NEW ZEALAND DATA SHEET

ENLAFAX® XR

1. Product Name

Enlafax XR, 37.5 mg, 75 mg and 150 mg, modified release capsule.

2. Qualitative and Quantitative Composition

Each modified release capsule contains 42.43 mg, 84.86 mg or 169.71 mg of venlafaxine hydrochloride, equivalent to 37.5 mg, 75 mg or 150 mg of venlafaxine free base, respectively.

Excipient with known effect: gelatin capsule

Allergen declaration: Contains sulfites.

For the full list of excipients, see section 6.1.

3. Pharmaceutical Form

Enlafax XR 37.5 mg – White opaque cap and body containing one 37.5 mg tablet. Capsule printed with 'VEN' on cap and '37.5' on body.

Enlafax XR 75 mg – flesh opaque cap and body containing two 37.5 mg tablets. Capsule printed with 'VEN' on cap and '75' on body.

Enlafax XR 150 mg – scarlet opaque cap and body containing three 50 mg tablets. Capsule printed with 'VEN' on cap and '150' on body.

4. Clinical Particulars

4.1 Therapeutic indications

Enlafax XR is indicated for the treatment of:

- Major depression
- Generalised anxiety disorder
- Social anxiety disorder
- Panic disorder.

Enlafax XR is also indicated for the prevention of relapse and recurrence of major depression where appropriate.

4.2 Dose and method of administration

Adults

Major depression, generalised anxiety disorder and social anxiety disorder

The usual recommended dose for the treatment of major depression, generalised anxiety disorder 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 375 mg given once daily. Dose increments should be made at intervals of approximately 2 weeks or more, but not less than 4 days.

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, at approximately the same time every day. Each capsule must be swallowed whole with fluid. Do not divide, crush, chew or dissolve.

Panic disorder

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

Patients not responding to the 75 mg/day dose may benefit from dose increases to a maximum of 225 mg/day. Dosage increases can be made in increments of 75 mg per day at intervals of approximately 2 weeks or more, but not less than 4 days.

Dosage adjustment in 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% in patients with renal impairment with a glomerular filtration rate (GFR) of 10 to 70 mL/min. Haemodialysis clearances of both venlafaxine and O-desmethylvenlafaxine (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 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.

Use in children and adolescents (under 18 years of age)

Safety and efficacy have not been established in this population. Consequently, Enlafax XR should not be used in patients under 18 years of age (see section 4.4).

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 whenever possible that the dose be tapered gradually to minimise the risk of discontinuation symptoms. In clinical trials with venlafaxine, 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 capsules once daily (see also Major Depression, Generalised Anxiety Disorder and Social Anxiety Disorder above). The time period required for tapering 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 the active substance or to any of the excipients listed in section 6.1.

Monoamine oxidase inhibitors (MAOIs)

Venlafaxine 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 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 Serotonin and Noradrenaline Reuptake Inhibitor (SNRI) in combination with MAOIs and RIMA, and in patients who have recently discontinued an SNRI and have been started on a MAOI (see sections 4.4 and 4.5).

4.4 Special warnings and precautions for use

Overdose

Patients should be advised not to use alcohol, considering its CNS-effects and potential of clinical worsening of psychiatric conditions, and the potential for adverse interactions with venlafaxine including CNS-depressant effects (see section 4.5). Overdose with venlafaxine has been reported predominantly in combination with alcohol and/or other medicinal products, including cases with fatal outcome (see section 4.9).

Prescription for venlafaxine should be written for the smallest quantity consistent with good patient management, in order to reduce the risk of overdose (see section 4.9).

Clinical worsening and suicide risk

The risk of suicide attempt is inherent in depression and may persist until significant remission occurs. The risk must be considered in all depressed patients.

Patients with depression may experience worsening of their depressive symptoms and/or the emergence of suicidality (suicidal ideation and behaviours) whether or not they are taking antidepressant medications, and this risk may persist until significant remission occurs. As improvement may not occur during the first few weeks or more of treatment, all patients treated with venlafaxine 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.

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

24 years of age; there was a reduction in the risk of suicidality with antidepressants compared to placebo in adults age 65 years and older.

