PROPOSED CLEAN PROFESSIONAL INFORMATION FOR

VENLOR XR 37,5 mg TABLET, VENLOR XR 75 mg TABLET, VENLOR XR 150 mg TABLET, VENLOR XR 225 mg TABLET AND VENLOR XR 300 mg TABLET

SCHEDULING STATUS

S5

1. NAME OF THE MEDICINE

VENLOR XR 37,5 mg TABLET, 37,5 mg, prolonged-release tablets.

VENLOR XR 75 mg TABLET, 75 mg, prolonged-release tablets.

VENLOR XR 150 mg TABLET, 150 mg, prolonged-release tablets.

VENLOR XR 225 mg TABLET, 225 mg, prolonged-release tablets.

VENLOR XR 300 mg TABLET, 300 mg, prolonged-release tablets.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

VENLOR XR 37,5 mg TABLET: Each prolonged-release tablet contains venlafaxine hydrochloride equivalent to venlafaxine 37,5 mg.

VENLOR XR 75 mg TABLET: Each prolonged-release tablet contains venlafaxine hydrochloride equivalent to venlafaxine 75 mg.

VENLOR XR 150 mg TABLET: Each prolonged-release tablet contains venlafaxine hydrochloride equivalent to venlafaxine 150 mg.

VENLOR XR 225 mg TABLET: Each prolonged-release tablet contains venlafaxine hydrochloride equivalent to venlafaxine 225 mg.

VENLOR XR 300 mg TABLET: Each prolonged-release tablet contains venlafaxine hydrochloride equivalent to venlafaxine 300 mg.

Contains sugar:

VENLOR XR TABLET (37,5 mg, 75 mg, 150 mg, 225 mg, 300 mg):

lactose monohydrate 40 % *w/w.*

VENLOR XR 37,5 mg TABLET: mannitol 5,00 mg per tablet.

VENLOR XR 75 mg TABLET: mannitol 10,00 mg per tablet.

VENLOR XR 150 mg TABLET: mannitol 20,00 mg per tablet.

VENLOR XR 225 mg TABLET: mannitol 30,00 mg per tablet.

VENLOR XR 300 mg TABLET**:** mannitol 40,00 mg per tablet.

For the full list of excipients, see **section 6.1**.

3. PHARMACEUTICAL FORM

VENLOR XR TABLET are film coated, prolonged-release tablets.

VENLOR XR 37,5 mg TABLET:	Round, biconvex, white to off white coloured tablets with a little pierce in one side.
VENLOR XR 75 mg TABLET:	Round, biconvex, white to off white coloured tablets with a little pierce in one side.
VENLOR XR 150 mg TABLET:	Round, biconvex, white to off white coloured tablets with a little pierce in one side.
VENLOR XR 225 mg TABLET:	Round, biconvex, white to off white coloured tablets with a little pierce in one side.
VENLOR XR 300 mg TABLET:	Round, biconvex, white to off white coloured tablets with a little pierce in one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

VENLOR XR TABLET is indicated for the treatment of depression, including depression with associated anxiety. VENLOR XR TABLET 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, VENLOR XR TABLET may be used to prevent

recurrence. Safety and efficacy beyond one year have not been demonstrated. When VENLOR XR TABLET is used for long-term, it should periodically be re-evaluated for the usefulness of the product in individual patients.

VENLOR XR TABLET is also indicated for the treatment of generalised anxiety disorder and for the treatment of Social Anxiety Disorder. The effectiveness of VENLOR XR TABLET 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 of VENLOR XR TABLET 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.

VENLOR XR TABLET should be administered once daily, at approximately the same time either in the morning or in the evening.

Maintenance, continuation and extended treatment

The need for long-term therapy with VENLOR XR TABLET must be periodically re-assessed.

Whether the dose of antidepressant needed to induce remission is identical to the dose needed to maintain and/or sustain euthymia is unknown.

