AUSTRALIAN PRODUCT INFORMATION

EFEXOR®-XR

(venlafaxine hydrochloride) modified release capsule

1 NAME OF THE MEDICINE

Venlafaxine hydrochloride

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each EFEXOR-XR modified release capsule contains 37.5 mg, 75 mg or 150 mg of venlafaxine (as hydrochloride) as the active ingredient.

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

3 PHARMACEUTICAL FORM

Modified release capsules.

Venlafaxine hydrochloride is released from spheroids within the capsule. Drug release is controlled by diffusion through the coating membrane on the spheroids and is not pH dependent.

EFEXOR-XR 37.5 mg: hard gelatin capsule, grey cap and peach body with "W" on the cap and "37.5" on the body in red ink, containing white to off-white spheroids of about 1 mm in diameter.

EFEXOR-XR 75 mg: hard gelatin capsule, peach cap and body with "W" on the cap and "75" on the body in red ink, containing white to off white spheroids of about 1 mm diameter.

EFEXOR-XR 150 mg: hard gelatin capsule, dark orange cap and body with "W" on the cap and "150" on the body in white ink, containing white to off white spheroids of about 1 mm diameter.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

EFEXOR-XR is indicated for the treatment of:

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

4.2 DOSE AND METHOD OF ADMINISTRATION

Dosage

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 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 EFEXOR-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 EFEXOR-XR be taken with food, at approximately the same time each day. Each capsule must be swallowed whole with fluid. Do not divide, crush, chew, or dissolve. EFEXOR-XR should be administered once daily.

Panic Disorder

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

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

Maintenance/Continuation/Extended Treatment

The physician should periodically re-evaluate the usefulness of long-term EFEXOR-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 EFEXOR-XR treatment should be periodically assessed.

It is generally agreed that acute episodes of panic disorder require several months or longer of sustained pharmacological therapy beyond response to the acute episode. Longer-term efficacy was demonstrated in one study (Study 5) in which patients responding during 12 weeks of acute treatment with EFEXOR-XR were assigned randomly to placebo or to the same dose of EFEXOR-XR (75, 150, or 225 mg/day) during 6 months of maintenance treatment as they had received during the acute stabilisation phase (See Section 5.1 PHARMACODYNAMIC PROPERTIES - Clinical Trials - Panic Disorder).

Discontinuing EFEXOR-XR

When EFEXOR-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 EFEXOR-XR, tapering was achieved by reducing the daily dose by 75 mg at 1 week intervals. To facilitate tapering below 75 mg of EFEXOR-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 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 EFEXOR-XR. In some patients, discontinuation may need to occur very gradually over periods of months or longer.

Method of Administration

Oral use.

Dosage Adjustment

Renal Impairment

Patients with renal impairment should receive lower doses of EFEXOR-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 ODV in humans are low. The total daily dose of venlafaxine should be reduced by 50% in haemodialysis patients.

Hepatic Impairment

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.

Use 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.

4.3 CONTRAINDICATIONS

Hypersensitivity to venlafaxine or any excipients in the formulation.

Monoamine Oxidase Inhibitors (MAOIs)

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

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

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 4.9 OVERDOSE).

Clinical Worsening and Suicide Risk

Patients with major depression, both adult and paediatric, may experience worsening of their depression and/or the emergence of suicidal ideation and behaviour (suicidality) or unusual changes in behaviour, whether or not they are taking antidepressant medications, and this risk may persist until significant remission occurs. Suicide is a known risk of depression and certain other psychiatric disorders, and these disorders themselves are the strongest predictors of suicide. Antidepressants may have a role in inducing worsening of depression and the emergence of suicidality in certain patients during the early phases of treatment. As improvement may not occur during the first few weeks or more of treatment, patients should be monitored appropriately and

observed closely for clinical worsening and suicidality, especially at the beginning of a course of treatment or at the time of dose changes, either increases or decreases.

Pooled analyses of short-term placebo-controlled trials of antidepressant medicines (Selective Serotonin Reuptake Inhibitors [SSRIs] and others) showed that these medicines increase the risk of suicidality in children, adolescents, and young adults (ages 18-24 years) with major depression and other psychiatric disorders. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults older than 24 years of age; there was a reduction in the risk of suicidality with antidepressants compared to placebo in adults aged 65 years and older.

