APPROVED PACKAGE INSERT

SCHEDULING STATUS: S5

PROPRIETARY NAME AND DOSAGE FORM:

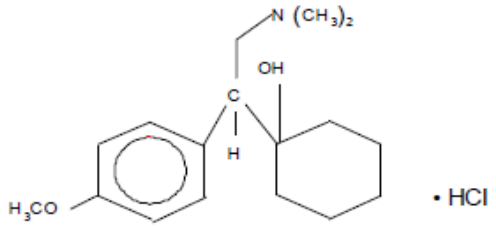
EFEXOR® XR 75 mg Capsules

EFEXOR® XR 150 mg Capsules

COMPOSITION:

Extended release capsules containing venlafaxine hydrochloride equivalent to either 75 mg or 150 mg venlafaxine.

It is designated (R/S)-1-[(2-dimethylamino)-1-(4-methoxyphenyl)ethyl] cyclohexanol hydrochloride or (±)-1-[α-[(dimethylamino)methyl]-p-methoxybenzyl] cyclohexanol hydrochloride. Its molecular weight is 313,87. The structural formula is shown below.



Molecular Formula

PHARMACOLOGICAL CLASSIFICATION:

A1.2 Psychoanaleptics (antidepressants)

PHARMACOLOGICAL ACTION:

Pharmacodynamic properties:

Studies have shown that venlafaxine and its major metabolite, O-desmethylvenlafaxine are inhibitors of serotonin and norepinephrine re-uptake and also weakly inhibit dopamine re-uptake.

Venlafaxine and O-desmethylvenlafaxine reduce beta-adrenergic responsiveness after both acute (single dose) and chronic administration. Venlafaxine and its major metabolite appear to be equipotent with respect to their overall action on neurotransmitter re-uptake and receptor binding.

Venlafaxine has virtually no affinity for rat brain muscarinic, histaminergic or adrenergic receptors *in vitro*. Venlafaxine does not possess monoamine oxidase (MAO) inhibitory activity.

Pharmacokinetic properties:

Absorption:

Venlafaxine is well absorbed and undergoes extensive first-pass metabolism.

After administration of EFEXOR XR, peak plasma concentrations of venlafaxine and O-desmethylvenlafaxine are attained within 6,0 +/- 1,5 and 8,8 +/- 2,2 hours, respectively.

The extent of absorption (AUC) is the same as the venlafaxine immediate release tablet.

Fluctuations in plasma concentrations are slightly lower following treatment with EFEXOR XR capsule than the immediate release tablet.

Metabolism:

Venlafaxine is extensively metabolised in the liver. O-desmethylvenlafaxine is the major active metabolite of venlafaxine.

Distribution:

The mean disposition half-life of venlafaxine and O-desmethylvenlafaxine is approximately 5 and 11 hours, respectively.

Plasma concentrations of venlafaxine and O-desmethylvenlafaxine generally correlated well with dose levels. Venlafaxine and O-desmethylvenlafaxine are less than 35 % bound to plasma proteins. (Venlafaxine and O-desmethylvenlafaxine are 27 % and 30 % bound to plasma proteins respectively).

Elimination:

Venlafaxine and its metabolites are excreted primarily through the kidneys. Approximately 87 % of a venlafaxine dose is recovered in the urine within 48 hours as either unchanged venlafaxine, unconjugated O-desmethylvenlafaxine, conjugated O-desmethylvenlafaxine, or other minor metabolites.

Elderly:

A 20 % reduction in clearance was noted for O-desmethylvenlafaxine in subjects over 60 years old: *The magnitude of the differences that were seen is insufficient to warrant dosage adjustment based solely on age.*

Clinical issues related to absorption/metabolism/elimination:

Effects of food:

Administration of venlafaxine with food has no effect on the extent of absorption of venlafaxine or on the subsequent formation of O-desmethylvenlafaxine.

Patients with renal impairment:

In patients with moderate to severe impairment of renal function, the total clearance of both venlafaxine and O-desmethylvenlafaxine was reduced, and t½ was prolonged. The reduction in total clearance was most pronounced in subjects with creatinine clearance less than 30 ml/min. Dosage adjustment is recommended for these patients (see DOSAGE AND DIRECTIONS FOR USE).