Discontinuing VENLOR XR TABLET

Dose tapering is recommended whenever possible when discontinuing VENLOR XR TABLET therapy (see **section 4.4**). Tapering over at least a two-week period is recommended if VENLOR XR TABLET has been used for more than 6 weeks. Tapering can be achieved by reducing the daily dose by 75 mg at 1-week intervals**.** The period required for tapering may depend on the dose,

duration of therapy and the individual patient. Patients should be advised to consult their doctor before abruptly discontinuing VENLOR XR TABLET (see **section 4.4**).

Special populations

Patients with renal impairment

Patients with renal impairment should receive lower doses of VENLOR XR TABLET.

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

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

Patients with hepatic impairment

The total daily dose of VENLOR XR TABLET 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 VENLOR XR TABLET and a further reduction should be considered. Since there is a variability in clearance between patients with hepatic impairment, individualisation of dosing, including further dose reductions (> 50 %), may be desirable in some patients.

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

Elderly patients

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

Paediatric population

VENLOR XR TABLET is contraindicated in children under 18 years of age (see **section 4.3**).

Method of administration

It is recommended that VENLOR XR TABLET be taken with food. Each tablet should be swallowed whole with fluid. Do not divide, crush, chew or place the tablet in water, as the coating is intended to ensure prolonged release.

VENLOR XR TABLET keeps its shape during the whole digestion releasing the active ingredient and is eliminated intact in the faeces.

4.3 Contraindications

VENLOR XR TABLET is contraindicated in:

- patients with known hypersensitivity to venlafaxine hydrochloride or to any of the excipients of VENLOR XR TABLET (see **section 6.1**)
- patients taking monoamine oxidase inhibitors (MAOIs)
- patients who have discontinued treatment with a MAOI in less than 14 days (see **section 4.5**)
- children under 18 years of age (see **section 4.4**)
- pregnancy and breastfeeding (see **section 4.6**).

VENLOR XR TABLET must be discontinued for at least 7 days before starting treatment with a MAOI. Severe adverse reactions have been reported when venlafaxine therapy is initiated soon after discontinuation of an MAOI and when an MAOI is initiated soon after discontinuation of VENLOR XR TABLET.

4.4 Special warnings and precautions for use

Suicide/suicidal thoughts or clinical worsening

All patients treated with VENLOR XR TABLET should be monitored appropriately and observed closely for clinical worsening and suicidality. Patients, their families, and their caregivers should be encouraged to be alert to the emergence of anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restless), hypomania, mania, other unusual changes in behaviour, worsening of depression, and suicidal ideation,

especially when initiating therapy or during any change in dose or dosage regimen. The risk of suicide attempt must be considered especially in depressed patients, and the smallest quantity of medicine, consistent with good patient management, should be provided to reduce the risk of overdose. Risk assessment for suicide should be performed regularly. Suicide is a known risk of depression and certain other psychiatric disorders, and these disorders themselves are strong predictors of suicide. Studies showed that antidepressant medicines (SSRIs and others) increase the risk of suicidality in children, adolescents and young adults (ages 18 to 24 years) with major depression and other psychiatric disorders (see **section 4.3**).

Patients with major depressive disorder may experience worsening of their depression and/or emergence of suicidal ideation and behaviour, whether or not they are taking antidepressant medicines. This risk may persist until significant remission occurs. A causal role, however, for antidepressant medicines in inducing such behaviour has not been established. Patients being treated with VENLOR XR TABLET should, nevertheless, be observed closely for clinical worsening and suicidality, especially at the beginning of a course of therapy, or at any time of dose changes, either increases or decreases.
Because of the possibility of co-morbidity between major depressive disorder and other psychiatric and non-psychiatric disorders, the same precautions observed when treating patients with major depressive disorder should be observed when treating patients with other psychiatric and non-psychiatric disorders.

The following symptoms have been reported in patients being treated with antidepressants for major depressive disorder as well as for other indications, both psychiatric and non-psychiatric: anxiety, agitation, panic attacks, insomnia, irritability, hostility (aggressiveness, impulsivity, akathisia, hypomania, and mania). Although a causal link between the emergence of suicidal impulses has not been established, consideration should be given to changing the therapeutic regimen, including possibly discontinuing VENLOR XR TABLET, 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, VENLOR XR TABLET should be tapered (see **section 4.2**).

