: 7, 14 and 28 modified release capsules

Some strengths, pack sizes and/or pack types may not be marketed.

Australian Register of Therapeutic Goods (ARTG)

AUST R 143533 – ENLAFAX-XR venlafaxine 75mg modified release capsule blister pack

AUST R 143552 – ENLAFAX-XR venlafaxine 150mg modified release capsule blister pack

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking it to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

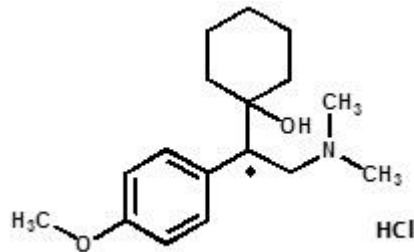
ENLAFAX-XR capsules are a modified-release formulation, which release the active ingredient, venlafaxine hydrochloride, by a combination of swelling of the hydrophilic polymer (hypromellose), diffusion and erosion. Two strengths of ENLAFAX-XR capsules are available containing either 75 mg or 150 mg of venlafaxine (as hydrochloride).

Venlafaxine hydrochloride is a white crystalline solid with a solubility of 572 mg/mL in water (adjusted to ionic strength of 0.2 M with sodium chloride).

Chemical Structure

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

Structural formula :



Molecular formula : $C_{17}H_{27}NO_2 \cdot HCl$ Molecular weight : 313.87

CAS Number

99300-78-4

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 (Prescription Only Medicine)

8 SPONSOR

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9 DATE OF FIRST APPROVAL

30/04/2009

10 DATE OF REVISION

27/06/2023

Summary Table of Changes

Section Changed	Summary of New Information
2, 3, 6.1, 6.5	Minor editorial changes

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