PT. Pfizer Indonesia
Local Product Document

Generic Name: Venlafaxine hydrochloride
Trade Name: Efexor XR
CDS Effective Date: June 09, 2021
Supersedes: July 10, 2019

1. TRADE NAME OF THE MEDICINAL PRODUCT

Efexor XR 75 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Efexor XR capsules containing 75 mg of venlafaxine as venlafaxine hydrochloride.

3. PHARMACEUTICAL FORM

Extended-release capsule
Efexor XR 75 mg capsules are opaque peach capsules printed in red with "W" and "75".

4. CLINICAL PARTICULARS

4.1. Indications

Efexor XR is indicated for the:
- Treatment of depression, including depression with associated anxiety.
- For prevention of relapse and prevention of recurrence of depression.
- Treatment of anxiety or generalized anxiety disorder, including long-term treatment.
- Treatment of social anxiety disorder.
- Treatment of panic disorder.

4.2. Posology and Method of Administration

The recommended starting dose of venlafaxine extended-release capsules is 75 mg given once daily.

Patients not responding to the initial 75 mg/day dose may benefit from dose increases to a maximum of 225 mg/day. While the recommended dose for moderately depressed patients is up to 225 mg/day for immediate-release venlafaxine, more severely depressed patients in one study responded to a mean dose of 350 mg/day (range of 150 to 375 mg/day).

Extended-release venlafaxine dosage increases can be made at intervals of approximately 2 weeks or more, but not less than 4 days.

Patients treated with venlafaxine immediate-release tablets may be switched to venlafaxine extended-release capsules at the nearest equivalent daily dosage. For example, venlafaxine immediate-release tablets 37.5 mg twice daily may be switched to venlafaxine extended-release capsules 75 mg once daily. Individual dosage adjustments may be necessary.

Gradual dose tapering is recommended when discontinuing venlafaxine therapy (See sections 4.4 and 4.8).

Tapering over at least a two-week period is recommended if venlafaxine 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. However, the time period required for tapering and the amount of dose reduction may depend on the dose, duration of therapy, and the individual patient. In some patients, discontinuation may need to occur very gradually over periods of months or longer.

It is recommended that venlafaxine extended-release capsules be taken with food, at approximately the same time each day. Capsules must be swallowed whole with fluid and not divided, crushed, chewed, or placed in water.

Panic Disorder

It is recommended that initial single doses of 37.5 mg/day of venlafaxine extended-release capsules be used for 4 to 7 days. In clinical trials establishing the efficacy of Efexor XR in outpatients with panic disorder, initial doses of 37.5 mg/day for 4 to 7 days were followed by doses of 75 mg/day, with maximum doses of 225 mg/day. Although a dose-response relationship for effectiveness in patients with panic disorder was not clearly established in fixed-dose studies, certain patients not responding to 75 mg/day may benefit from dose increases to a maximum of approximately 225 mg/day. Dose increases should be in increments of up to 75 mg/day, as needed, and should be made at intervals of not less than 4 days.

- **Use in Patients with Renal Impairment**

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.

The total daily dose of venlafaxine should be reduced by 50% in hemodialysis patients.

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

- **Use in Patients with 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, individualization of dosage may be desirable.

- **Use in Elderly Patients**

No specific dose adjustments of venlafaxine are recommended based on patient age. However, as with any therapy, caution should be exercised in treating the elderly (e.g. due to the possibility of renal impairment. See also dosage recommendations for renal impairment). The lowest effective dose should always be used, and patients should be carefully monitored when an increase in the dose is required.

- **Use in Children and Adolescents**

There is insufficient experience with the use of venlafaxine in patients younger than 18 years of age (See section 4.8). Efficacy in patients less than 18 years of age has not been established. Therefore, venlafaxine is not recommended for use in patients less than 18 years of age.

In pediatric clinical trials, the adverse reaction, suicidal ideation, was observed. There were also increased reports of hostility and, especially in major depressive disorder, self-harm.