Patients with hepatic impairment:

In patients with compensated hepatic cirrhosis (mild to moderate hepatic impairment), the pharmacokinetic disposition of both venlafaxine and O-desmethylvenlafaxine was significantly altered. The reduction in both the metabolism of venlafaxine and elimination of O-desmethylvenlafaxine resulted in significantly higher plasma concentrations of both. Dosage adjustment is recommended in these patients (see DOSAGE AND DIRECTIONS FOR USE).

INDICATIONS:

EFEXOR XR is indicated for the treatment of depression, including depression with associated anxiety. EFEXOR XR is indicated for the prevention of relapses of an episode of depression in patients responding to an initial six to eight weeks of treatment. In patients responding to six months of relapse prevention, EFEXOR XR may be used to prevent recurrence. Safety and efficacy beyond one year have not been demonstrated. When EFEXOR XR is used for long-term it should periodically be re-evaluated for the usefulness of the product in the individual patient.

EFEXOR XR is indicated for the treatment of generalised anxiety disorder and for the treatment of Social Anxiety Disorder. The effectiveness of EFEXOR XR in the treatment of Social Anxiety Disorder for more than 12 weeks has not been demonstrated.

CONTRAINDICATIONS:

Hypersensitivity to venlafaxine or any excipients in the formulation.

Concomitant use in patients taking monoamine oxidase inhibitors (MAOIs).

EFEXOR XR must not be initiated for at least 14 days after discontinuation of treatment with a MAOI. EFEXOR XR must be discontinued for at least 7 days before starting treatment with any MAOI (see INTERACTIONS). Severe adverse reactions have been reported when EFEXOR therapy is initiated soon after discontinuation of an MAOI and when an MAOI is initiated soon after discontinuation of EFEXOR. These reactions have included tremor, myoclonus, diaphoresis, nausea, vomiting, flushing, dizziness, hyperthermia with features resembling neuroleptic malignant syndrome, seizures and death (see INTERACTIONS).

Children under 18 years (see WARNINGS AND SPECIAL PRECAUTIONS and SIDE EFFECTS).

Pregnancy and lactation (see PREGNANCY AND LACTATION).

WARNINGS AND SPECIAL PRECAUTIONS:

All patients treated with EFEXOR XR should be monitored appropriately and observed closely for clinical worsening and suicidality. Patients, their families, and their caregivers should be encouraged to be alert to the emergence of anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restless), 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. The risk of suicide attempt must be considered especially in depressed patients, and the smallest quantity of medicine, consistent with good patient management, should be provided to reduce the risk of overdose. Risk assessment for suicide should be performed regularly.

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 (SSRIs and others) showed that these medicines increase the risk of suicidality in children, adolescents, and young adults (aged 18 – 24 years) with major depression and other psychiatric disorders.

Serotonin syndrome, a potentially life threatening condition, may occur with EFEXOR XR treatment, particularly with concomitant use of other agents that may affect the serotonergic neurotransmitter systems.

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

Patients with major depressive disorder may experience worsening of their depression and/or emergence of suicidal ideation and behaviour, whether or not they are taking antidepressant medicine. This risk may persist until significant remission occurs. A causal role, however, for antidepressant medicines in inducing such behaviour has not been established. Patients being treated with EFEXOR XR should nevertheless, be observed closely for clinical worsening and suicidality, especially at the beginning of a course of therapy, or at any time of dose changes, either increases or decreases.

Because of the possibility of co-morbidity between major depressive disorder and other psychiatric and non-psychiatric disorders, the same precautions observed when treating patients with major depressive disorder should be observed when treating patients with other psychiatric and non-psychiatric disorders.

The following symptoms have been reported in patients being treated with antidepressants for major depressive disorder as well as for other indications, both psychiatric and non-psychiatric: anxiety, agitation, panic attacks, insomnia, irritability, hostility (aggressiveness, impulsivity, akathisia, hypomania and mania). Although a causal link between the emergence of suicidal impulses has not been established, consideration should be given to changing the therapeutic regimen, including possibly discontinuing EFEXOR XR, in patients for whom such symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms. If the decision is made to discontinue treatment, EFEXOR XR should be tapered (see DOSAGE AND DIRECTIONS FOR USE).

EFEXOR XR 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.

