**SCHEDULING STATUS**

S5

## 1. NAME OF THE MEDICINE

Venlafaxine XR 37,5 Adco, 37,5 mg, extended-release capsules
Venlafaxine XR 75 Adco, 75 mg, extended-release capsules
Venlafaxine XR 150 Adco, 150 mg, extended-release capsules
Venlafaxine XR 225 Adco, 225 mg, extended-release capsules

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each extended-release capsule contains venlafaxine hydrochloride equivalent to 37,5 mg, 75 mg, 150 mg or 225 mg venlafaxine.
Venlafaxine XR Adco is sugar free.

*Excipients with known effect:*
Each 150 mg extended-release capsule contains 0,20 mg of Allura Red AC (E129) and 0,40 mg of Sunset Yellow FCF (E110).
Each 225 mg extended-release capsule contains 0,02 mg of Carmoisine (E122).

For the full list of excipients, refer to section 6.1.

## 3. PHARMACEUTICAL FORM

Extended-release capsules.
Venlafaxine XR 37,5 Adco: Light grey opaque / peach opaque size “3” hard gelatine capsules having thick and thin radial circular bands on the body in red ink and thick and thin radial circular bands on the cap in red ink, filled with white to off white, round, biconvex, film-coated mini tablets.
Venlafaxine XR 75 Adco: Peach opaque / peach opaque size “1” hard gelatine capsules having thick and thin radial circular bands on the body in red ink and thick and thin radial circular bands on the cap in red ink, filled with white to off white, round, biconvex, film-coated mini tablets.
Venlafaxine XR 150 Adco: Dark orange / dark orange opaque size “0” hard gelatine capsules having thick and thin radial circular bands on the body in white ink and thick and thin radial circular bands on the cap in white ink, filled with white to off white, round, biconvex, film-coated mini tablets.

Venlafaxine XR 225 Adco: Pink opaque / pink opaque, size “00” hard gelatine capsules having thick and thin radial circular bands on the body in blue ink and thick and thin radial circular band on the cap in blue ink filled with mini tablets.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Venlafaxine XR Adco is indicated for the treatment of depression, including depression with associated anxiety.

Venlafaxine XR Adco 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, Venlafaxine XR Adco may be used to prevent recurrence. Safety and efficacy beyond one year have not been demonstrated. When Venlafaxine XR Adco is used for long-term it should periodically be re-evaluated for the usefulness of the product in the individual patient.

Venlafaxine XR Adco is indicated for the treatment of generalised anxiety disorder and for the treatment of Social Anxiety Disorder. The effectiveness of Venlafaxine XR Adco 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 Venlafaxine XR Adco 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.

Venlafaxine XR Adco 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 are eliminated and may be seen in stools.

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

**Special populations**

*Elderly*

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

*Renal impairment*

Patients with renal impairment should receive lower doses of Venlafaxine XR Adco.

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

The total daily dose of Venlafaxine XR Adco should be reduced by 50 % in haemodialysis patients. Because of individual variability in clearance in these patients, individualisation of dosage may be desirable.

*Hepatic impairment*

The total daily dose of Venlafaxine XR Adco 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 Venlafaxine XR Adco 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.

**Paediatric population**

Not for use in children under 18 years (see section 4.3).

**Maintenance, continuation and extended treatment**

The need for long-term therapy with Venlafaxine XR Adco 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 Venlafaxine XR Adco**

Dose tapering is recommended whenever possible when discontinuing Venlafaxine XR Adco therapy (see sections 4.4 & 4.8). Tapering over at least a two-week period is recommended if Venlafaxine XR Adco 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 one-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 Venlafaxine XR Adco (see section 4.4 & 4.8).

**Method of administration**

It is recommended that Venlafaxine XR Adco 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**

Venlafaxine XR Adco is contraindicated in:

- Patients with a known hypersensitivity to venlafaxine or to any of the ingredients listed in section 6.1.
- Patients concomitantly taking monoamine oxidase inhibitors (MAOI's).
- Venlafaxine XR Adco must not be initiated for at least 14 days after discontinuation of treatment with a MAOI. Venlafaxine XR Adco 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 Venlafaxine XR Adco therapy is initiated soon after discontinuation of a MAOI and when a MAOI is initiated soon after discontinuation of Venlafaxine XR Adco. 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 section 4.4).
- Pregnancy and lactation (see section 4.6).