As with adults, decreased appetite, weight loss, increased blood pressure, and increased serum cholesterol have been observed in children and adolescents (ages 6 to 17 years; See section 4.8). Regular measurement of weight and blood pressure is recommended if venlafaxine is used in children and adolescents. Discontinuation of venlafaxine treatment should be considered in children and adolescents who experience a sustained increase in blood pressure. Measurement of serum cholesterol levels should be considered during long-term treatment of children and adolescent (See section 4.8). Safety in children younger than 6 years of age has not been evaluated.

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. Venlafaxine has been shown to be efficacious during long-term (up to 12 months) treatment.

Discontinuing Efexor XR
Discontinuation effects are well known to occur with the abrupt withdrawal of other antidepressants. While the discontinuation effects of Efexor XR has not been systematically evaluated in controlled clinical trials, a retrospective survey of events occurring during taper or following discontinuation of Efexor XR revealed the following events that occurred with an incidence of at least 3% and at least twice the placebo incidence: dizziness, dry mouth, insomnia, nausea, nervousness and sweating.

In addition, a retrospective survey of events occurring during taper or following discontinuation of Efexor XR tablets revealed the following events that occurred at an incidence of at least 5% and at least twice the placebo incidence: fatigue, headache, nausea, dizziness, sleep disturbance and nervousness. Diarrhea and one hypomanic episode was also reported.

In post-marketing experience, symptoms reported following discontinuation, dose reduction or tapering of venlafaxine at various doses have also included confusion, paresthesia, sweating, vertigo and vomiting. It is therefore recommended that when discontinuing Efexor XR after more than one week's therapy, the dose should be gradually reduced over at least one week and the patient monitored in order to minimize the risk of discontinuation symptoms.

Dose tapering is recommended when discontinuing venlafaxine therapy. Tapering over at least a two-week period is recommended if venlafaxine has been used for more than 6 weeks. The period required for tapering may depend on the dose, duration of therapy and the individual patient.

4.3. Contraindications

1. Hypersensitivity to venlafaxine or any other component of the product.
2. Concomitant use of venlafaxine and any monoamine oxidase inhibitor (MAOI).

Venlafaxine must not be initiated for at least 14 days after discontinuation of treatment with an MAOI; a shorter interval may be justified in the case of a reversible MAOI. Venlafaxine must be discontinued for at least 7 days before starting treatment with any MAOI (See section 4.5).

4.4. Special Warnings and Special Precautions for Use

Suicide/Suicidal Thoughts or Clinical Worsening

All patients treated with venlafaxine 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 restlessness), hypomania, mania, other unusual changes in behavior, 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 patients with depression, and the smallest quantity of drug, consistent with good patient management, should be provided to reduce the risk of overdose (See also section 4.8).

Suicide is a known risk of depression and certain other psychiatric disorders, and these disorders themselves are strong predictors of suicide. Pooled analyses of short-term placebo-controlled trials of antidepressant medicines (selective serotonin reuptake inhibitors [SSRIs] and others) showed that these medicines increase the risk of suicidality in children, adolescents, and young adults (ages 18-24 years) with major depression and other psychiatric disorders. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults older than 24 years of age; there was a reduction in the risk of suicidality with antidepressants compared to placebo in adults age 65 years and older.

Aggression

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

Discontinuation

Discontinuation effects are well known to occur with antidepressants, and sometimes these effects can be protracted and severe (See section 4.8). Suicide/suicidal thoughts and aggression have been observed in patients during changes in venlafaxine dosing regimen, including during discontinuation (see above in section 4.4 - Suicide/Suicidal Thoughts or Clinical Worsening and Aggression). It is therefore recommended that the dosage of venlafaxine be tapered gradually and individually and the patients be closely monitored during discontinuation (See section 4.2). In some patients, discontinuation could take months or longer.

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.

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.

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, and opioids (e.g., fentanyl, dextromethorphan, tramadol, tapentadol, meperidine, methadone, pentazocine), with drugs that impair metabolism of serotonin including MAOIs, e.g., methylene blue, or with antipsychotics or other dopamine antagonists. Symptoms of serotonin syndrome may include mental status changes (e.g., agitation, hallucinations, and coma), autonomic instability (e.g., tachycardia, labile blood pressure, and hyperthermia), neuromuscular aberrations (e.g., hyperreflexia, incoordination), and/or gastrointestinal symptoms (e.g., nausea, vomiting, and diarrhea). 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).