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 Discontinuation Effects below).

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 EFEXOR-XR should be written for the smallest quantity of capsules consistent with good patient management in order to reduce the possibility of overdosage. This is particularly so at the times of treatment initiation or dosage change. Events reported in overdose include electrocardiogram changes (QRS prolongation, QT prolongation), cardiac arrhythmias (ventricular fibrillation; ventricular tachycardia, including 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 NMS-like reactions 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 CONTRAINDICATIONS).

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 (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.

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

Treatment with EFEXOR-XR 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 EFEXOR-XR in pre-marketing depression studies, 3% (19/705) experienced sustained hypertension [defined as treatment-emergent supine diastolic blood pressure (SDBP) ≥ 90 mm Hg and ≥ 10 mm Hg above baseline for 3 consecutive on-therapy visits]. Among patients treated with 37.5 to 225 mg per day of EFEXOR-XR in pre-marketing GAD studies, 0.5% (5/1011) experienced sustained hypertension. Experience with the immediate-release venlafaxine showed that sustained hypertension was dose-related, increasing from 3 to 7% at 100 to 300 mg per day to 13% at doses above

300 mg per day. An insufficient number of patients received mean doses of EFEXOR-XR 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 EFEXOR-XR 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 EFEXOR-XR treated patients compared with a mean decrease of 0.2 mm Hg for placebo-treated patients. In placebo-controlled pre-marketing GAD studies with EFEXOR-XR 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 mm Hg was observed for EFEXOR-XR treated patients compared with a mean decrease of 0.9 and 0.8 mm Hg, 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 EFEXOR-XR 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 EFEXOR-XR 75 mg.

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

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

Sustained increases of SDBP could have adverse consequences. Therefore it is recommended that patients receiving EFEXOR-XR 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 EFEXOR immediate release tablet-treated patients and 0.0% of placebo-treated patients for at least 3 months in placebo-controlled clinical trials.

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

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

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

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

Hyponatraemia

Cases of hyponatraemia, and/or the Syndrome of Inappropriate Antidiuretic Hormone secretion (SIADH) may occur with venlafaxine, usually in volume-depleted or dehydrated patients. Elderly patients, patients taking diuretics, and patients who are otherwise volume depleted, may be at greater risk for this event.

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

Use in Patients with Pre-existing Heart Disease

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

Venlafaxine should be used with caution in patients with unstable heart disease (e.g. myocardial infarction; significant left ventricular dysfunction, ventricular arrhythmia). In these patients, assessment of the cardiovascular system (e.g. 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 EFEXOR 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 EFEXOR-XR or placebo in the depression GAD and Social Anxiety Disorder trials were analysed. The mean change from baseline in corrected QT interval (QTc) for EFEXOR-XR treated patients in depression studies was increased relative to that for placebo-treated patients (increase of 4.7 msec for EFEXOR-XR and decrease of 1.9 msec for placebo). The mean change from baseline QTc for EFEXOR-XR treated patients in the GAD studies did not differ significantly from placebo. The final on-therapy mean increase from baseline in QTc (3 msec) was significant for EFEXOR-XR treated patients in the Social Anxiety Disorder short-term studies. In the 6 month study, the final on-therapy mean increase from baseline in QTc with EFEXOR-XR 150 to 225 mg (3 msec) was significant, but the increase was not significantly different from the small mean increase (0.5 msec) with placebo. The value for EFEXOR-XR 75 mg was a 0.05 msec decrease.

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

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

QTc Prolongation/Torsade de Pointes (TdP)

Cases of QTc prolongation, torsade de pointes (TdP), ventricular tachycardia and sudden death have been reported during the postmarketing 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.

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

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

There is also a report of a withdrawal syndrome, confirmed by two challenges in a 32-year-old woman who had received venlafaxine 300 mg daily for 8 months. It is, therefore, recommended that the dosage of EFEXOR-XR 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 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 EFEXOR-XR and weight loss agents is not recommended. EFEXOR-XR is not indicated for weight loss alone or in combination with other products.