**4.4 Special warnings and precautions for use**

*Suicide/suicidal thoughts or clinical worsening*

Patients with major depressive disorder, both adults and children, may experience worsening of their depression and or the emergence of suicidal ideation and behaviour, whether or not they are taking antidepressant medicines. This risk may persist until significant remission occurs. A casual role, however, for antidepressant medicine in inducing such behaviour has not been established. Patients being treated with Venlafaxine XR Adco 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 disorders 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 Venlafaxine XR Adco, 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, Venlafaxine XR Adco should be tapered (see section 4.2).

Patients with a history of suicide-related events, or those exhibiting a significant degree of suicidal ideation prior to commencement of treatment, are known to be at greater risk of suicidal thoughts or suicide attempts and should receive careful monitoring during treatment. A meta-analysis of placebo-controlled clinical trials of antidepressant medicines in adult patients with psychiatric disorders showed an increased risk of suicidal behaviour with antidepressants compared to placebo in patients less than 25 years old.

Close supervision of patients, and in particular those at high risk, should accompany medicine therapy, especially in early treatment and following dose changes. Patients (and caregivers of patients) 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.

*Serotonin syndrome*

Serotonin syndrome, a potentially life-threatening condition may occur with Venlafaxine XR Adco treatment, particularly with concomitant use of other medicines that may affect the serotonergic neurotransmitter system (including triptans, SSRIs, SNRIs, amphetamines, lithium, sibutramine, St. John's Wort [Hypericum perforatum], 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).
Serotonin syndrome symptoms may include mental status changes (e.g., agitation, hallucinations, coma), autonomic instability (e.g., tachycardia, labile blood pressure, hyperthermia),

neuromuscular aberrations (e.g., hyperreflexia, incoordination) and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhoea). Serotonin syndrome in its most severe form, can resemble Neuroleptic Malignant Syndrome (NMS), which includes hyperthermia, muscle rigidity, autonomic instability with possible rapid fluctuation of vital signs and mental status changes.

If concomitant treatment with Venlafaxine XR Adco and other medicines 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 XR Adco with serotonin precursors (such as tryptophan supplements) is not recommended.

*Narrow-angle glaucoma*
Mydriasis may occur in association with Venlafaxine XR Adco. It is recommended that patients with raised intraocular pressure or patients at risk for acute narrow-angle glaucoma (angle-closure glaucoma) be closely monitored.

*Blood pressure*
Dose-related increases in blood pressure have been frequently reported with venlafaxine. In some cases, severely elevated blood pressure requiring immediate treatment has been reported in post-marketing experience. All patients should be carefully screened for high blood pressure and pre-existing hypertension should be controlled before initiation of treatment. Blood pressure should be reviewed periodically, after initiation of treatment and after dose increases.
Caution should be exercised in patients whose underlying conditions might be compromised by increases in blood pressure, e.g., those with impaired cardiac function.

*Heart rate*
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.

*Cardiac disease and risk of dysrhythmia*
Venlafaxine XR Adco 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.

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 venlafaxine, 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 Venlafaxine XR Adco to patients at high risk of serious cardiac dysrhythmias or QTc prolongation (see section 5.1).

*Convulsions*

Convulsions may occur with Venlafaxine XR Adco therapy. Venlafaxine XR Adco should be introduced with caution in patients with a history of convulsions and concerned patients should be closely monitored. Treatment should be discontinued in any patient who develops seizures.

*Hyponatraemia*

Cases of hyponatraemia and/or the Syndrome of Inappropriate Antidiuretic Hormone (SIADH) secretion may occur with Venlafaxine XR Adco. This has most frequently been reported 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 reduced platelet function. Bleeding events related to SSRI and SNRI use have ranged from ecchymoses, hematomas, epistaxis, and petechiae to gastrointestinal and life-threatening haemorrhages. The risk of haemorrhage may be increased in patients taking Venlafaxine XR Adco. As with other serotonin-reuptake inhibitors, Venlafaxine XR Adco should be used cautiously in patients predisposed to bleeding, including patients on anticoagulants and platelet inhibitors.

*Postpartum haemorrhage*

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

*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.