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.

In clinical trials with venlafaxine, seizures were reported in 0.2% of all venlafaxine-treated patients. All patients recovered. No seizures occurred in Efexor XR-treated patients during clinical trials. However, as with all antidepressants, Efexor XR should be introduced with care in patients with a history of seizure and should be discontinued in any patient who develops seizures.

During clinical trials, rash developed in 3% of patients treated with venlafaxine. Patients should be advised to notify their physician if they develop a rash, urticaria or related allergic phenomenon.

Abuse and Dependence

Clinical studies have shown no evidence of drug-seeking behavior, development of tolerance, or dose escalation over time among patients taking venlafaxine. However, physicians should evaluate patients for a history of drug abuse, and follow such patients closely, observing them for signs of misuse or abuse of Efexor XR.

In vitro studies revealed that venlafaxine has virtually no affinity for opiate, benzodiazepine, phencyclidine (PCP), or N-methyl-D-aspartic acid (NMDA) receptors. Venlafaxine was not found to have any significant central nervous system (CNS) stimulant activity in rodents. In primate drug discrimination studies, venlafaxine showed no significant stimulant or depressant abuse liability. In a self-administration study, rhesus monkeys have been shown to self-administer venlafaxine intravenously.

The clearances of venlafaxine and its active metabolite are decreased and half-lives increased in patients with moderate to severe renal impairment or cirrhosis of the liver. Therefore, Efexor XR should be used with caution in these patients. A lower daily dose might be necessary in such patients and treatment may be provided with Efexor XR Tablets as indicated above under "Posology and Method of Administration".

Cardiovascular System

Venlafaxine has not been evaluated in patients with a recent history of myocardial infarction or unstable heart disease. Therefore, it should be used with caution in these patients. Clinically significant electrocardiogram findings were observed in 1% of the venlafaxine-treated patients compared with 0.2% of the placebo-treated patients. Clinically significant changes in PR, QRS or QTc intervals were rarely observed in patients treated with venlafaxine during clinical trials. The mean heart rate was increased by approximately 4 beats/minute during treatment with venlafaxine.

Increases in blood pressure have been reported in patients treated with high doses of venlafaxine. Blood pressure monitoring is advisable in patients receiving daily doses of >200 mg.

Dose-related increases in blood pressure have been reported in some patients treated with venlafaxine. Cases of elevated blood pressure requiring immediate treatment have been reported in post-marketing experience. Measurement of blood pressure is recommended for patients receiving venlafaxine. 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.

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.

Cases of QTc prolongation, Torsade de Pointes (TdP), ventricular tachycardia and sudden death have been reported during the post-marketing use of venlafaxine. The majority of reports occurred in association with overdose or in patients with other risk factors for QTc prolongation/TdP. Therefore, venlafaxine should be used with caution in patients with risk factors for QTc prolongation.

Convulsions

Convulsions may occur with venlafaxine therapy. As with all antidepressants, venlafaxine should be introduced with caution in patients with a history of convulsions.

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) be closely monitored.

Mania/Hypomania

Mania/hypomania may occur in a small proportion of patients with mood disorders who have received antidepressants, including venlafaxine. As with other antidepressants, venlafaxine should be used cautiously in patients with a history or family history of bipolar disorder.

Hyponatremia

Cases of hyponatremia and/or the syndrome of inappropriate antidiuretic hormone (SIADH) secretion 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.

Bleeding

Drugs that inhibit serotonin uptake may lead to abnormalities of platelet aggregation. There have been reports of bleeding abnormalities with venlafaxine ranging from skin and mucous membrane bleeding and gastrointestinal hemorrhage, to life-threatening hemorrhage. As with other SRIs, venlafaxine should be used cautiously in patients predisposed to bleeding, including patients on anti-coagulants and platelet inhibitors.

Weight Loss

The safety and efficacy of venlafaxine therapy in combination with weight loss agents, including phentermine, have not been established. Co-administration of venlafaxine hydrochloride and weight loss agents is not recommended. Venlafaxine hydrochloride is not indicated for weight loss, alone or in combination with other products.

Serum Cholesterol

Clinically relevant increases in serum cholesterol were recorded in 5.3% of venlafaxine-treated patients and 0.0% 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.