Seizures

Seizures have been reported with venlafaxine therapy and in overdose. EFEXOR-XR, as with all antidepressants, should be introduced with care, in patients with a history of seizure disorders. EFEXOR-XR 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 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 EFEXOR XR is not approved for use in treating bipolar depression.

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

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

Skin/Allergic Reactions

Patients should be advised to notify their 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.

Postpartum haemorrhage

SSRI/SNRIs may increase the risk of postpartum haemorrhage (see Section 4.6 FERTILITY, PREGNANCY AND LACTATION and 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)).

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 PHARMACODYNAMIC PROPERTIES).

Electroconvulsive Therapy

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

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.

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 the Elderly

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

EFEXOR-XR is not indicated for use in children and adolescents younger than 18 years of age as safety and effectiveness has not been demonstrated. Therefore, EFEXOR-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 Clinical Worsening and Suicide Risk above 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 EFEXOR-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 EFEXOR-XR in combination with a MAOI or reversible MAOIs, or within at least 14 days of discontinuing MAOI treatment. Allow at least 7 days after stopping EFEXOR-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, 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 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 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).

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

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

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

Drugs that Prolong 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).

Ethanol

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.

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 *CNS Active Drugs above*). 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 ($t_{½}$) was unchanged. The mechanism explaining this finding is unknown.

Risperidone

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

Indinavir

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

Cimetidine

At steady-state cimetidine has been shown to inhibit the first-pass metabolism of venlafaxine but had no apparent effect on the formation or elimination of ODV, which is present in much greater quantity in the systemic circulation. The overall pharmacological activity of venlafaxine plus ODV is expected to increase only slightly in most patients. No dosage adjustment seems necessary when EFEXOR-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 EFEXOR-XR is administered with cimetidine.

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 in the plasma concentrations of metoprolol by approximately 30-40% without altering the plasma concentrations of its active metabolite, α-hydroxymetoprolol. Metoprolol did not alter the pharmacokinetic profile of venlafaxine or its active metabolite, 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 EFEXOR-XR have regular monitoring of blood pressure (See Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE - Sustained Hypertension).

Antihypertensive and Hypoglycaemic Agents

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

Drugs Metabolised by Cytochrome P450 Isoenzymes

In vitro studies indicate that venlafaxine is a relatively weak inhibitor of CYP2D6 and that venlafaxine does not inhibit CYP1A2, CYP2C9 or CYP3A4. Some of these findings have been confirmed with drug interaction studies between venlafaxine and imipramine (metabolised by CYP2D6) and diazepam (metabolised by CYP2C19). Therefore, EFEXOR-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

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 when combining venlafaxine with a CYP3A4 inhibitor.

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 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).

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/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.

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 that 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.

Use in Pregnancy – Category B2

The safety of venlafaxine in human pregnancy has not been established. There are no adequate and well-controlled studies in pregnant women. Venlafaxine must 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 (Serotonin and Noradrenaline Reuptake Inhibitors), 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.

Epidemiological data have suggested that the use of SSRIs in pregnancy, particularly in late pregnancy, may increase the risk of persistent pulmonary hypertension in the new born (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. Observational data indicate an increased risk (less than 2-fold) of postpartum haemorrhage following SSRI/SNRI exposure within the month prior to birth (see Sections 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE and 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)).

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 ODV ingested by breast fed infants can be as high as 9.2% of maternal intake. Therefore, the use of EFEXOR-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 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 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Clinical Trials

The information included in the adverse events clinical trials subsection are those that were observed in short-term, placebo-controlled studies with EFEXOR-XR and has been based on data from a pool of three 8- and 12-week controlled clinical trials in Major Depressive Disorder (dose range of 75 – 225 mg/day), on data up to 8 weeks from a pool of five controlled clinical trials in Generalised Anxiety Disorder with EFEXOR-XR (dose range 37.5 – 225 mg/day), on data up to 12 weeks from a pool of five controlled clinical trials in Social Anxiety Disorder (dose range of 75 – 225 mg/day), and on data up to 12 weeks from a pool of four controlled clinical trials in Panic Disorder (dose range of 75 – 225 mg/day). (The adverse events occurring at an incidence ≥ 2% among EFEXOR-XR treated patients or at an incidence greater than the placebo treated patients are provided in the table below). The table shows the percentage of patients 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.