Patients with co-morbid depression associated with other 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.

Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients who exhibit the above symptoms or 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 also Discontinuation effects of venlafaxine).

Prescriptions for venlafaxine should be written for the smallest quantity of capsules consistent with good patient management, in order to reduce the risk of overdose.

Information for patients and caregivers

Patients, their families and their caregivers should be encouraged to be alert 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 or dosage regimen. 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 Paediatric use).

The patient has the right to treatment meeting appropriate ethical and professional standards, and the patient needs to be fully informed with frank discussion of risk/benefit issues relating to this medicine's efficacy and safety when used in the treatment regimen proposed.

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

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), 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).

Symptoms of serotonin syndrome 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.

If concomitant treatment with venlafaxine and other agents that may affect the serotonergic and/or dopaminergic neurotransmitter systems is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases. The concomitant use of venlafaxine with serotonin precursors (such as tryptophan supplements) is not recommended (see section 4.5).

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

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.

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 venlafaxine in pre-marketing depression studies, 3% (19/705) experienced sustained hypertension [defined as treatment emergent supine diastolic blood pressure (SDBP) ≥ 90 mmHg and ≥ 10 mmHg above baseline for 3 consecutive on-therapy visits]. Among patients treated with 37.5 to 225 mg per day of venlafaxine 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 modified release venlafaxine 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 venlafaxine 75 to 225 mg per 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 placebo-controlled pre-marketing GAD studies with venlafaxine 37.5 to 225 mg per day up to 8 weeks or up to 6 months, a final on-drug mean increase in SDBP of 0.3 mmHg was observed for venlafaxine treated patients compared with a mean decrease of 0.9 and 0.8 mmHg, respectively, 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 venlafaxine 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 venlafaxine 75 mg.

In pre-marketing depression studies, 0.7% (5/705) of the venlafaxine 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 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 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 mmHg, SDBP up to 8 weeks; 8 to 28 mmHg 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 3 months in placebo-controlled clinical trials.

Treatment with venlafaxine 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). Venlafaxine 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-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 150 to 225 mg group; however the total cholesterol value was only slightly increased (0.01 mmol/L) for the venlafaxine 75 mg group.

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

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

Myocardial infarction and unstable heart disease

Venlafaxine has not been evaluated in patients with a recent history of myocardial infarction or unstable heart disease. Therefore it should be used with caution in these patients.

Patients with these diagnoses were systematically excluded from any clinical studies during the product's trials.

Evaluation of the electrocardiograms for 769 patients who received immediate release venlafaxine 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 venlafaxine 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 treated patients in depression studies was increased relative to that for placebo-treated patients (increase of 4.7 msec for venlafaxine and decrease of 1.9 msec for placebo). The mean change from baseline QTc for venlafaxine 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 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 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 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 treated patients in both the GAD and depression studies was significantly higher than for placebo (a mean increase of 3-4 beats per minute for venlafaxine 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 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 75 mg (2 beats per minute) and venlafaxine 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/TdP

Cases of QTc prolongation, torsades 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 including congenital long QT syndrome, age >65 years, female sex, structural heart disease/LV dysfunction, medical conditions such as renal or hepatic disease, use of medicines that inhibit the metabolism of venlafaxine, and the concomitant use of other QTc prolonging medicines (see section 4.5). Hypokalaemia and hypomagnesaemia should be corrected prior to treatment.

In high risk patients (e.g. congenital long QT syndrome or multiple risk factors), an ECG should be performed prior to starting treatment, at steady state, after dose increases or after starting any potentially interacting medicine. Electrolytes should be monitored periodically and any abnormalities should be corrected prior to starting venlafaxine. An ECG should be performed in all patients experiencing symptoms that could be indicative of an arrhythmia (e.g. dizziness, palpitations, syncope or new onset seizures).

Consideration should be given to stopping venlafaxine treatment or reducing the dose if the QTc interval is >500 ms or increases by >60 ms.