4.5. Interaction with Other Medicinal Products and Other Forms of Interaction

Monoamine Oxidase Inhibitors

Severe adverse reactions have been reported in patients who have recently been discontinued from an MAOI and started on venlafaxine, or have recently had venlafaxine therapy discontinued prior to initiation of an MAOI (See section 4.3). These reactions have included tremor, myoclonus, diaphoresis, nausea, vomiting, flushing, dizziness, and hyperthermia with features resembling NMS, seizures, and death.

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, meperidine, methadone, pentazocine) or St. John's Wort (*Hypericum perforatum*), with drugs, that impair the metabolism of serotonin such as MAOIs, including linezolid (an antibiotic, which is a reversible non-selective MAOI) and methylene blue); or with serotonin precursors such as tryptophan supplements (See sections 4.3 and 4.4).

Serotonin syndrome symptoms may include mental status changes, autonomic instability, neuromuscular aberrations and/or gastrointestinal symptoms. (See section 4.4)

If concomitant treatment with venlafaxine and 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).

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).

Indinavir

A pharmacokinetic study with indinavir has shown a 28% decrease in area under the concentration versus time curve (AUC) and a 36% decrease in C_{max} for indinavir. Indinavir did not affect the pharmacokinetics of venlafaxine and O-desmethylvenlafaxine (ODV).

The clinical significance of this interaction is unknown.

Ethanol

Venlafaxine has been shown not to increase the impairment of mental and motor skills caused by ethanol. However, as with all CNS-active drugs, patients should be advised to avoid alcohol consumption while taking venlafaxine.

Haloperidol

A pharmacokinetic study with haloperidol has shown 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 venlafaxine 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 ODV. The overall pharmacological activity of venlafaxine plus ODV is expected to increase only slightly in most patients. In the elderly and in patients with hepatic 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 ODV. This should be taken into account in patients treated with imipramine and venlafaxine concomitantly.

Ketoconazole

A pharmacokinetic study with ketoconazole in extensive metabolizers (EM) and poor metabolizers (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 (See section 4.5, Potential for Other Drugs to Affect Venlafaxine).

Metoprolol

Concomitant administration of venlafaxine (50 mg every 8 hours for 5 days) and metoprolol (100 mg every 24 hours for 5 days) to healthy volunteers in a pharmacokinetic interaction study for both drugs resulted in increase in plasma concentrations of metoprolol by approximately 30%-40% without altering the plasma concentrations of its active metabolite, α-hydroxymetoprolol. Venlafaxine appeared to reduce the blood pressure lowering effect of metoprolol in this study of healthy volunteers. The clinical relevance of this finding in hypertensive patients is unknown. Metoprolol did not alter the pharmacokinetic profile of venlafaxine or its active metabolite, ODV.

Caution should be exercised with co-administration of venlafaxine and metoprolol.

Risperidone

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

Diazepam

Diazepam does not appear to affect the pharmacokinetics of either venlafaxine or ODV. Venlafaxine has no effects on the pharmacokinetics and pharmacodynamics of diazepam and its active metabolite, desmethyldiazepam.

Lithium

The steady-state pharmacokinetics of venlafaxine and ODV are not affected when lithium is co-administered. Venlafaxine has no effect on the pharmacokinetics of lithium (See also subheading above, CNS Active Drugs).

Drugs Highly Bound to Plasma Proteins

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

Drugs Metabolized by Cytochrome P450 Isoenzymes

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

Potential for Other Drugs to Affect Venlafaxine

The metabolic pathways for venlafaxine include CYP2D6 and CYP3A4. Venlafaxine is primarily metabolized to its active metabolite, ODV, by the cytochrome P450 enzyme, CYP2D6. 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 and venlafaxine may increase the levels of venlafaxine and ODV (See section 4.5). Therefore, caution is advised when combining venlafaxine with a CYP3A4 inhibitor.

CYP2D6 and CYP3A4 Inhibitors

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

Electroconvulsive Therapy

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

Drug-Laboratory Test Interactions

False-positive urine immunoassay screening tests for 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.