Serotonin syndrome

Serotonin syndrome, a potentially life-threatening condition, may occur with VENLOR XR TABLET treatment, particularly with concomitant use of other medicines that may affect the serotonergic neurotransmitter systems (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 **section 4.3** and **section 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 NMS, which includes hyperthermia, muscle rigidity, autonomic instability with possible rapid fluctuation of vital signs and mental status changes.

If concomitant treatment with venlafaxine 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 with serotonin precursors (such as tryptophan supplements) is not recommended.

Narrow-angle glaucoma

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

Cardiac disease and risk of dysrhythmia

VENLOR XR TABLET should not be used in patients with an identified very high risk of serious ventricular dysrhythmia or uncontrolled hypertension. VENLOR XR TABLET has not been evaluated in patients with a recent history of myocardial infarction or unstable heart disease. It should therefore be used with caution in these patients.

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 to patients at high risk of serious cardiac dysrhythmia or QTc prolongation.

Blood pressure

Dose-related increases in blood pressure have been reported in some patients treated with VENLOR XR TABLET. Regular blood pressure monitoring is recommended for patients receiving VENLOR XR TABLET. Pre-existing hypertension should be controlled before treatment with VENLOR XR TABLET. Caution should be exercised in patients whose underlying conditions might be compromised by increases in blood pressure.

Heart rate

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

Convulsions

Convulsions may occur with VENLOR XR TABLET therapy. VENLOR XR TABLET should be introduced with care in patients with a history of convulsions. VENLOR XR TABLET should be discontinued in any patient who develops seizures.

Mania/hypomania

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

Aggression

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

Hyponatraemia

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

Abnormal bleeding

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

VENLOR XR TABLET may be associated with an increased risk of blood loss during surgery.

Postpartum haemorrhage

Serotonin and Norepinephrine Reuptake Inhibitors (SNRIs), such as VENLOR XR TABLET, may increase the risk of postpartum haemorrhage (see **section 4.6** and **4.8**)**.**

Allergic reactions

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

Serum cholesterol

Increases in serum cholesterol may occur in patients treated with VENLOR XR TABLET. Measurement of serum cholesterol levels should be considered during long-term treatment.

Renal and Hepatic impairment

VENLOR XR TABLET should be used with caution in patients with renal impairment, moderate to severe hepatic impairment or cirrhosis of the liver. Dosage adjustment may be necessary (see **section 4.2**).

Sexual dysfunction

Serotonin-norepinephrine reuptake inhibitors (SNRIs) such as VENLOR XR TABLET 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 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 VENLOR XR TABLET therapy. Confirmatory tests, such as gas chromatography/mass spectrometry, will distinguish venlafaxine from PCP and amphetamine.

Discontinuation of treatment

Discontinuation effects are well-known to occur. It is therefore recommended that VENLOR XR TABLET be tapered gradually, and the patient be monitored (see **section 4.2**). Suicide/suicidal thoughts and aggression have been observed in patients during changes in venlafaxine dosing regimen, including during discontinuation.

The following symptoms have been reported in association with abrupt discontinuation or dose reduction, or tapering of VENLOR XR TABLET treatment: Hypomania, anxiety, agitation, nervousness, confusion, insomnia or other sleep disturbances, fatigue, somnolence, paraesthesia, dizziness, convulsion, vertigo, headache, flu-like symptoms, tinnitus, impaired coordination and balance, tremor, sweating, dry mouth, anorexia, diarrhoea, nausea and

vomiting. 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 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 prolonged (2 to 3 months or more). It is therefore advised that venlafaxine 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**). In some patients, discontinuation could take months or longer.

Use in elderly patients

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

Abuse and dependence

Clinical studies did not show evidence of drug-seeking behaviour, development of tolerance, or dose escalation over time. VENLOR XR TABLET 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 CNS stimulant activity in rodents. In primate medicine discrimination studies, venlafaxine showed no significant stimulant or depressant abuse liability.

Mannitol and lactose

VENLOR XR TABLET contains mannitol which may have a mild laxative effect.

VENLOR XR TABLET contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take VENLOR XR TABLET.