Discontinuation effects of venlafaxine

Discontinuation effects are well known to occur with antidepressants, and sometimes these effects can be protracted and severe (see section 4.8). Suicide/suicidal thoughts and aggression have been observed in patients during changes in venlafaxine dosing regimen, including during discontinuation (see section 4.4). 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 venlafaxine be tapered gradually and individually and the patients be closely 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 sections 4.2 and 4.8). In some patients, discontinuation could take months or longer.

Sexual dysfunction

Selective serotonin reuptake inhibitors (SSRIs)/serotonin norepinephrine reuptake inhibitors (SNRIs) may cause symptoms of sexual dysfunction (see section 4.8). There have been reports of long-lasting sexual dysfunction where the symptoms have continued despite discontinuation of SSRIs/SNRI.

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

Seizures

Seizures may occur with venlafaxine therapy. Venlafaxine, as with all antidepressants, should be introduced with care, in patients with a history of seizure disorders. Venlafaxine should be discontinued in any patient who develops seizures.

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. Prior to initiating treatment with an antidepressant, patients should be adequately screened to determine if they are at risk for bipolar disorder. It should be noted that venlafaxine is not approved for use in treating bipolar depression.

Aggression

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

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 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, 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 5.1).

Electroconvulsive therapy

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

Paediatric use

Safety and effectiveness in individuals younger than 18 years of age have not been established. Venlafaxine should not be used in such patients.

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.

Pooled analyses of 24 short-term (4 to 16 weeks), placebo-controlled trials of nine antidepressant medicines (SSRIs and others) in 4,400 children and adolescents with major depression (16 trials), obsessive compulsive disorder (4 trials) and other psychiatric disorders (4 trials) have revealed a greater risk of adverse events representing suicidal behaviour or thinking during the first few months of treatment in those receiving antidepressants. The average risk of such events in patients treated with an antidepressant was 4% compared with 2% of patients given placebo. There was considerable variation in risk among the antidepressants, but there was a tendency towards an increase for almost all antidepressants studied. The risk of suicidality was most consistently observed in the major depression trials, but there were signals of risk arising from trials in other psychiatric indications (obsessive compulsive disorder and social anxiety disorder) as well. No suicides occurred in these trials. It is unknown whether the suicidality risk in children and adolescent patients extends to use beyond several months. The 9 antidepressant medicines in the pooled analyses included 5 SSRIs (citalopram, fluoxetine, fluvoxamine, paroxetine, sertraline) and 4 non-SSRIs (bupropion, mirtazapine, nefazodone, venlafaxine) (see section 4.4 and 4.8).

Use in the elderly

No overall differences in effectiveness or safety were observed between elderly (aged 65 years and older) and younger patients. Venlafaxine 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.

Use in renal impairment

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.

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

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

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 Interaction with other medicines and other forms of interaction

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 venlafaxine in patients taking monoamine oxidase inhibitors (MAOIs) or reversible MAOIs (e.g. moclobemide, linezolid and intravenous methylene blue) is contraindicated (see section 4.3).

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 take venlafaxine 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 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, and 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 sections 4.3 and 4.4).

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).

As with other antidepressants, co-administration of venlafaxine 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 in combination with opiates.

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

Medicines that prolong QTc interval

The risk of QTc prolongation and/or ventricular arrhythmias (e.g. torsades de pointes) is increased with concomitant use of other medicines which prolong the QTc interval (e.g. some antipsychotics and antibiotics). Please check the data sheets of other medicines administered for information on their effect on the QTc interval (see section 4.4).

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.

Alcohol

Patients should be advised not to use alcohol, considering its CNS-effects and potential of clinical worsening of psychiatric conditions, and the potential for adverse interaction with venlafaxine including CNS depressant effects.

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 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 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 has no effect on the pharmacokinetics of lithium (see also 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 healthy volunteers in a pharmacokinetic interaction study for both drugs resulted in an increase in the plasma concentrations of metoprolol by approximately 30-40% without altering the plasma concentrations of its active metabolite, α-hydroxymetoprolol. Venlafaxine appeared to reduce the blood pressure lowering effect of metoprolol in this study of healthy volunteers. The clinical relevance of this finding in hypertensive patients is unknown. Metoprolol did not alter the pharmacokinetic profile of venlafaxine or its active metabolite, ODV. Caution should be exercised with co-administration of venlafaxine and metoprolol.