4.6. Fertility, Pregnancy and Lactation

The safety of venlafaxine in human pregnancy has not been established. Venlafaxine must be administered to pregnant women only if the expected benefits outweigh the possible risks. If venlafaxine is used until or shortly before birth, discontinuation effects in the newborn should be considered. Some neonates exposed to venlafaxine late in the third trimester have developed complications requiring tube feeding, respiratory support, or prolonged hospitalization. Such complications can arise immediately upon delivery.

When venlafaxine was administered orally to pregnant rats throughout gestation and lactation, there was a decrease in pup weight, an increase in stillborn pups, and an increase in pup deaths during the first 5 days of lactation, when dosing began during pregnancy and continued until weaning. The cause of these deaths is not known. These effects occurred at 10 times the human daily dose (on a mg/kg basis) or 2.5 times (on a mg/m^2 basis) the human daily dose of 375 mg of venlafaxine. The no-effect dose for rat pup mortality was 1.4 times the human dose, on a mg/kg basis, or 0.25 times the human dose, on a mg/m^2 basis.

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.

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

Venlafaxine and ODV are excreted in human milk; therefore, the use of Efexor XR in nursing women cannot be recommended.

4.7. Effects on Ability to Drive and Use Machines

Venlafaxine did not affect psychomotor, cognitive, or complex behavior performance in healthy volunteers. However, any psychoactive drug 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

Adverse Drug Reaction Table

ADRs by SOC and CIOMS frequency category listed in order of decreasing medical seriousness within each frequency category and SOC.

System Organ Class	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	Frequency Not Known (cannot be estimated from the available data)
Blood and lymphatic system disorders				Agranulocytosis*§, Aplastic anaemia*§, Pancytopenia*§, Neutropenia*§	Thrombocytopenia*	
Immune system disorders				Anaphylactic reaction*§		
Endocrine disorders				Inappropriate antidiuretic hormone secretion*§	Blood prolactin increased*	
Metabolism and nutrition disorders		Decreased appetite		Hyponatraemia*		
Psychiatric disorders	Insomnia	Abnormal dreams, Nervousness, Libido decreased, Agitation*, Anorgasmia	Confusional state*, Mania, Hypomania, Depersonalisation, Hallucination, Abnormal orgasm, Bruxism*, Apathy	Delirium*§		
Nervous system disorders	Headache*, Dizziness, Sedation	Akathisia*, Tremor, Paraesthesia, Dysgeusia	Syncope, Myoclonus, Balance disorder* Coordination abnormal*, Dyskinesia*	Neuroleptic malignant syndrome*§, Serotonin syndrome*§, Convulsion, Dystonia*	Tardive dyskinesia*	

System Organ Class	**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**	**Frequency Not Known (cannot be estimated from the available data)**
Eye disorders		Visual impairment, Accommodation disorder, Mydriasis,		Angle closure glaucoma*§		
Ear and labyrinth disorders		Tinnitus*				
Cardiac disorders		Tachycardia, Palpitations		Torsade de pointes*§, Ventricular tachycardia*§, Ventricular fibrillation*§, Electrocardiogram QT prolonged*, Stress cardiomyopathy (takotsubo cardiomyopathy)*§		
Vascular disorders		Hypertension, Hot flush	Orthostatic hypotension, Hypotension*			
Respiratory, thoracic and mediastinal disorders		Dyspnoea*, Yawning		Interstitial lung disease*§, Pulmonary eosinophilia*§		
Gastrointestinal disorders	Nausea, Dry mouth, Constipation	Diarrhoea*, Vomiting	Gastrointestinal haemorrhage*	Pancreatitis*		
Hepatobiliary disorders			Liver function test abnormal*	Hepatitis*§		
Skin and subcutaneous tissue disorders	Hyperhidrosis*	Rash, Pruritus*, Night sweats*	Urticaria*, Alopecia*, Ecchymosis, Photosensitivity reaction	Stevens-Johnson syndrome*§, Toxic epidermal necrolysis*§, Angioedema*§, Erythema multiforme*§		
Musculoskeletal and connective tissue disorders		Hypertonia		Rhabdomyolysis*§		