*Allergic phenomenon*

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 Venlafaxine XR Adco therapy in combination with weight loss

medicines, including phentermine, have not been established. Co-administration of Venlafaxine XR Adco and weight loss medicines is not recommended. Venlafaxine XR Adco is not indicated for weight loss alone or in combination with other products.

*Mania/hypomania*

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

*Aggression*

Aggression may occur in a small number of patients who have received antidepressants, including Venlafaxine XR Adco. This has been reported under initiation, dose changes and discontinuation of treatment.

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

*Discontinuation of treatment*

Withdrawal symptoms, when treatment is discontinued, are common, particularly if discontinuation is abrupt (see section 4.8). In clinical trials, adverse events seen on treatment discontinuation (tapering and post-tapering) occurred in approximately 31 % of patients treated with venlafaxine and 17 % of patients taking placebo.

The risk of withdrawal symptoms may be dependent on several factors, including the duration and dose of therapy and the rate of dose reduction. Dizziness, sensory disturbances (including paraesthesia), sleep disturbances (including insomnia and intense dreams), agitation or anxiety, nausea and/or vomiting, tremor and headache are the most frequently reported reactions. Generally, these symptoms are mild to moderate; however, in some patients they may be severe in intensity. They usually occur within the first few days of discontinuing treatment, but there have been less frequent reports of such symptoms in patients who have inadvertently missed a dose. Generally, these symptoms are self-limiting and usually resolve within 2 weeks, though in some individuals they may be extended (2 to 3 months or more). It is therefore advised that Venlafaxine XR Adco should be gradually tapered when discontinuing treatment over a period of several weeks or months, according to the patient's needs (see section 4.2).

*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.

*Akathisia/psychomotor restlessness*

The use of venlafaxine has been associated with the development of akathisia, characterised by a subjectively unpleasant or distressing restlessness and need to move often accompanied by an inability to sit or stand still. This is most likely to occur within the first few weeks of treatment. In patients who develop these symptoms, increasing the dose may be detrimental.

*Dry mouth*

Dry mouth is reported in 10 % of patients treated with venlafaxine. This may increase the risk of caries, and patients should be advised upon the importance of dental hygiene.

*Diabetes*

In patients with diabetes, treatment with an SSRI or Venlafaxine XR Adco 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 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 XR Adco therapy. Confirmatory tests, such as gas chromatography/mass spectrometry, will distinguish venlafaxine from PCP and amphetamine.

*Colourants*

Venlafaxine XR 150 Adco contains Allura Red AC (E129) and Sunset Yellow FCF (E110), which may cause allergic reactions.

Venlafaxine XR 225 Adco contains Carmoisine (E122), which may cause allergic reactions.

**Paediatric population**

Venlafaxine XR Adco should not be used in the treatment of children and adolescents under the age of 18 years. Suicide-related behaviours (suicide attempt and suicidal thoughts) and hostility (predominantly aggression, oppositional behaviour and anger) were more frequently observed in clinical trials among children and adolescents treated with antidepressants compared to those treated with placebo.

**4.5 Interaction with other medicines and other forms of interaction**

***Monoamine Oxidase Inhibitors (MAOI)***

*Irreversible non-selective MAOIs*

Venlafaxine XR Adco must not be used in combination with irreversible non-selective MAOIs. Venlafaxine XR Adco must not be initiated for at least 14 days after discontinuation of treatment with an irreversible non-selective MAOI. Venlafaxine XR Adco must be discontinued for at least 7 days before starting treatment with an irreversible non-selective MAOI (see sections 4.3 and 4.4).

*Reversible, selective MAO- inhibitor (moclobemide)*

Due to the risk of serotonin syndrome, the combination of Venlafaxine XR Adco with a reversible and selective MAOI, such as moclobemide, is not recommended. Following treatment with a reversible MAO-inhibitor, a shorter withdrawal period than 14 days may be used before initiation of Venlafaxine XR Adco treatment. It is recommended that Venlafaxine XR Adco should be discontinued for at least 7 days before starting treatment with a reversible MAOI (see section 4.4).

*Reversible, non-selective MAOI (linezolid)*

The antibiotic linezolid is a weak reversible and non-selective MAOI and should not be given to patients treated with Venlafaxine XR Adco (see section 4.4).