Risperidone

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

Drug 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 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

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

CYP3A4 inhibitors

Concomitant use of CYP3A4 inhibitors (such as erythromycin, fluconazole, ketoconazole and grapefruit juice) and venlafaxine may increase levels of venlafaxine and ODV. Therefore caution is advised if a patient's therapy includes a CYP3A4 inhibitor and venlafaxine concomitantly.

In vitro 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 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.

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

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/m^2 basis.

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

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 fetal size and pup weight at birth with 60 mg/kg/day may be correlated with maternal toxicity.

Pregnancy

The safety of venlafaxine in human pregnancy has not been established. There are no adequate and well-controlled studies in pregnant women. Venlafaxine must be administered to pregnant women only 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, or SSRIs, 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, 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.

Some epidemiological studies have suggested an increased risk of congenital abnormalities associated with use of SSRIs and SNRIs in pregnancy. The relevance for venlafaxine treatment remains unknown.

Some epidemiological data suggests that the use of SSRIs and SNRIs in pregnancy may be associated with a small but statistically significant increase in pre-term delivery.

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 discontinue antidepressant medication during pregnancy were more likely to experience a relapse of major depression than women who continued antidepressant medication.

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

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 ODV ingested by breast fed infants can be as high as 9.2% of maternal intake. Therefore, the use of venlafaxine 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 judgement, 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 Undesirable effects

Adverse effects are listed in the following table in Council for International Organizations of Medical Sciences (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.

System organ class	Adverse effects
Blood and lymphatic system disorders	

Rare	Thrombocytopenia*, agranulocytosis*, aplastic anaemia*, pancytopenia*, neutropenia*
Immune system disorders	
Rare	Anaphylactic reaction*
Endocrine disorders	
Rare	Inappropriate antidiuretic hormone secretion*
Very rare	Blood prolactin increased*
Metabolism and nutrition disorders	
Common	Decreased appetite
Uncommon	Hyponatraemia*
Psychiatric disorders	
Very common	Insomnia
Common	Confusional state*, depersonalisation*, abnormal dreams, nervousness, libido decreased, agitation*, anorgasmia
Uncommon	Mania, hypomania, hallucination, abnormal orgasm, bruxism*, apathy
Rare	Delirium*
Not known	Aggression
Nervous system disorders	
Very common	Headache*, dizziness, sedation
Common	Akathisia*, tremor, paraesthesia, dysgeusia
Uncommon	Syncope, myoclonus, balance disorder*, coordination abnormal*, dyskinesia*
Rare	Neuroleptic malignant syndrome*, serotonergic syndrome*, convulsion, dystonia*
Very rare	Tardive dyskinesia*
Eye disorders	
Common	Visual impairment, accommodation disorder, mydriasis
Rare	Angle closure glaucoma*
Ear and labyrinth disorders	
Common	Tinnitus*
Cardiac disorders	
Common	Tachycardia, palpitations*
Rare	Torsades de pointes*, ventricular tachycardia*, ventricular fibrillation*, electrocardiogram QT prolonged*, stress cardiomyopathy (takotsubo cardiomyopathy)*
Vascular disorders	
Common	Hypertension, hot flush.
Uncommon	Orthostatic hypotension, hypotension*.
Respiratory, thoracic and mediastinal disorders	
Common	Dyspnoea*, yawning