System Organ Class	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	Frequency Not Known (cannot be estimated from the available data)
Renal and urinary disorders		Urinary hesitation, Urinary retention, Pollakiuria*	Urinary incontinence*			
Reproductive system and breast disorders		Erectile dysfunction, Ejaculation disorder	Metrorrhagia*, Menorrhagia*			
General disorders and administration site conditions		Fatigue, Asthenia, Chills*			Mucosal Haemorrhage*	
Investigations		Weight decreased, Weight increased	Blood cholesterol increased		Bleeding time prolonged*	
Injury, poisoning and procedural complications			Bone fracture			

*ADR identified post-marketing.
§ADR frequency estimated using "The Rule of 3."
ADR = Adverse Drug Reaction

Discontinuation Effects

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, paresthaesia, 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 premarketing studies, the majority of discontinuation reactions were mild and resolved without treatment (See sections 4.2 and 4.4). While these events are generally self-limiting, there have been reports of serious discontinuation symptoms, and sometimes these effects can be protracted and severe.

Pediatric Patients

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 (See section 4.2).

In pediatric clinical trials, the adverse reaction suicidal ideation was observed. There were also increased reports of hostility and, especially in major depressive disorder, self-harm.

Particularly, the following adverse reactions were observed in pediatric patients: abdominal pain, agitation, dyspepsia, ecchymosis, epistaxis, and myalgia.

4.9. Overdose

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

Published retrospective studies report that venlafaxine overdosage may be associated with an increased risk of fatal outcomes compared to that observed with SSRI antidepressant products, but lower than that for tricyclic antidepressants. Epidemiological studies have shown that venlafaxine treated patients have a higher burden of suicide risk factors than SSRI-treated patients. The extent to which the finding of an increased risk of fatal outcomes can be attributed to the toxicity of venlafaxine in overdosage as opposed to some characteristics of venlafaxine-treated patients is not clear. Prescriptions for venlafaxine should be written for the smallest quantity of drug consistent with good patient management, in order to reduce the risk of overdose.

Management of Overdosage/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 drug absorption.

Forced diuresis, dialysis, hemoperfusion and exchange transfusion are unlikely to be of benefit. No specific antidotes for venlafaxine are known.

5. PHARMACOLOGICAL PROPERTIES

Venlafaxine and its active metabolite, O-desmethylvenlafaxine, are potent inhibitors of neuronal serotonin and norepinephrine reuptake and weak inhibitors of dopamine reuptake. The antidepressant activity of venlafaxine is thought to be associated with potentiation of neurotransmitter activity in the central nervous system (CNS). Venlafaxine and O-desmethylvenlafaxine have no significant affinity for muscarinic, histaminergic, or α_1-adrenergic receptors *in vitro*. Activity at these receptors is potentially associated with various anticholinergic, sedative, and cardiovascular effects seen with other psychotropic drugs. In preclinical rodent models, venlafaxine demonstrated activity predictive of antidepressant and anxiolytic actions, and cognitive enhancing properties.

5.1. Pharmacodynamic Properties

Depression

The efficacy of venlafaxine extended-release capsules as a treatment for depression, including depression with associated anxiety, was established in two placebo-controlled, short-term studies. Populations in both trials consisted of outpatients meeting DSM-III-R or DSM-IV criteria for major depression.

The first study compared extended-release venlafaxine 75 to 150 mg/day, immediate-release venlafaxine 75 to 150 mg/day, and placebo for 12 weeks. Extended-release venlafaxine showed significant advantage over placebo starting at Week 2 of treatment on the Hamilton Rating Scale for Depression (HAM-D) Score and HAM-D Depressed Mood Item, at Week 3 on the Montgomery-Asberg Depression Rating Scale (MADRS) total, and at Week 4 on the Clinical Global Impressions (CGI) Severity of Illness Scale. All advantages were maintained through the end of treatment. Extended-release venlafaxine also showed significant advantage over immediate-release venlafaxine at Weeks 8 and 12 on the HAM-D total and CGI Severity of Illness Scale and at Week 12 for all efficacy variables.

The second study compared treatment with extended-release venlafaxine 75 to 225 mg/day and placebo for up to 8 weeks. Sustained statistical improvement over placebo was seen beginning at Week 2 for the CGI Severity of Illness Scale, beginning at Week 4 for the HAM-D total and MADRS total, and beginning at Week 3 for the HAM-D Depressed Mood Item.

