SCHEDULING STATUS: S5

1. NAME OF THE MEDICINE

EFEXOR® XR 75 mg capsules

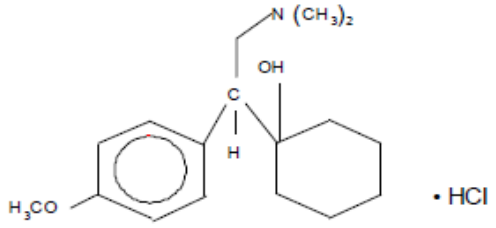
EFEXOR® XR 150 mg capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Sugar free.

Venlafaxine hydrochloride 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

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Capsules

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.

4. CLINICAL PARTICULARS

4.1 Therapeutic 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 medicine 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.

4.2 Posology and method of administration

Posology

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.

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.

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 section 4.4). 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 section 4.4).

Special populations

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.

Elderly patients

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

Paediatric population

See section 4.3.

Method of administration

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.

4.3 Contraindications

- Hypersensitivity to venlafaxine or any excipients in the formulation (listed in section 6.1).
- 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 section 4.5). 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 section 4.5).
- Children under 18 years (see sections 4.4 and 4.8).
- Pregnancy and lactation (see section 4.6).

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 EFEXOR XR including CNS depressant effects (section 4.5). Overdose with EFEXOR XR has been reported predominantly in combination with alcohol and/or other medicines, including cases with fatal outcome (section 4.9).

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

Suicide/suicidal thoughts or clinical worsening

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.

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 section 4.2).

Serotonin syndrome

Serotonin syndrome, a potentially life-threatening condition, may occur with EFEXOR XR treatment, particularly with concomitant use of other medicines that may affect the serotonergic neurotransmitter system (including triptans, SSRIs, SNRIs, tricyclic antidepressants, amphetamines, lithium, sibutramine, St. John's Wort [*Hypericum perforatum*], opioids [e.g. buprenorphine, fentanyl and its analogues, tramadol, dextromethorphan, tapentadol, pethidine, methadone and pentazocine]), with medicines that impair metabolism of serotonin (such as MAOIs e.g. methylene blue), with serotonin precursors (such as tryptophan supplements) or with antipsychotics or other dopamine antagonists (see sections 4.3 and 4.5).

Narrow-angle glaucoma

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.

Cardiac disease and risk of arrhythmia

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.

In post-marketing experience, cases of QTc prolongation, Torsade de Pointes (TdP), ventricular tachycardia and fatal cardiac dysrhythmias have been reported with the use of EFEXOR XR, especially in overdose or in patients with other risk factors for QTc prolongation/TdP. The balance of risks and benefits should be considered before prescribing EFEXOR XR to patients at high risk of serious cardiac dysrhythmia or QTc prolongation.

Convulsions

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

Mania/hypomania

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

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.

Hyponatraemia

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.

Abnormal bleeding

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. SSRIs/SNRIs may increase the risk of postpartum haemorrhage (see sections 4.6 and 4.8). 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.

Co-administration with weight loss medicines

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

Serum cholesterol

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 of treatment

Discontinuation effects are well-known to occur. It is therefore recommended that EFEXOR XR be tapered gradually, and the patient monitored (see section 4.2).

The following symptoms have been reported in association with abrupt discontinuation or dose-reduction, or tapering of 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.

Sexual dysfunction

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

Diabetes

In patients with diabetes, treatment with a SSRI or EFEXOR XR may alter glycaemic control. Insulin and/or oral antidiabetic dosage may need to be adjusted.

Medicine-laboratory test interactions

False-positive urine immunoassay screening tests for phencyclidine (PCP) and amphetamine have been reported in patients taking EFEXOR XR. This is due to lack of specificity of the screening tests. False-positive test results may be expected for several days following discontinuation of EFEXOR XR therapy. Confirmatory tests, such as gas chromatography/mass spectrometry, will distinguish EFEXOR XR from PCP and amphetamine.

Paediatric population

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 section 4.3).

Use in elderly patients

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

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.