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

***Serotonin syndrome***

Serotonin syndrome, a potentially life-threatening condition, may occur with Venlafaxine XR Adco treatment, particularly with concomitant use of other medicines that may affect the serotonergic neurotransmitter system (including triptans, SSRIs, SNRIs, amphetamines, lithium, sibutramine, St. John's Wort [*Hypericum perforatum*], 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 4.4).

If concomitant treatment with Venlafaxine XR Adco and an SSRI, an SNRI or a serotonin 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 XR Adco with serotonin precursors (such as tryptophan supplements) is not recommended (see section 4.4).

***CNS-active medicines***

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

***Ethanol***

Venlafaxine has been shown not to increase the impairment of mental and motor skills caused by ethanol. However, Venlafaxine XR Adco is a CNS-active medicine and patients should be advised to avoid alcohol consumption.

***Medicines that prolong the QT interval***

The risk of QTc prolongation and/or ventricular dysrhythmias (e.g., TdP) is increased with concomitant use of other medicines which prolong the QTc interval. Co-administration of such medicines should be avoided (see section 4.4).

Relevant classes include:

- class Ia and III anti-dysrhythmics (e.g. quinidine, amiodarone, sotalol, dofetilide)
- some antipsychotics (e.g. thioridazine)
- some macrolides (e.g. erythromycin)
- some antihistamines
- some quinolone antibiotics (e.g. moxifloxacin)

The above list is not exhaustive and other individual medicines known to significantly increase QT interval should be avoided.

***Effect of other medicines on venlafaxine***

*Ketoconazole (CYP3A4 inhibitor)*

A pharmacokinetic study with ketoconazole in CYP2D6 extensive (EM) and poor metabolisers (PM) resulted in higher AUC of venlafaxine and O-desmethylvenlafaxine following administration of ketoconazole. Concomitant use of CYP3A4 inhibitors (e.g., atazanavir, clarithromycin, indinavir, itraconazole, voriconazole, posaconazole, ketoconazole, nelfinavir, ritonavir, saquinavir, telithromycin) and Venlafaxine XR Adco may increase levels of venlafaxine and O-desmethylvenlafaxine. Therefore, caution is advised if a patient's therapy includes a CYP3A4 inhibitor and Venlafaxine XR Adco concomitantly.

*CYP2D6 and 3A4 inhibitors*

The concomitant use of Venlafaxine XR Adco with medicine treatment(s) that potentially inhibit

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

***Effect of Venlafaxine XR Adco on other medicines***

*Lithium*

Serotonin syndrome may occur with the concomitant use of Venlafaxine XR Adco and lithium (see section 4.4, serotonin syndrome).

*Diazepam*

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

It is unknown whether a pharmacokinetic and/or pharmacodynamic interaction with other benzodiazepines exists.

*Imipramine*

Venlafaxine did not affect the pharmacokinetics of imipramine and 2-OH-imipramine. There was a dose-dependent increase of 2-OH-desipramine AUC by 2,5 to 4,5-fold when venlafaxine 75 mg to 150 mg daily was administered. Imipramine did not affect the pharmacokinetics of venlafaxine and O-desmethylvenlafaxine. The clinical significance of this interaction is unknown. Caution should be exercised with co-administration of Venlafaxine XR Adco and imipramine.

*Haloperidol*

A pharmacokinetic study with haloperidol has shown a 42 % decrease in total oral clearance, a 70 % increase in AUC, an 88 % increase in Cmax, but no change in half-life for haloperidol. This should be taken into account in patients treated with haloperidol and Venlafaxine XR Adco concomitantly. The clinical significance of this interaction is unknown.

*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.

*Risperidone*

Venlafaxine increased the risperidone AUC by 50 % 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.

*Metoprolol*

Concomitant administration of venlafaxine and metoprolol to healthy volunteers in a pharmacokinetic interaction study for both medicines resulted in an increase of plasma concentrations of metoprolol by approximately 30 to 40 % without altering the plasma concentrations of its active metabolite, α-hydroxymetoprolol. The clinical relevance of this finding in hypertensive patients is unknown. Metoprolol did not alter the pharmacokinetic profile of venlafaxine or its active metabolite, O-desmethylvenlafaxine. Caution should be exercised with co-administration of Venlafaxine XR Adco and metoprolol.