Dose-related increases in blood pressure have been reported in some patients treated with EFEXOR XR. Cases of elevated blood pressure requiring immediate treatment have been reported in post-

marketing experience. Regular blood pressure monitoring is recommended for patients receiving EFEXOR XR. Pre-existing hypertension should be controlled before treatment with EFEXOR XR. Caution should be exercised in patients whose underlying conditions might be compromised by increases in blood pressure.

Increases in heart rate can occur, particularly with higher doses. Caution should be exercised in patients whose underlying conditions might be compromised by increases in heart rate.

Convulsions may occur with EFEXOR XR therapy. EFEXOR XR should be introduced with care in patients with a history of convulsions.

Mania/hypomania may occur in a small proportion of patients with mood disorders who have received EFEXOR XR. EFEXOR XR should be used cautiously in patients with a history or family history of bipolar disorder.

Aggression may occur in a small proportion of patients who have received EFEXOR XR treatment, dose reduction or discontinuation. EFEXOR XR should be used cautiously in patients with a history of aggression.

Cases of hyponatraemia and/or the Syndrome of Inappropriate Antidiuretic Hormone (SIADH) secretion may occur with EFEXOR XR, 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.

Medicines that inhibit serotonin uptake may lead to abnormalities of platelet aggregation. The risk of skin and mucous membrane bleeding, including gastrointestinal haemorrhage, may be increased in patients taking EFEXOR XR. EFEXOR XR should be used cautiously in patients predisposed to bleeding, including patients on anti-coagulants and platelet inhibitors.

Patients should be advised to notify their doctor if they develop a rash, hives, or a related allergic phenomenon.

The safety and efficacy of EFEXOR XR 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.

Clinically relevant increases in serum cholesterol were recorded in 5,3 % of EFEXOR XR-treated patients and 0 % of placebo-treated patients treated for at least 3 months in placebo-controlled clinical trials. Measurement of serum cholesterol levels should be considered during long-term treatment.

Discontinuation effects are well-known to occur. It is therefore recommended that EFEXOR XR be tapered gradually and the patient monitored (see DOSAGE AND DIRECTIONS FOR USE).

The following symptoms have been reported in association with abrupt discontinuation or dose-reduction, or tapering of EFEXOR XR treatment: Hypomania, anxiety, agitation, nervousness, confusion, insomnia or other sleep disturbances, fatigue, somnolence, paraesthesia, dizziness, convulsion, vertigo, headache, flu-like symptoms, tinnitus, impaired coordination and balance, tremor, sweating, dry mouth, anorexia, diarrhoea, nausea and vomiting. In premarketing studies, the majority of discontinuation reactions were mild and resolved without treatment.

Paediatric use:

Safety and efficacy in individuals below 18 years of age have not been established. In clinical trials in Major Depressive Disorder, there were increased reports of hostility and suicide-related adverse events such as suicidal ideation and self-harm (see CONTRAINDICATIONS).

Use in elderly patients:

EFEXOR XR appears to pose no exceptional safety problems for healthy elderly patients.

Effects on activities requiring concentration and performance:

EFEXOR XR may impair judgement, thinking and motor skills. Therefore, patients should be cautioned about their ability to drive or operate hazardous machinery.

Abuse and dependence:

Clinical studies did not show evidence of drug-seeking behaviour, development of tolerance, or dose escalation over time. *In vitro* studies revealed that EFEXOR XR has virtually no affinity for opiate, benzodiazepine, phencyclidine (PCP) or N-methyl-D-aspartic acid (NMDA) receptors. EFEXOR XR was not found to have any significant CNS stimulant activity in rodents. In primate medicine discrimination studies, EFEXOR XR showed no significant stimulant or depressant abuse liability.

INTERACTIONS:

Monoamine oxidase inhibitors (see CONTRAINDICATIONS):

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

CNS active medicines:

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

Serotonin syndrome, a potentially life threatening condition which may occur with EFEXOR XR treatment, particularly with concomitant use of other agents that may affect the serotonergic neurotransmitter system (including triptans, SSRIs, other SNRIs, lithium, sibutramine, tramadol, or St. John's Wort [*Hypericum perforatum*]), with medicines which impair metabolism of serotonin (such as MAOIs; including linezolid [an antibiotic which is a reversible non-selective MAOI], see CONTRAINDICATIONS), 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 CONTRAINDICATIONS and WARNINGS AND SPECIAL PRECAUTION).