Rare	Interstitial lung disease*, pulmonary eosinophilia*
Gastrointestinal disorders	
Very common	Nausea, dry mouth, constipation
Common	Diarrhoea*, vomiting
Uncommon	Gastrointestinal haemorrhage*
Rare	Pancreatitis*
Hepatobiliary disorders	
Uncommon	Liver function test abnormal*
Rare	Hepatitis*
Skin and subcutaneous tissue disorders	
Very Common	Hyperhidrosis*
Common	Rash, pruritus*, night sweats*
Uncommon	Angioedema*, urticaria*, alopecia*, ecchymosis, photosensitivity reaction
Rare	Stevens-Johnson syndrome*, toxic epidermal necrolysis*, erythema multiforme*
Musculoskeletal and connective tissue disorders	
Common	Hypertonia
Rare	Rhabdomyolysis*
Renal and urinary disorders	
Common	Urinary hesitation, urinary retention, pollakiuria*
Uncommon	Urinary incontinence*, proteinuria
Reproductive system and breast disorders	
Common	Erectile dysfunction, ejaculation disorder
Uncommon	Metrorrhagia*, menorrhagia*
General disorders and administration site conditions	
Common	Fatigue, asthenia, chills*
Uncommon	Mucosal haemorrhage*
Investigations	
Common	Blood cholesterol increased, weight decreased, weight increased
Rare	Bleeding time prolonged*
Injury, poisoning and procedural complications	
Uncommon	Bone fracture

* Identified post-marketing

Discontinuation effects

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). 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, paraesthaesia, dizziness, convulsion, vertigo, headache, flu-like symptoms, tinnitus, impaired coordination and balance, tremor, sweating, dry mouth,

anorexia, diarrhoea, nausea, vomiting, visual impairment, and hypertension. In pre-marketing studies, the majority of discontinuation reactions were mild and resolved without treatment (see sections 4.2 and 4.4). While these events are generally self-limiting, 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 venlafaxine 75 mg and venlafaxine 150-225 mg, respectively.

Paediatric patients (see section 4.4)

In general, the adverse reaction profile of venlafaxine in placebo-controlled clinical trials in children and adolescents (aged 6 to 17) was similar to that seen in adults.

As with adults, decreased appetite, weight loss, increased blood pressure and increased serum cholesterol were observed. Particularly, 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.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://pophealth.my.site.com/carmreportnz/s/.

4.9 Overdose

In managing overdosage, consider the possibility of multiple medication involvement (see section 4.5).

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 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, including cases with fatal outcome. The most commonly reported events in overdose include tachycardia, changes in level of consciousness (ranging from somnolence to coma), mydriasis, seizures, and vomiting. Other events reported include electrocardiogram changes (e.g. prolongation of QTc 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 studies report that venlafaxine overdosage may be associated with an increased risk of fatal outcomes compared to that observed with SSRI antidepressant products, but lower than that for tricyclic antidepressants. Epidemiological studies have shown that venlafaxine-treated patients have a higher burden of suicide risk factors than SSRI patients. The extent to which

the finding of an increased risk of fatal outcomes can be attributed to the toxicity of venlafaxine in overdosage as opposed to some characteristics of venlafaxine-treated patients is not clear.

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 dialysable because haemodialysis clearance of both compounds is low.

Severe poisoning may require complex emergency treatment and monitoring. Therefore, in event of suspected overdose involving venlafaxine, prompt contact with National Poisons Centre is recommended.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764 766).

5. Pharmacological Properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other antidepressants, ATC code: N06AX16

Enlafax XR capsules are an extended-release formulation, which release the active constituent, venlafaxine hydrochloride, from a tablet/tablets within the capsule. 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 (CNS). Preclinical studies have shown that venlafaxine and its major metabolite, O-desmethylvenlafaxine, 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 re-uptake and receptor binding. Studies in animals show that tricyclic antidepressants may reduce β-adrenergic receptor responsiveness following chronic administration. In contrast, venlafaxine and ODV reduce β-adrenergic responsiveness after both acute (single dose) and chronic administration.

Venlafaxine has no significant affinity for rat brain muscarinic, H_1-histaminergic or α_1-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 CNS stimulant activity in rodents. In primate drug discrimination studies, venlafaxine showed no significant stimulant or depressant abuse liability.

Clinical trials

Major depression

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

Generalised anxiety disorder

Five placebo-controlled trials were conducted to evaluate the efficacy of venlafaxine in the treatment of anxiety. Two trials were eight-week studies, utilising venlafaxine doses of 75 mg, 150 mg and 225 mg/day and of 75 mg and 150 mg/day. In one of these, buspirone was found not to be significantly different to placebo or to venlafaxine. However, venlafaxine was found to be superior to placebo. Two other trials were the first eight weeks of two long term studies, utilising venlafaxine doses of 75 mg-225 mg/day and of 37.5 mg, 75 mg and 150 mg/day.