*Indinavir*

A pharmacokinetic study with indinavir has shown a 28 % decrease in AUC and a 36 % decrease in Cmax for indinavir. Indinavir did not affect the pharmacokinetics of venlafaxine and O-desmethylvenlafaxine. The clinical significance of this interaction is unknown.

*Medicines metabolised by cytochrome P450 isoenzymes*

In vivo studies indicate that venlafaxine is a relatively weak inhibitor of CYP2D6. Venlafaxine did not inhibit CYP3A4b (alprazolam and carbamazepine), CYP1A2 (caffeine), and CYP2C9 (tolbutamide) or CYP2C19 (diazepam) *in vivo*.

*Oral contraceptives*

In post-marketing experience unintended pregnancies have been reported in subjects taking oral contraceptives while on venlafaxine. There is no clear evidence these pregnancies were a result of medicine interaction with venlafaxine. No interaction study with hormonal contraceptives has been performed.

**4.6 Fertility, pregnancy and lactation**

Venlafaxine XR Adco must not be administered to pregnant or lactating women.

Observational data indicate an increased risk (less than 2-fold) of postpartum haemorrhage following SSRIs/SNRIs exposure within the month prior to birth (see sections 4.4 & 4.8).

**Women of child-bearing potential / Contraception in males and females**

Patients should be advised to notify their doctor if they become pregnant or intend to become pregnant during treatment with Venlafaxine XR Adco.

**Pregnancy**

Venlafaxine XR Adco must not be administered to pregnant women. Safety during human pregnancy and lactation has not been established (see section 4.3).

Some neonates exposed to venlafaxine late in the third trimester have developed complications requiring tube-feeding; respirator; support or extended hospitalisation. Such complications can arise immediately upon delivery.

**Breastfeeding**

Venlafaxine and its active metabolite, O-desmethylvenlafaxine, are excreted in human milk. Therefore, mothers on treatment with Venlafaxine XR Adco should not breastfeed (see section 4.3).

**4.7 Effects on ability to drive and use machines**

Venlafaxine XR Adco causes dizziness and sedation; it may therefore impair judgment, thinking, and motor skills. Patients receiving Venlafaxine XR Adco should therefore be cautioned about their ability to drive or operate hazardous machinery.

**4.8 Undesirable effects**

**a) Summary of the safety profile**

The most frequent observed adverse reactions reported in clinical studies were nausea, dry mouth, headache and sweating (including night sweats). The occurrence of many frequently observed adverse events is dose related.

**b) Tabulated list of adverse reactions**

| System Organ Class | Frequency | Side Effect |
|---|---|---|
| **Blood and lymphatic system disorders** | *Frequency unknown* | Agranulocytosis*, aplastic anaemia*, pancytopaenia*, neutropaenia*, thrombocytopaenia* |
| **Immune system disorders** | *Frequency unknown* | Anaphylactic reaction* |
| **Endocrine disorders** | *Frequency unknown* | Inappropriate antidiuretic hormone secretion*, increased blood prolactin* |
| **Metabolism and nutrition disorders** | *Frequent* | Decreased appetite |
| | *Frequency* | Hyponatraemia*, increased appetite* |

| | | |
|---|---|---|
| | *unknown* | |
| **Psychiatric disorders** | *Frequent* | Insomnia, abnormal dreams, nervousness, decreased libido, anorgasmia |
| | *Less frequent* | Mania, hypomania, hallucination, derealisation, apathy, abnormal orgasm, apathy |
| | *Frequency unknown* | Suicidal ideation and suicidal behaviours [a], aggression [b], confusional state*, depersonalisation*, agitation*, bruxism* |
| **Nervous system disorders** | *Frequent* | Dizziness, sedation, tremor, paraesthesia, dysgeusia |
| | *Less frequent* | Syncope, myoclonus, convulsion |
| | *Frequency unknown* | Headache*[c], akathisia*, balance disorder*, abnormal coordination*, dyskinaesia*, serotonin syndrome*, neuroleptic malignant syndrome (NMS)*, dystonia*, tardive dyskinaesia* |
| **Eye disorders** | *Frequent* | Visual impairment, mydriasis, accommodation disorder, including blurred vision |
| | *Frequency unknown* | Angle-closure glaucoma* |
| **Ear and labyrinth disorders** | *Frequency unknown* | Vertigo, tinnitus* |
| **Cardiac disorders** | *Less frequent* | Ventricular fibrillation |
| | *Frequency unknown* | Tachycardia, palpitations*, Torsade de Pointes*, ventricular tachycardia*, electrocardiogram QT extended* |
| **Vascular disorders** | *Frequent* | Hypertension, hot flushes |
| | *Less frequent* | Orthostatic hypotension |
| | *Frequency unknown* | Hypotension* |
| **Respiratory, thoracic and mediastinal disorders** | *Frequent* | Yawning |
| | *Frequency unknown* | Dyspnoea*, interstitial lung disease*, pulmonary eosinophilia*, pharyngitis*, |