4.5 Interaction with other medicines and other forms of interaction

Monoamine oxidase inhibitors (see section 4.3)

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 section 4.3). 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

Serotonin syndrome, a potentially life-threatening condition which may occur with EFEXOR XR treatment, particularly with concomitant use of other medicines that may affect the serotonergic neurotransmitter system (including triptans, SSRIs, other SNRIs, tricyclic antidepressants, amphetamines, lithium, sibutramine, tramadol, or St. John's Wort [*Hypericum perforatum*]), opioids [e.g. buprenorphine]), with medicines which impair metabolism of serotonin (such as MAOIs, including linezolid [an antibiotic], selegiline [for Parkinson's disease]), (see section 4.3), or with serotonin precursors (such as tryptophan supplements). Serotonin syndrome symptoms may include mental status changes, autonomic instability, neuromuscular aberrations and/or gastrointestinal symptoms

(see sections 4.3 and 4.4).

If concomitant treatment of 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 section 4.4).

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

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 EFEXOR XR including CNS depressant effects.

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 metabolising 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 medicine(s) that produce simultaneous inhibition of these two enzyme systems.

4.6 Fertility, 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 section 4.3).

Pregnancy

Some neonates exposed to EFEXOR XR late in the third trimester have developed complications requiring tube-feeding, respiratory support or prolonged hospitalisation. Such complications can arise immediately upon delivery.

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 and 4.8).

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

Breastfeeding

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

Fertility

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.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of the safety profile

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.

Tabulated summary of adverse reactions

Side effects reported in clinical trials were categorised utilising the incidence rate as follows: Very common: ≥ 1/10; common: ≥ 1/100 to < 1/10; uncommon: ≥ 1/1 000 to < 1/100; rare: ≥ 1/10 000 to < 1/1 000; very rare: < 1/10 000; not known (cannot be estimated from the available data).

MedDRA System Organ Class	**Frequency**	**Adverse reactions**
Metabolism and nutrition disorders	Common	Decreased appetite
Psychiatric disorders	Very common	Insomnia
	Common	Abnormal dreams, nervousness, decreased libido, anorgasmia, abnormal orgasm
	Uncommon	Mania, hypomania, hallucination, derealisation, apathy
	Rare	Manic reaction
	Not known	Suicidal ideation and suicidal behaviours[a], aggression[b]
Nervous system disorders	Very common	Dizziness, sedation
	Common	Tremor, paraesthesia, dysgeusia
	Uncommon	Syncope, myoclonus
	Rare	Convulsion
Eye disorders	Common	Visual impairment, accommodation disorder, including blurred vision, mydriasis
Ear and labyrinth disorders	Not known	Vertigo
Cardiac disorders	Common	Tachycardia
	Rare	Ventricular fibrillation
Vascular disorders	Common	Hypertension, hot flush
	Uncommon	Orthostatic hypotension
Respiratory, thoracic and mediastinal disorders	Common	Yawning
Gastrointestinal disorders	Very common	Nausea, dry mouth, constipation
	Common	Vomiting, abdominal pain
Skin and subcutaneous tissue disorders	Common	Rash
	Uncommon	Ecchymosis, photosensitivity reaction

Musculoskeletal and connective tissue disorders	Common	Hypertonia, back pain
Renal and urinary disorders	Common	Urinary hesitation, urinary retention
	Uncommon	Urinary incontinence
Reproductive system and breast disorders	Common	Erectile dysfunction[b], ejaculation disorder[b]
General disorders and administration site conditions	Common	Fatigue, asthenia, pain, chest pain
Investigations	Common	Weight decreased, weight increased, blood cholesterol increased

[a] Cases of suicidal ideation and suicidal behaviours have been reported during EFEXOR XR therapy or early after treatment discontinuation (see section 4.4).

[b] See section 4.4.