Adverse Event Incidence in Clinical Trials								
	Major Depressive Disorder[1,5]		**Generalised Anxiety Disorder[2]**		**Social Anxiety Disorder[3]**		**Panic Disorder[4]**	
Body System Preferred term	**Efexor-XR n=357**	**Placebo n=285**	**Efexor-XR n=1381**	**Placebo n=555**	**Efexor-XR n=819**	**Placebo n=695**	**Efexor-XR n=1001**	**Placebo n=662**
Body as a whole								
Headache	-	-	-	-	38%	34%	-	-
Asthenia	8%	7%	12%	8%	19%	9%	10%	8%
Abdominal Pain	-	-	-	-	6%	4%	-	-
Accidental Injury	-	-	-	-	4%	3%	-	-
Cardiovascular								
Hypertension	4%	1%	-	-	5%	3%	4%	3%
Vasodilatation[6]	4%	2%	4%	2%	3%	2%	3%	2%
Palpitation	-	-	-	-	3%	1%	-	-
Digestive								
Nausea	31%	12%	35%	12%	31%	9%	21%	14%
Constipation	8%	5%	10%	4%	9%	3%	9%	3%
Anorexia[7]	8%	4%	8%	2%	17%	2%	8%	3%
Vomiting	4%	2%	5%	3%	3%	2%	-	-
Diarrhoea	-	-	-	-	8%	6%	-	-
Dyspepsia	-	-	-	-	7%	6%	-	-
Flatulance	4%	3%	-	-	-	-	-	-
Metabolic/Nutritional								
Weight loss	3%	0%	-	-	2%	<1%	-	-

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

1. Incidence, rounded to the nearest %, for events reported by at least 2% of patients treated with Efexor XR, 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 EFEXOR-XR reporting rate was less than or equal to the placebo rate are not included. These events are: abdominal pain, accidental injury, anxiety, back pain, diarrhoea, dysmenorrhoea, dyspepsia, flu syndrome, headache, infection, myalgia, pain, palpitation, pharyngitis, rhinitis, tinnitus, and urinary frequency.
3. Adverse events for which the EFEXOR-XR reporting rate was less than or equal to the placebo rate are not included. These events are: arthralgia, back pain, dysmenorrhoea, flu syndrome, infection, pain, pharyngitis, rhinitis, and upper respiratory infection.
4. Adverse events for which the EFEXOR-XR reporting rate was less than or equal to the placebo rate are not included. These events are: abdominal pain, abnormal vision, accidental injury, anxiety, back pain, diarrhoea, dysmenorrhoea, dyspepsia, flu syndrome, headache, infection, nervousness, pain, paraesthesia, pharyngitis, rash, rhinitis, and vomiting.
5. <1% indicates an incidence greater than zero but less than 1%.
6. Mostly “hot flashes”.
7. Mostly “decreased appetite” and “loss of appetite”.
8. Mostly “vivid dreams”, “nightmare” and “increased dreaming”.
9. Mostly “blurred vision” and “difficulty focusing eyes”.
10. Males only – Mostly “delayed ejaculation”.
11. Incidence is based on number of male patients.
12. Females only – Mostly “delayed orgasm”, “abnormal orgasm” or “anorgasmia”.

The following table lists adverse reactions from combined analyses of the clinical studies for Major Depression, Generalised Anxiety Disorder, Social Anxiety Disorder, and Panic Disorder. The adverse reactions have been presented using the 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%.

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

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, 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 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 EFEXOR-XR 75 mg and EFEXOR-XR 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 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. Additionally, the following adverse reactions were observed: abdominal pain, agitation, dyspepsia, ecchymosis, epistaxis and myalgia. In paediatric clinical trials, there were increased reports of hostility and, especially in major depression, suicide-related adverse events such as suicidal ideation and self-harm.

Post-marketing Experience

The following table lists adverse reactions derived from post-marketing spontaneous reports in patients with major depression, generalised anxiety disorder, social anxiety disorder and panic disorder. Adverse reactions are shown in CIOMS frequency categories: 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.

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 (takotsubo 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

Not known: Postpartum haemorrhage*

* This event has been reported for the therapeutic class of SSRIs/SNRIs (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE and 4.6 FERTILITY, PREGNANCY AND LACTATION).