Generalized Anxiety Disorder

The efficacy of venlafaxine extended-release capsules as a treatment for GAD was established in two short-term (8-week), placebo-controlled, fixed-dose studies; one long-term (6-month), placebo-controlled, fixed-dose study; and one long-term (6-month), placebo-controlled, flexible-dose study in outpatients meeting DSM-IV criteria for GAD.

One short-term study evaluating extended-release venlafaxine doses of 75, 150, and 225 mg/day, and placebo showed that the 225 mg/day dose was more effective than placebo on the Hamilton Rating Scale for Anxiety (HAM-A) total score, both the HAM-A anxiety and tension items, and the CGI scale. While there was also evidence for superiority over placebo for the 75 and 150 mg/day doses, these doses were not as consistently effective as the highest dose.

A second short-term study evaluating extended-release venlafaxine doses of 75 and 150 mg/day, and placebo showed that both doses were more effective than placebo on some of these same outcomes; however, the 75 mg/day dose was more consistently effective than the 150 mg/day dose.

Two long-term (6-month) studies, one with extended-release venlafaxine doses of 37.5, 75, and 150 mg/day and the other evaluating doses of 75 to 225 mg/day, showed that doses of 75 mg or higher were more effective than placebo on the HAM-A total, both the HAM-A anxiety and tension items, and the CGI scale after short-term (Week 8) and long-term (Month 6) treatment.

Social Anxiety Disorder (Social Phobia)

The efficacy of Efexor XR capsules as a treatment for Social Anxiety Disorder (also known as Social Phobia) was established in two double-blind, parallel group, 12-week, multicenter, placebo-controlled, flexible-dose studies in adult outpatients meeting DSM-IV criteria for Social Anxiety

Disorder. Patients received doses in a range of 75 to 225 mg/day. Efficacy was assessed with the Liebowitz Social Anxiety Scale (LSAS). In these two trials, Efexor XR was significantly more effective than placebo on change from baseline to endpoint on the LSAS total score.

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.

Panic Disorder

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

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

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

In a longer-term study, adult outpatients meeting DSM-IV criteria for panic disorder who had responded during a 12-week open phase with 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.

Cardiac Electrophysiology

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

5.2. Pharmacokinetic Properties

At least 92% of a single oral dose of venlafaxine is absorbed. After administration of Efexor XR, the peak plasma concentration of venlafaxine and ODV are attained within 6.0 ± 1.5 and 8.8 ± 2.2 hours, respectively. The rate of absorption of venlafaxine from the Efexor XR capsules is slower than its rate of elimination. Therefore, the apparent elimination half-life of venlafaxine following administration of Efexor XR capsules (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 daily dose of venlafaxine were administered as either the immediate-release tablet, or the extended release capsule, 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 Efexor immediate-release tablet.

Venlafaxine undergoes extensive first-pass metabolism in the liver, primarily by CYP2D6 to the major metabolite ODV. Venlafaxine is also metabolized to N-desmethylvenlafaxine, catalysed by CYP3A3/4, and other minor metabolites.

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 ODV, conjugated ODV, or other minor metabolites. Administration of Efexor XR with food has no effect on the absorption of venlafaxine, or on the subsequent formation of ODV. Subject age and sex do not significantly affect the pharmacokinetics of venlafaxine. No accumulation of venlafaxine or ODV has been observed during chronic administration in healthy subjects.

Patients with Hepatic Impairment

The pharmacokinetic disposition of venlafaxine and ODV are significantly altered in some patients with compensated hepatic cirrhosis (moderate hepatic impairment) following oral administration of single-dose venlafaxine. In patients with hepatic impairment, mean plasma clearance of venlafaxine and ODV are reduced by approximately 30% to 33% and mean elimination half-lives are prolonged by 2-fold or more compared to normal subjects.