| | | |
|---|---|---|
| | | rhinitis* |
| **Gastrointestinal disorders** | *Frequent* | Nausea, dry mouth, constipation, vomiting |
| | *Frequency unknown* | Gastrointestinal haemorrhage*, pancreatitis*, diarrhoea*, anorexia*, dyspepsia*, eructation*, flatulence* |
| **Hepato-biliary disorders** | *Frequency unknown* | Abnormal liver function test*, hepatitis* |
| **Skin and subcutaneous tissue disorders** | *Frequent* | Rash |
| | *Less frequent* | Ecchymosis, photosensitivity reaction |
| | *Frequency unknown* | Hyperhidrosis* (including night sweats), pruritus*, urticaria*, alopecia*, angioedema*, Stevens-Johnson syndrome*, toxic epidermal necrolysis*, erythema multiforme* |
| **Musculoskeletal, connective tissue and bone disorders** | *Frequent* | Hypertonia |
| | *Frequency unknown* | Rhabdomyolysis*, myalgia* |
| **Renal and urinary disorders** | *Frequent* | Urinary hesitation, urinary retention |
| | *Frequency unknown* | Urinary incontinence*, pollakiuria* |
| **Reproductive system and breast disorders** | *Frequent* | Erectile dysfunction, ejaculation disorder |
| | *Frequency unknown* | Menorrhagia*, metrorrhagia*, postpartum haemorrhage [c]; |
| **General disorders and administration site conditions** | *Frequent* | Fatigue, asthenia, pain |
| | *Frequency unknown* | Mucosal haemorrhage*, chills* |
| **Investigations** | *Frequent* | Decreased weight, increased weight, increased blood cholesterol |
| | *Frequency unknown* | Extended bleeding time* |

* ADR identified post-marketing

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

[b] See section 4.4

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

**c) Description of selected adverse reactions**

*Discontinuation of treatment*

Discontinuation of Venlafaxine XR Adco (particularly when abrupt) commonly leads to withdrawal symptoms. Dizziness, sensory disturbances (including paraesthesia), sleep disturbances (including insomnia and intense dreams), agitation or anxiety, nausea and/or vomiting, tremor, vertigo, headache and flu syndrome are the most commonly reported reactions. Generally, these events are mild to moderate and are self-limiting; however, in some patients, they may be severe and/or extended. It is therefore advised that when Venlafaxine XR Adco treatment is no longer required, gradual discontinuation by dose tapering should be carried out (see sections 4.2 and 4.4).

**Reporting of suspected adverse reactions**

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions 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 venlafaxine 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 reported events include electrocardiographic changes (e.g., prolongation of QT interval, bundle branch block, QRS prolongation (see section 5.1), ventricular tachycardia, bradycardia, hypotension, hypoglycaemia vertigo, and deaths.

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

the 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. Administration of activated charcoal may also limit absorption of the active substance. Forced diuresis, dialysis, hemoperfusion and exchange transfusion are unlikely to be of benefit. No specific antidotes for Venlafaxine XR Adco are known.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Category A. 1.2. Psychoanaleptics (antidepressants)

Pharmacotherapeutic group: Other antidepressants - ATC code: NO6A X16.

**Mechanism of action**

The mechanism of venlafaxine's antidepressant action in humans is believed to be associated with its potentiation of neurotransmitter activity in the central nervous system. Preclinical studies have shown that venlafaxine and its major metabolite, O-desmethylvenlafaxine (ODV), are inhibitors of serotonin and noradrenaline reuptake. Venlafaxine also weakly inhibits dopamine uptake. Venlafaxine and its active metabolite reduce β-adrenergic responsiveness after both acute (single dose) and chronic administration. Venlafaxine and ODV are very similar with respect to their overall action on neurotransmitter reuptake and receptor binding.