If concomitant treatment of EFEXOR XR 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 EFEXOR XR with serotonin precursors (such as tryptophan supplements) is not recommended (see WARNINGS AND SPECIAL PRECAUTION).

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 EFEXOR XR and O-desmethylvenlafaxine. The clinical significance of this interaction is unknown.

Ethanol:

EFEXOR XR has been shown not to increase the impairment of mental and motor skills caused by ethanol. However patients should be advised to avoid alcohol consumption while taking EFEXOR XR.

Haloperidol:

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

Cimetidine:

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

Imipramine:

Venlafaxine did not affect the pharmacokinetics of imipramine and 2-OH-imipramine. However, desipramine AUC, C_{max} and C_{min} increased by about 35 % in the presence of venlafaxine. There was an increase of 2-OH-desipramine AUC by 2,5 to 4,5 fold. Imipramine did not affect the pharmacokinetics of venlafaxine and O-desmethylvenlafaxine. This should be taken into account in patients treated with imipramine and EFEXOR XR concomitantly.

Ketoconazole:

A pharmacokinetic study with ketoconazole in extensive (EM) and poor metabolisers (PM) of CYP2D6 resulted in higher plasma concentrations of both venlafaxine and O-desmethylvenlafaxine in subjects following administration of ketoconazole.

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 medicines resulted in an increase of plasma concentrations of metoprolol by approximately 30 – 40 % without altering the plasma concentrations of its active metabolite, α-hydroxymetoprolol.

EFEXOR XR 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 EFEXOR XR or its active metabolite, O-desmethylvenlafaxine. Caution should be exercised with co-administration of EFEXOR XR and metoprolol.

Risperidone:

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

Diazepam:

Diazepam does not appear to affect the pharmacokinetics of either venlafaxine or O-desmethylvenlafaxine. EFEXOR XR has no effects on the pharmacokinetics and pharmacodynamics of diazepam and its active metabolite, desmethyldiazepam.

Lithium:

The steady-state pharmacokinetics of venlafaxine and O-desmethylvenlafaxine are not affected when lithium is co-administered. Venlafaxine also has no effects on the pharmacokinetics of lithium.

Medicines highly bound to plasma proteins:

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

Medicines metabolised by cytochrome P450 isoenzymes:

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

Potential for other medicines to affect EFEXOR XR:

The metabolic pathways for EFEXOR XR include CYP2D6 and CYP3A4. EFEXOR XR is primarily metabolised to its active metabolite, O-desmethylvenlafaxine, by the cytochrome P450 enzyme CYP2D6. CYP3A4 is a minor pathway relative to CYP2D6 in the metabolism of EFEXOR XR.

CYP2D6 inhibitors:

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

CYP3A4 inhibitors:

Concomitant use of CYP3A4 inhibitors and EFEXOR XR may increase levels of EFEXOR XR and O-desmethylvenlafaxine. Therefore caution is advised when combining EFEXOR XR with a CYP3A4 inhibitor.

CYP2D6 and 3A4 inhibitors:

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

PREGNANCY AND LACTATION:

EFEXOR XR must not be administered to pregnant or lactating women. Safety during human pregnancy and lactation has not been established (see CONTRAINDICATIONS). Some neonates exposed to EFEXOR XR late in the third trimester have developed complications requiring tube-feeding, respiratory support or prolonged hospitalization. Such complications can arise immediately upon delivery.

In pre-clinical safety studies, reduced fertility was observed in a study in which both male and female rats were exposed to the major metabolite of EFEXOR XR (ODV). This ODV exposure was approximately 2 to 3 times that of a human EFEXOR XR dose of 225 mg/day. The human relevance of this finding is unknown.

Venlafaxine and O-desmethylvenlafaxine are excreted in human milk; therefore, mothers on treatment with EFEXOR XR should not breastfeed.

Patients should be advised to notify their doctor if they become pregnant or intend to become pregnant during therapy.

DOSAGE AND DIRECTIONS FOR USE:

The usual recommended dose for EFEXOR XR is 75 mg, given once daily. If after several weeks further clinical improvement is required, the dose may be increased to 150 mg, given once daily. If needed, the dose can be further 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 dose for depressed patients may be further increased, if needed, up to 375 mg, given once daily.