Four studies demonstrated superiority of venlafaxine over placebo on at least five of the following efficacy scales: HAM-A total score, the HAM-A psychic anxiety factor, the Hospital Anxiety and Depression (HAD) anxiety subscale, and the CGI severity of illness scale, as well as the HAM-A anxious mood and tension item. Two of these four studies continued for up to six months. These two studies, which utilised venlafaxine doses of 75 mg–225 mg/day and 37.5 mg, 75 mg and 150 mg/day demonstrated superiority of venlafaxine over placebo on the HAM-A total score, HAM-A psychic anxiety factor, the HAD anxiety factor, and the CGI severity of illness scale, as well as the HAM-A anxious mood item.

The fifth trial was a short-term (8 week) comparison of the efficacy of 2 fixed doses of venlafaxine (75 mg and 150 mg) with placebo and diazepam followed by a comparison of the long-term (6-month) efficacy of venlafaxine and placebo in the prevention of relapse. The most important results were the primary efficacy variables at week 8 using an LOCF analysis. These demonstrated no significant differences between either venlafaxine and placebo, or diazepam and placebo for any of the primary efficacy variables. In view of this failure to demonstrate any effectiveness of either venlafaxine or diazepam over placebo, the long-term outcomes of this study are not of clinical or theoretical value. In conclusion, this study showed no anxiolytic effect of either diazepam or placebo in the short-term (8 week phase).

Baseline and final mean HAM-A total and CGI severity scores for placebo controlled GAD studies

Study Number	---------- HAM-A Total----------			---------- CGI Severity ---------		
Treatment	n	Baseline	Final	n	Baseline	Final
210 (8-week study)						
Placebo	96	24.1	14.7	96	4.4	3.2
Venlafaxine (mg)						
75	86	24.7	13.5	86	4.5	3.0
150	81	24.5	12.3	81	4.5	2.9
225	86	23.6	11.9	86	4.4	2.8
214 (8-week study)						
Placebo	98	23.7	15.4	98	4.3	3.3
Venlafaxine (mg)						
75	87	23.7	13.0	87	4.2	2.8
150	87	23.0	13.6	87	4.2	3.0
Buspirone	93	23.8	14.3	93	4.2	3.2

218 (6-month study)						
Placebo	123	24.9	16.2	123	4.4	3.5
Venlafaxine (mg)						
75–225	115	25.0	11.6	115	4.4	2.7
377 (8-week period)						
Placebo	96	27.7	15.1	89	4.8	3.2
Venlafaxine (mg)						
75	181	28.0	12.8	160	4.9	2.9
150	169	28.0	14.2	146	4.9	3.1
Diazepam	89	28.4	13.5	79	4.8	2.9
378 (6-month study)						
Placebo	129	26.7	15.6	129	4.6	3.2
Venlafaxine (mg)						
37.5	138	26.6	12.6	138	4.4	2.6
75	130	26.3	10.4	129	4.4	2.4
150	131	26.3	9.5	131	4.6	2.2

Depression relapse/recurrence

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

Social anxiety disorder

The efficacy of venlafaxine 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 the Diagnostic and Statistical Manual (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 the table below. In these five trials, venlafaxine was significantly more effective than placebo on change from baseline to endpoint on the LSAS total score.

[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.

Summary of results for primary efficacy variable in ITT patients at final on-therapy visit: 12 week and 6 month

Variable Study Number Treatment Group	No. of Patients	Raw baseline Score	Adjusted Final On-therapy Score	Adjusted Mean Change from Baseline	p-value vs. Placebo
Short-term (12 week) Studies					
LSAS					
Study 1					
Placebo	138	86.7	69.0	-19.9	
Venlafaxine[a]	133	91.1	57.8	-31.0	<0.001
Study 2[b]					
Placebo	135	87.4	66.9	-22.1	
Venlafaxine[a]	126	90.8	56.3	-32.8	0.003
Study 3					
Placebo	132	83.6	64.5	-19.1	
Venlafaxine[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	133	86.2	51.5	-35.0	<0.001
Paroxetine	136	87.2	47.3	-39.2	<0.001
Long-term (6 month) Study					
LSAS					
Study 5					
Placebo	126	89.3	65.6	-23.5	
Venlafaxine (total)[d]	238	89.0	51.2	-37.8	<0.001
Venlafaxine 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 was 75-225 mg/day; b: Data shown are for ITT population; c: Flexible dose range for paroxetine was 20-50 mg/day; d: Primary treatment group. Abbreviations: ITT = intent to treat; LSAS = Liebowitz Social Anxiety Scale.