Injury, Poisoning and Procedural Complications

Uncommon: Bone fracture

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 (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 2.75 g of venlafaxine with naproxen and levothyroxine. 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, 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 torsade de pointes), bradycardia, hypotension, hypoglycaemia, vertigo, and death. Serotonin toxicity has been reported in association with venlafaxine overdose. Severe poisoning symptoms may occur in adults after intake of approximately 3 grams of venlafaxine.

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.

Management of Overdosage

Severe poisoning may require complex emergency treatment and monitoring. Therefore, in event of suspected overdose involving venlafaxine, prompt contact with Poisons Information Centre on 13 11 26 (Australia) is recommended.

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.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (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 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 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, H1-histaminergic or α1-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.

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).

Clinical Trials

Major Depression

Three double blind, placebo controlled trials, of up to 12 weeks duration, have examined the clinical efficacy of EFEXOR-XR in the treatment of major depression. One of these studies also incorporated an active comparator, paroxetine. These studies showed EFEXOR-XR 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 EFEXOR-XR in the treatment of anxiety. Two trials were eight-week studies, utilising EFEXOR-XR 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 EFEXOR-XR. However, EFEXOR-XR was found to be superior to placebo. Two other trials were the first eight-weeks of two long term studies, utilising EFEXOR-XR doses of 75 mg-225 mg/day and of 37.5 mg, 75 mg and 150 mg/day.

Four studies demonstrated superiority of EFEXOR-XR 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 EFEXOR-XR doses of 75 mg–225 mg/day and 37.5 mg, 75 mg and 150 mg/day demonstrated superiority of EFEXOR-XR 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 EFEXOR-XR (75 mg and 150 mg) with placebo and diazepam followed by a comparison of the long-term (6-month) efficacy of EFEXOR-XR 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 XR (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 XR (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 XR (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 XR (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 XR (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 EFEXOR-XR during an initial 8-week open-label treatment phase and were randomly assigned to continuation on EFEXOR-XR or placebo for 6 months demonstrated a significantly lower relapse rate for patients taking EFEXOR-XR compared with those on placebo.

In a second long-term study, outpatients with a history of recurrent depression who had responded to EFEXOR (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 EFEXOR or placebo for 12 months. Significantly fewer patients taking EFEXOR compared with those on placebo had a reappearance of depression.

Social Anxiety Disorder

The efficacy of EFEXOR-XR 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]

[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.

The results of these trials are presented in the table below. In these five trials, EFEXOR-XR was significantly more effective than placebo on change from baseline to endpoint on the LSAS total score.

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 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	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 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

Panic Disorder

The efficacy of EFEXOR-XR capsules as a treatment for panic disorder was established in two double-blind, 12-week, multicentre, placebo-controlled studies in adult outpatients meeting DSM-IV criteria for panic

disorder, with or without agoraphobia. Patients received fixed doses of 75 or 150 mg/day in one study (Study 1) and 75 or 225 mg/day in the other study (Study 2).

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

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

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

Primary Efficacy Variable PAAS: Percent of Patients Free of Full-Symptom Panic Attacks, Final On-Therapy (12 weeks in Studies 1 and 2, 10 weeks in Studies 3 and 4), ITT Population.

Study	Treatment	n	Number (%) Panic Free	p-value vs. Placebo[a]
1				
	Placebo	154	53 (34.4)	
	Venlafaxine XR 75 mg	157	85 (54.1)	<0.001
	Venlafaxine XR 150 mg	158	97 (61.4)	<0.001
	Paroxetine	160	96 (60.0)	<0.001
2				
	Placebo	157	73 (46.5)	
	Venlafaxine XR 75 mg	156	100 (64.1)	<0.001
	Venlafaxine XR 225 mg	160	112 (70.0)	<0.001
	Paroxetine	151	89 (58.9)	0.008
3				
	Placebo	155	63 (40.6)	
	Venlafaxine XR 75-225 mg	155	79 (51.0)	0.056
4[b]				
	Placebo	168	88 (52.4)	
	Venlafaxine XR 75-225 mg	160	88 (55.0)	0.622

Abbreviations: PAAS = Panic and Anticipatory Anxiety Scale; ITT= Intent to treat,
a: Chi-square p-values obtained from logistic regression model logit (response) = Treatment + center in studies 1, 3 and 4 and logistic regression model logit (response) = baseline + treatment + center in study 2.
b: excluding site 39127.