It is recommended that EFEXOR XR be taken with food. Each capsule should be swallowed whole with fluid. Do not divide, crush, chew or place capsule in water.

EFEXOR XR should be administered once daily, at approximately the same time either in the morning or in the evening. The extended-release formulation contains spheroids, which release the medicine slowly into the digestive tract. The insoluble portion of these spheroids is eliminated and may be seen in stools.

Depressed patients, who are currently being treated at a therapeutic dose with EFEXOR, may be switched to EFEXOR XR at the nearest equivalent dose (mg/day). Individual dosage adjustments may however be necessary.

Patients with renal impairment:

Patients with renal impairment should receive lower doses of EFEXOR XR.

The total daily dose of EFEXOR XR should be reduced by 25 – 50 % for patients with renal impairment with a glomerular filtration rate (GFR) of 10 – 70 ml/min.

The total daily dose of EFEXOR XR should be reduced by 50 % in haemodialysis patients.

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

Patients with hepatic impairment:

The total daily dose of EFEXOR XR should be reduced by 50 % in patients with mild to moderate hepatic impairment. Patients with severe hepatic impairment have not been studied; therefore, caution should be used if considering treating these patients with EFEXOR XR and a further reduction

should be considered. Since there is a variability in clearance between hepatically impaired patients, individualisation of dosing, including further dose reductions (> 50 %), may be desirable in some patients.

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

Children:

See CONTRAINDICATIONS.

Elderly patients:

No specific dosage adjustments of EFEXOR XR are recommended based on patient age.

Maintenance, continuation and extended treatment:

The need for long-term therapy with EFEXOR XR must be periodically reassessed. Whether the dose of antidepressant needed to induce remission is identical to the dose needed to maintain and/or sustain euthymia is unknown.

Discontinuing EFEXOR XR:

Dose tapering is recommended whenever possible when discontinuing EFEXOR XR therapy (see WARNINGS AND SPECIAL PRECAUTIONS). Tapering over at least a two-week period is recommended if EFEXOR XR has been used for more than 6 weeks. In clinical trials with venlafaxine extended-release capsules, tapering was achieved by reducing the daily dose by 75 mg at 1-week intervals. The period required for tapering may depend on the dose, duration of therapy and the individual patient. Patients should be advised to consult their doctor before abruptly discontinuing EFEXOR XR (see WARNINGS AND SPECIAL PRECAUTIONS).

SIDE EFFECTS:

The most commonly observed adverse events associated with the use of EFEXOR XR are nervous system complaints. The occurrence of many frequently observed adverse events is dose related.

Side effects reported in clinical trials were categorised utilising the incidence rate as follows:

Very common: ≥ 1/10 (≥ 10 %), Common: ≥ 1/100 and < 1/10 (≥ 1 % and < 10 %), Uncommon: ≥ 1/1 000 and < 1/100 (≥ 0,1 % and < 1 %), Rare: ≥ 1/10 000 and < 1/1 000 (≥ 0,01 % and < 0,1 %), Very rare: < 1/10 000

System Organ Class	Frequency	Side Effect
Body as a whole	Common	Asthenia/fatigue, headache, pain, abdominal pain, back pain, chest pain
	Uncommon	Photosensitivity reaction
Cardiovascular system	Common	Hypertension, vasodilation (mostly hot flashes/flushes)
	Uncommon	Postural hypotension, syncope, tachycardia
Digestive system	Common	Decreased appetite, constipation, nausea, vomiting
Haematologic and lymphatic system	Uncommon	Ecchymosis
Metabolic and nutritional	Common	Increased serum cholesterol (particularly with prolonged administration and possibly with higher doses), weight loss
	Uncommon	Weight gain
Central nervous system	Common	Abnormal dreams, decreased libido, dizziness, dry mouth, hypertonia, insomnia, nervousness, paraesthesia, sedation, tremor
	Uncommon	Apathy, hallucinations, myoclonus
	Rare	Convulsion, manic reaction
Respiratory system	Common	Yawning
Skin and appendages	Uncommon	Rash
Special senses	Common	Abnormality of accommodation, mydriasis, visual disturbance
	Uncommon	Altered taste sensation
Urogenital	Common	Abnormal ejaculation/orgasm (males), anorgasmia, erectile dysfunction, impaired urination (mostly hesitancy)
	Uncommon	Abnormal orgasm (females), urinary retention