Panic disorder

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

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

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

In a longer-term study, adult outpatients meeting DSM-IV criteria for panic disorder who had responded during a 12-week open phase with venlafaxine (75 to 225 mg/day) were randomly assigned to continue the same venlafaxine dose (75, 150, or 225 mg) or switch to placebo for observation for relapse during a 6-month double-blind phase. Response during the open phase was defined as $\geq$1 full-symptom panic attack per week during the last 2 weeks of the open phase and a

CGI Improvement score of 1 (very much improved) or 2 (much improved). Relapse during the double-blind phase was defined as having 2 or more full symptom panic attacks per week for 2 consecutive weeks or having discontinued due to loss of effectiveness. Patients receiving continued venlafaxine treatment experienced significantly lower relapse rates over the subsequent 6 months compared with those receiving placebo.

Cardiac electrophysiology

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

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 450 mg/day. Mean ± SD steady state plasma clearance of venlafaxine and ODV is 1.3 ± 0.6 and 0.4 ± 0.2 L/h/kg, respectively; apparent elimination half-life is 5 ± 2 and 11 ± 2 hours, respectively; and apparent (steady-state) volume of distribution is 7.5 ± 3.7 and 5.7 ± 1.8 L/kg, respectively.

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 pre-systemic metabolism of venlafaxine (which primarily forms the active metabolite, ODV) reduces the absolute bioavailability of venlafaxine to 42% ± 15%.

After administration of venlafaxine (150 mg q24 hours), the peak plasma concentrations (C_{max}) of venlafaxine (150 ng/mL) and ODV (260 ng/mL) were attained within 6.0 ± 1.5 and 8.8 ± 2.2 hours, respectively. The rate of absorption of venlafaxine from the venlafaxine capsule is slower than its rate of elimination. Therefore, the apparent elimination half-life of venlafaxine following administration of 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 venlafaxine capsule. Therefore, the 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 2215 ng/mL, and the degree of ODV binding to human plasma proteins is 30% ± 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 pre-systemic 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 (see section 4.5).

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.

Enlafax XR capsules contain inert matrixes, which release the active substance slowly into the digestive tract. The insoluble portion of matrix is eliminated and may be seen in faeces.

Food-drug interactions

Administration of Enlafax XR with food has no effect on the absorption of venlafaxine or on the subsequent formation of ODV.

Special populations

Age and gender

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.

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.

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.

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). Fetotoxicity 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. Fetal survival and morphologic development were not affected. In another teratology study, rabbits were given venlafaxine dosages up to 90 mg/kg/day. Fetotoxicity evidenced by

resorption and fetal 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

Enlafax XR modified release capsules also contain the following excipients:

- Hypromellose
- Eudragit RS 100
- Eudragit E12.5
- sodium lauryl sulfate
- magnesium stearate
- titanium dioxide (E171)
- gelatin
- black ink.

The 75 mg capsule shell also contains iron oxide red (E172).
The 150 mg capsule shell also contains eythrosine (E172) and indigo carmine (E132).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store at or below 25°C.

6.5 Nature and contents of container

PVC/PE/PVDC/Al calendar blister packs. Pack sizes of 28 or 84 modified release capsules.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Not applicable.

7. Medicines Schedule

Prescription Medicine

8. Sponsor Details

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9. Date of First Approval

12 March 2009

10. Date of Revision of the Text

11 June 2024

Section	Summary of updates
2	Editorial update to allergen declaration
4.8	Updated ADR reporting website
4.9	Removed information on doses of concern
6.1	Move allergen information to section 2