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

In a longer-term study (Study 5), adult outpatients meeting DSM-IV criteria for panic disorder who had responded during a 12-week open phase with EFEXOR-XR (75 to 225 mg/day) were randomly assigned to continue the same EFEXOR-XR dose (75, 150, or 225 mg) or switch to placebo for observation for relapse during a 6-month double-blind phase. Response during the open phase was defined as ≥1 full-symptom panic attack per week during the last 2 weeks of the open phase and a CGI Improvement score of 1 (very much

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

Survival Analysis for Relapse of Panic Disorder, ITT Patients, Double-Blind Period

Therapy Group	No. of Patients	Number of Relapse (%)	Cumulative Probability of Relapse	p-values[a]
Placebo	80	40 (50.0)	0.523	
Venlafaxine	89	20 (22.5)	0.239	<0.001

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

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

After administration of EFEXOR-XR (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 EFEXOR-XR capsule is slower than its rate of elimination. Therefore, the apparent elimination half-life of venlafaxine following administration of EFEXOR-XR (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 EFEXOR-XR capsule. Therefore, the EFEXOR-XR 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.

Food-Drug Interactions

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

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 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 EFEXOR-XR (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.

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

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 $t_{½}$ 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.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

- Microcrystalline cellulose,
- Ethylcellulose,
- Hypromellose.

The capsule shells contain,

- Gelatin,
- Iron oxide red,
- Iron oxide yellow,
- Titanium dioxide,
- Purified talc.

In addition, the 37.5 mg capsule shells also contain iron oxide black. The 37.5 mg and 75 mg capsule shells are branded with Opacode S-1-15094/S-1-15095 red ink. The 150 mg capsule shells are branded with TekPrint SB-0007P white ink.

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 30°C.

6.5 NATURE AND CONTENTS OF CONTAINER

EFEXOR-XR 37.5 mg, 75 mg and 150 mg are packed in PVC/Al blister packs in pack sizes of 7, 14 and 28.

Some pack sizes may not be marketed.

Australian Register of Therapeutic Goods (ARTG)

AUST R 99802 – EFEXOR-XR venlafaxine (as hydrochloride) 37.5 mg modified release capsule blister pack

AUST R 60858 – EFEXOR-XR venlafaxine (as hydrochloride) 75 mg modified release capsule blister pack

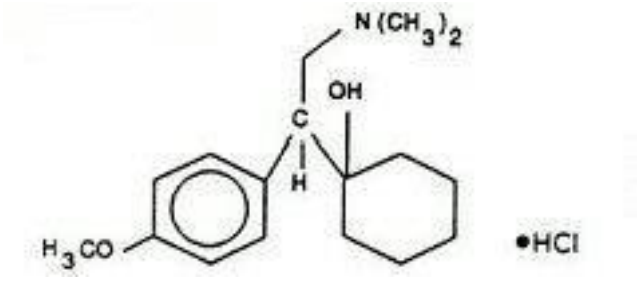
AUST R 60859 – EFEXOR-XR venlafaxine (as hydrochloride) 150 mg modified release capsule blister pack

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

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

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical Structure



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

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

Molecular weight: 313.87

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

CAS Number

99300-78-4

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 (Prescription Only Medicine)

8 SPONSOR

Viatris Pty Ltd

Level 1, 30 The Bond

30-34 Hickson Road

Millers Point NSW 2000

www.viatris.com.au

Phone: 1800 274 276

9 DATE OF FIRST APPROVAL

37.5 mg modified release capsule: 14/10/2004.

75 mg and 150 mg modified release capsule: 11/05/1998.

10 DATE OF REVISION

02/02/2026

Summary Table of Changes

Section Changed	Summary of New Information
All	Minor editorial changes

4.9	Addition of hypoglycaemia as a symptom of overdose.

EFEXOR® is a Viatris company trade mark

EFEXOR-XR_pi\Feb26/00 (CCDS 28-Apr-2023)