The following have been reported during post-marketing surveillance:

Body as a whole: Chills, angioedema, anaphylaxis

Cardiovascular: Palpitations, hypotension, QT prolongation, ventricular fibrillation, ventricular tachycardia (including Torsades de Pointes)

Digestive system: Bruxism, diarrhoea, gastrointestinal haemorrhage, pancreatitis, anorexia, increased appetite, dyspepsia, eructation, flatulence

Haematologic and lymphatic system: Mucous membrane bleeding, prolonged bleeding time, thrombocytopenia, blood dyscrasias (including agranulocytosis, aplastic anaemia, neutropaenia and pancytopaenia)

Metabolic: Abnormal liver function tests, hyponatraemia, hepatitis, Syndrome of Inappropriate Antidiuretic Hormone Secretion (SIADH), increased prolactin

Musculoskeletal: Rhabdomyolysis, myalgia

Central nervous system: Headache, confusion, depersonalisation, agitation, impaired coordination and balance, akathisia/psychomotor restlessness, neuroleptic malignant syndrome (NMS), serotonergic syndrome, delirium, extrapyramidal reactions (including dystonia and dyskinesia), tardive dyskinesia, aggression, amnesia, anxiety, depression, emotional lability, hypoaesthesia, somnolence, abnormal thinking and trismus

Respiratory: Pulmonary eosinophilia, pharyngitis and rhinitis

Skin: Sweating, including night sweats, alopecia, erythema multiforme, Stevens-Johnson Syndrome, pruritus, urticaria, toxic epidermal necrolysis

Special senses: Tinnitus, angle closure glaucoma

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

Children (see CONTRAINDICATIONS):

In general the adverse events profile of EFEXOR XR in children and adolescents was similar to that seen for adults. In paediatric clinical trials, there were increased reports of hostility and, especially in Major Depressive Disorders, suicide-related adverse events such as suicidal ideation and self-harm. 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.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

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

Published retrospective studies report that EFEXOR XR 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 EFEXOR XR-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 EFEXOR XR in overdosage as opposed to some characteristics of EFEXOR XR-treated patients is not clear. Prescriptions for EFEXOR XR should be written for the smallest quantity of medicine consistent with good patient management, in order to reduce the risk of overdose.

Recommended treatment:

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

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

Gastric lavage may be indicated if performed soon after ingestion or in symptomatic patients.

Administration of activated charcoal may also limit medicine absorption.

Forced diuresis, dialysis, haemoperfusion and exchange transfusion are unlikely to be of benefit. No specific antidotes for EFEXOR XR are known.

IDENTIFICATION:

EFEXOR XR 75 mg: Size 1 hard gelatine capsule, opaque peach cap and body branded in red ink, containing white to off-white spheroids of about 1 mm diameter.

EFEXOR XR 150 mg: Size 0 elongated hard gelatine capsule, opaque dark orange cap and body branded in white ink, containing white to off-white spheroids of about 1 mm diameter.

PRESENTATION:

EFEXOR XR 75 mg: White opaque plastic bottles containing 50 capsules. Blister packaging of 10's (one single blister strip), 30's (three blister strips of 10 each) or 28's (two blister strips of 14 each) packed in a carton box.

EFEXOR XR 150 mg: White opaque plastic bottles containing 50 capsules. Blister packaging of 10's (one single blister strip), 30's (three blister strips of 10 each) or 28's (two blister strips of 14 each) packed in a carton box.

STORAGE INSTRUCTIONS:

Store in a cool (below 25 °C), dry place. Keep well closed.

Keep out of reach of children.

REGISTRATION NUMBERS:

EFEXOR XR 75 mg: 32/1.2/0318

EFEXOR XR 150 mg: 32/1.2/0319

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION:

Pfizer Laboratories (Pty) Ltd

85 Bute Lane

Sandton 2196

South Africa

DATE OF PUBLICATION OF THIS PACKAGE INSERT:

02 March 2012

BOTSWANA: S2

EFEXOR XR 75 mg – Reg. No.: BOT0300583

EFEXOR XR 150 mg – Reg. No.: BOT 0300584

NAMIBIA: S3

EFEXOR XR 75 mg – Reg. No.: 04/1.2/1124

EFEXOR XR 150 mg – Reg. No.: 04/1.2/1125