Venlafaxine has virtually no affinity for rat brain muscarinic, cholinergic, H1-histaminergic or α1-adrenergic receptors *in vitro*. Pharmacological activity at these receptors may be related to various side effects seen with other antidepressant medicines, such as anticholinergic, sedative and cardiovascular side effects.

Venlafaxine does not possess monoamine oxidase (MAO) inhibitory activity.

*In vitro* studies revealed that venlafaxine has virtually no affinity for opiate or benzodiazepine sensitive receptors.

### 5.2 Pharmacokinetic properties

Venlafaxine is extensively metabolised, primarily to the active metabolite, O-desmethylvenlafaxine (ODV). Mean ± SD plasma half-lives of venlafaxine and ODV are 5 ± 2 hours and 11 ± 2 hours, respectively. Steady-state concentrations of venlafaxine and ODV are attained within 3 days of oral multiple-dose therapy. Venlafaxine and ODV exhibit linear kinetics over the dose range of 75 mg to 450 mg/day.

**Absorption**

At least 92 % of venlafaxine is absorbed following single oral doses of immediate-release venlafaxine. Absolute bioavailability is 40 % to 45 % due to pre-systemic metabolism. After immediate-release venlafaxine administration, the peak plasma concentrations of venlafaxine and ODV occur in 2 and 3 hours, respectively. Following the administration of venlafaxine extended-release capsules, peak plasma concentrations of venlafaxine and ODV are attained within 5,5 hours and 9 hours, respectively. When equal daily doses of venlafaxine are administered as either an immediate-release tablet or extended-release capsule, the extended-release capsule provides a slower rate of absorption, but the same extent of absorption compared with the immediate-release tablet. Food does not affect the bioavailability of venlafaxine and ODV.

**Distribution**

Venlafaxine and ODV are minimally bound at therapeutic concentrations to human plasma proteins (27 % and 30 %, respectively). The volume of distribution for venlafaxine at steady-state is 4,4 ± 1,6 L/kg following intravenous administration.

**Biotransformation**

Venlafaxine undergoes extensive hepatic metabolism. *In vitro* and *in vivo* studies indicate that venlafaxine is biotransformed to its major active metabolite, ODV, by CYP2D6. In vitro and in vivo studies indicate that venlafaxine is metabolised to a minor, less active metabolite, N-desmethylvenlafaxine, by CYP3A4. In vitro and in vivo studies indicate that venlafaxine is a weak inhibitor of CYP2D6. Venlafaxine did not inhibit CYP1A2, CYP2C9, or CYP3A4.

**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 (5 %), unconjugated ODV (29 %), conjugated ODV (26 %), or other minor inactive metabolites (27 %). Mean ± SD plasma steady-state clearances of venlafaxine and ODV are 1,3 ± 0,6 L/h/kg and 0,4 ± 0,2 L/h/kg, respectively.

**Special populations**

*Age and gender*

Subject age and gender do not significantly affect the pharmacokinetics of venlafaxine and ODV.

*CYP2D6 extensive/poor metabolisers*

Plasma concentrations of venlafaxine are higher in CYP2D6 poor metabolisers than extensive metabolisers. Because the total exposure (AUC) of venlafaxine and ODV is similar in poor and

extensive metabolisers, there is no need for different venlafaxine dosing regimens for these two groups.

*Hepatic impairment*
In Child-Pugh A (mildly hepatically impaired) and Child-Pugh B (moderately hepatically impaired) subjects, venlafaxine and ODV half-lives were extended compared to normal subjects. The oral clearance of both venlafaxine and ODV was reduced. A large degree of intersubject variability was noted. There are limited data in patients with severe hepatic impairment (see section 4.2).

*Renal impairment*
In dialysis patients, venlafaxine elimination half-life was extended by about 180 % and clearance reduced by about 57 % compared to normal subjects, while ODV elimination half-life was extended by about 142 % and clearance reduced by about 56 %. Dosage adjustment is necessary in patients with severe renal impairment and in patients that require haemodialysis (see section 4.2).