The following have been reported during post-marketing surveillance:

MedDRA System Organ Class	**Adverse reactions**
Infections and infestations	Pharyngitis, rhinitis
Blood and lymphatic system disorders	Agranulocytosis, aplastic anaemia, pancytopenia, neutropenia, thrombocytopaenia, mucous membrane bleeding
Immune system disorders	Anaphylactic reaction
Endocrine disorders	Inappropriate antidiuretic hormone secretion, increased blood prolactin
Metabolism and nutrition disorders	Hyponatraemia, increased appetite
Psychiatric disorders	Confusional state, depersonalisation, agitation, bruxism, delirium, anxiety, depression, emotional lability

Nervous system disorders	Headache[c], akathisia, balance disorder, abnormal coordination, dyskinesia, neuroleptic malignant syndrome (NMS), serotonin syndrome, dystonia, tardive dyskinesia, amnesia, hypoaesthesia, somnolence, abnormal thinking
Eye disorders	Angle-closure glaucoma
Ear and labyrinth disorders	Tinnitus
Cardiac disorders	Palpitations, torsade de pointes, ventricular tachycardia, prolonged electrocardiogram QT, stress cardiomyopathy (takotsubo cardiomyopathy)
Vascular disorders	Hypotension
Respiratory, thoracic and mediastinal disorders	Dyspnoea, interstitial lung disease, pulmonary eosinophilia
Gastrointestinal disorders	Diarrhoea, gastrointestinal haemorrhage, pancreatitis, dyspepsia, eructation, flatulence
Hepatobiliary disorders	Abnormal liver function test, hepatitis
Skin and subcutaneous tissue disorders	Hyperhidrosis (including night sweats), pruritus, urticaria, alopecia, angioedema, Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema multiforme
Musculoskeletal and connective tissue disorders	Rhabdomyolysis, myalgia, trismus
Renal and urinary disorders	Pollakiuria, urinary incontinence
Reproductive system and breast disorders	Menorrhagia, metrorrhagia, postpartum haemorrhage[d]
General disorders and administration site conditions	Chills, mucosal haemorrhage
Investigations	Prolonged bleeding time

[c] In pooled clinical trials, the incidence of headache with EFEXOR XR and placebo were similar.

[d] This event has been reported for the therapeutic class of SSRIs/SNRIs (see sections 4.4 and 4.6).

Paediatric population (see section 4.3)

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.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reaction Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8.

4.9 Overdose

In post-marketing experience, overdose with EFEXOR XR was reported predominantly in combination with alcohol and/or other medicines, 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, convulsion, and vomiting. Other events reported include electrocardiographic changes (e.g. prolongation of QT interval, bundle branch block, QRS prolongation), ventricular tachycardia, bradycardia, hypotension, hypoglycaemia, vertigo and death. Severe poisoning symptoms may occur in adults after intake of approximately 3 grams of EFEXOR XR.

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 medicines, 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.

Recommended treatment

Severe poisoning may require complex emergency treatment and monitoring. Therefore, in event of suspected overdose involving EFEXOR XR, prompt contact with the nearest hospital or poison centre is recommended.

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.

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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A 1.2 Psychoanaleptics (antidepressants)

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.

5.2 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 section 4.2).

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 section 4.2).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Anhydrous methanol

Ethylcellulose

Hypromellose

Methylene chloride

Microcrystalline cellulose

Hard gelatine capsules contain:

Gelatine

Red iron oxide (E172)

Talc

Titanium dioxide (E171)

Yellow iron oxide (E172)

EFEXOR XR 75 mg capsules: red printing ink

EFEXOR XR 150 mg capsules: white printing ink

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months.

6.4 Special precautions for storage

Store in a cool (at or below 25 °C), dry place.

6.5 Nature and contents of container

EFEXOR XR 75 mg: Clear or opaque PVC/aluminium 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: Clear or opaque PVC/aluminium 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.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Viatris Healthcare (Pty) Ltd

4 Brewery Street

Isando

Gauteng, 1609

Tel.: +27(011) 451 1300 / +27(071) 281 2503 (24 hours)

Manufacturer: Pfizer Ireland Pharmaceuticals, Newbridge, Republic of Ireland

8. REGISTRATION NUMBERS

EFEXOR XR 75 mg: 32/1.2/0318

EFEXOR XR 150 mg: 32/1.2/0319

9. DATE OF FIRST AUTHORISATION

11 May 1999

10. DATE OF REVISION OF THE TEXT

14 October 2024

BOTSWANA: S2

EFEXOR XR 75 mg – Reg. No.: BOT0300583

EFEXOR XR 150 mg – Reg. No.: BOT0300584

NAMIBIA: NS3

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

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