In a second study, venlafaxine was administered orally and intravenously in normal subjects (n = 21), and in Child-Pugh A (n = 8) and Child-Pugh B (n = 11) subjects, mildly and moderately hepatically impaired, respectively. Oral bioavailability approximately doubled in patients with hepatic impairment compared to normal subjects. In patients with hepatic impairment, venlafaxine oral elimination half-life was approximately twice as long and oral clearance was reduced by more than half compared to normal subjects. In patients with hepatic impairment, ODV oral elimination half-life was prolonged by about 40% while oral clearance for ODV was similar to that for normal subjects. A large degree of intersubject variability was noted.

Patients with Renal Impairment

Venlafaxine and ODV elimination half-lives increase with the degree of impairment in renal function. Elimination half-life increased by approximately 1.5-fold in patients with moderate renal impairment and by approximately 2.5-fold and 3-fold in patients with end-stage renal disease.

Age and Gender Studies

A population pharmacokinetic analysis of 404 immediate-release venlafaxine-treated patients from two studies involving both twice daily and three times daily regimens showed that dose-normalized trough plasma levels of either venlafaxine or ODV were unaltered by age or gender differences.

5.3. Preclinical Safety Data

Carcinogenicity

Venlafaxine was given by oral gavage to mice for 18 months at doses up to 120 mg/kg per day, which was 1.7 times the maximum recommended human dose, on a mg/m^2 basis. Venlafaxine was also given to rats by oral gavage for 24 months at doses up to 120 mg/kg per day. In rats receiving the 120 mg/kg dose, plasma concentrations of venlafaxine at necropsy were 6 times (female rats) and 1 times (male rats) the plasma concentrations of patients receiving the maximum recommended human dose. Plasma levels of ODV were lower in rats than in patients receiving the maximum recommended dose. Tumors were not increased by venlafaxine treatment in mice or rats.

Studies with venlafaxine in rats and mice revealed no evidence of carcinogenesis. Venlafaxine was not mutagenic in a wide range of *in vitro* and *in vivo* tests.

Mutagenicity

Venlafaxine and ODV were not mutagenic in the Ames reverse mutation assay in *Salmonella* bacteria or the Chinese hamster ovary/hypoxanthine guanine phosphoribosyl transferase (HGPRT) mammalian cell forward gene mutation assay. Venlafaxine was also not mutagenic or clastogenic in the *in vitro* BALB/c-3T3 mouse cell transformation assay, the sister chromatid exchange assay in cultured Chinese hamster ovary cells, or in the *in vivo* chromosomal aberration assay in rat bone marrow. O-desmethylvenlafaxine was not clastogenic in the *in vitro* Chinese hamster ovary cell chromosomal aberration assay, or in the *in vivo* chromosomal aberration assay in rat bone marrow.

Impairment of Fertility

Reproduction and fertility studies in rats showed no effect on male or female fertility at oral doses of up to 8 times the maximum recommended human daily dose, on a mg/kg basis, or of up to 2 times, on a mg/m2 basis.

Reduced fertility was observed in a study in which both male and female rats were exposed to the major metabolite of venlafaxine (ODV). This ODV 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.

Teratogenicity

Venlafaxine did not cause malformations in offspring of rats or rabbits given doses up to 11 times (rat) or 12 times (rabbit) the human dose of 375 mg/day of venlafaxine on a mg/kg basis, or 2.5 times (rat) and 4 times (rabbit) the human dose of 375 mg/day of venlafaxine, on a mg/m2 basis.

Other Information

The extended-release 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.

6. PHARMACEUTICAL PARTICULARS

6.1. List of Excipients

Microcrystalline cellulose, ethyl cellulose, hydroxypropylmethylcellulose, gelatin, red and yellow iron oxides (E172), titanium dioxide (E171) and printing ink # 75 mg capsules contain colorant red iron oxide (E172).

6.2. Incompatibilities

None known

6.3. Shelf Life

3 years

6.4. Special Precautions for Storage

Store below 25°C.

6.5. Nature and Contents of Container

PVC/ACLAR/aluminum foil blister strips in an outer carton: 28 capsules 75 mg

6.6. Instructions for Use/Handling

Not applicable

KEEP ALL MEDICAMENTS OUT OF REACH OF CHILDREN

Reg. No.
Efexor XR 75 mg:
Box, 2 blister @ 14 capsules: DKI2263200103A1

HARUS DENGAN RESEP DOKTER

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