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

**Capsule contents (mini tablets):**

*Core:*
Microcrystalline cellulose
Colloidal silicon dioxide
Magnesium stearate
Povidone
Talc
*Film-coating:*
Copovidone
Ethyl cellulose

**Gelatine capsules for Venlafaxine XR 37,5 Adco:**

*Gelatine capsule shell:*
Gelatine
Iron oxide black (E172)
Iron oxide red (E172)
Iron oxide yellow (E172)
Titanium dioxide (E171)
Water, purified
*Capsule printing ink:*

Butyl alcohol
Dehydrated alcohol (E1510)
Isopropyl alcohol
Propylene glycol (E1520)
Shellac (E904)
Ammonia solution, concentrated (E527)
Iron oxide red (E172)

**Gelatine capsules for Venlafaxine XR 75 Adco:**
*Gelatine capsule shell:*
Gelatine
Iron oxide black (E172)
Iron oxide red (E172)
Titanium dioxide (E171)
Water, purified
*Capsule printing ink:*
Butyl alcohol
Dehydrated alcohol (E1510)
Isopropyl alcohol
Propylene glycol (E1520)
Shellac (E904)
Ammonia solution, concentrated (E527)
Iron oxide red (E172)

**Gelatine capsules for Venlafaxine XR 150 Adco:**
*Gelatine capsule shell:*
Gelatine
Brilliant Blue FCF (E133)
Allura Red AC (E129)
Sunset Yellow FCF (E110)
Titanium dioxide (E171)
Water, purified
*Capsule printing ink:*
Butyl alcohol
Dehydrated alcohol (E1510)
Isopropyl alcohol
Propylene glycol (E1520)

Shellac (E904)
Sodium hydroxide
Povidone
Titanium dioxide (E171)

**Gelatine capsules for Venlafaxine XR 225 Adco:**
*Gelatine capsule shell:*
Carmoisine (E122)
Gelatine
Titanium dioxide (E171)
Water, purified
*Capsule printing ink:*
Butyl alcohol
Dehydrated alcohol (E1510)
Isopropyl alcohol
Propylene glycol (E1520)
Shellac (E904)
Ammonia solution, concentrated (E527)
Indigo Carmine (E132), lake

**6.2 Incompatibilities**
Not applicable.

**6.3 Shelf life**
3 years

**6.4 Special precautions for storage**
Store at or below 25 °C. Store in original packaging until required for use.
Protect from light and moisture. Keep HDPE containers tightly closed.

**6.5 Nature and contents of container**
Venlafaxine XR Adco extended-release capsules are packed in:

- Aluminium/aluminium foil blister strips (only for the 225 mg capsules)
- Aluminium foil and white opaque PVC-Aclar film blister strips
- Aluminium foil and white opaque PVC-PVdC film blister strips
- White HDPE containers with child resistant cap, and an absorbent cotton (only for the 37,5 mg, 75 mg and 150 mg capsules)

Pack sizes: 10 or 14 capsules per blister strip in a pack of 10, 14, 28, 30 or 100 capsules in an outer carton along with professional information and/or patient information leaflet. 30, 100, 500 or 1 000 capsules per HDPE container.
Not all pack sizes may be marketed.

### 6.6 Special precautions for disposal and other handling

No special requirements.

## 7. HOLDER OF CERTIFICATE OF REGISTRATION

Adcock Ingram Limited
1 New Road, Erand Gardens
Midrand
1685
South Africa
Customer Care: 0860 ADCOCK / 232625

## 8. REGISTRATION NUMBER(S)

| | |
|---|---|
| Venlafaxine XR 37,5 Adco: | 43/1.2/0577 |
| Venlafaxine XR 75 Adco: | 43/1.2/0578 |
| Venlafaxine XR 150 Adco: | 43/1.2/0579 |
| Venlafaxine XR 225 Adco: | 52/1.2/0438 |

## 9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

| | |
|---|---|
| Venlafaxine XR 37,5 Adco: | 30 September 2011 |
| Venlafaxine XR 75 Adco: | 30 September 2011 |
| Venlafaxine XR 150 Adco: | 30 September 2011 |
| Venlafaxine XR 225 Adco: | 15 December 2020 |

## 10. DATE OF REVISION OF THE TEXT

13 May 2025