Paediatric population

Safety and efficacy in individuals below 18 years of age have not been established. In clinical trials in Major Depressive Disorder, there were increased reports of hostility and suicide-related adverse events such as suicidal ideation and self-harm (see **section 4.3**).

4.5 Interaction with other medicines and other forms of interaction

Monoamine oxidase inhibitors

Severe adverse reactions have been reported in patients who have recently been discontinued from a MAOI and started on VENLOR XR TABLET or have recently had VENLOR XR TABLET therapy discontinued prior to initiation of a MAOI (see **section 4.3**). These reactions have included tremor, myoclonus, diaphoresis, nausea, vomiting, flushing, dizziness, hyperthermia with features resembling neuroleptic malignant syndrome, seizures, and death.

CNS active medicines

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

Serotonin syndrome

Serotonin syndrome, a potentially life threatening condition which may occur with VENLOR XR TABLET treatment, particularly with concomitant use of other medicines that may affect the serotonergic neurotransmitter system (including triptans, SSRIs, other SNRIs, lithium, sibutramine, tramadol, or St. John's Wort [*Hypericum perforatum*]), with medicines which impair metabolism of serotonin (such as MAOIs; including linezolid [an antibiotic which is a reversible non-selective MAOI], (see **section 4.3**), or with serotonin precursors (such as tryptophan supplements). Serotonin syndrome symptoms may include mental status changes, autonomic instability, neuromuscular aberrations and/or gastrointestinal symptoms (see **section 4.3** and **section 4.4**).

If concomitant treatment of VENLOR XR TABLET with an SSRI, an SNRI or a 5-hydroxytryptamine receptor agonist (triptan) is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases. The concomitant use of VENLOR XR TABLET with serotonin precursors (such as tryptophan supplements) is not recommended (see **section 4.4**).

Indinavir

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

Ethanol

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

Haloperidol

A pharmacokinetic study with haloperidol has shown for haloperidol a 42 % decrease in total oral clearance, a 70 % increase in AUC, an 88 % increase in C_{max}, but no change in half-life. This should be taken into account in patients treated with haloperidol and VENLOR XR TABLET 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 or renal dysfunction this interaction may be more pronounced.

Imipramine

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

Ketoconazole

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

Concomitant use of CYP3A4 inhibitors (e.g., atazanavir, clarithromycin, indinavir, itraconazole, voriconazole, posaconazole, ketoconazole, nelfinavir, ritonavir, saquinavir, telithromycin) and venlafaxine may increase levels of venlafaxine and ODV. Therefore, caution is advised if a patient's therapy includes a CYP3A4 inhibitor and VENLOR XR TABLET concomitantly.

Metoprolol

Concomitant administration of venlafaxine (50 mg every 8 hours for 5 days) and metoprolol (100 mg every 24 hours for 5 days) to healthy volunteers in a pharmacokinetic interaction study for both medicines resulted in an increase of plasma concentrations of metoprolol by approximately 30 to 40 % without altering the plasma concentrations of its active metabolite, α-hydroxymetoprolol. Venlafaxine as in VENLOR XR TABLET 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 VENLOR XR TABLET and metoprolol.

Risperidone

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

Diazepam

Diazepam does not appear to affect the pharmacokinetics of either venlafaxine or ODV. VENLOR XR TABLET has no effects on the pharmacokinetics and pharmacodynamics of diazepam and its active metabolite, desmethyldiazepam. It is unknown whether a pharmacokinetic and/or pharmacodynamic interaction with other benzodiazepines exists.

Lithium

The steady-state pharmacokinetics of venlafaxine and ODV are not affected when lithium is co-administered. Venlafaxine as in VENLOR XR TABLET also has no effects on the pharmacokinetics of lithium.

Serotonin syndrome may occur with the concomitant use of venlafaxine and lithium (see serotonin syndrome).

Monoamine Oxidase Inhibitors (MAOI)

Irreversible non-selective MAOIs

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

Reversible, selective MAO-A inhibitor (moclobemide)

Due to the risk of serotonin syndrome, the combination of venlafaxine 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 treatment. It is recommended that venlafaxine as in VENLOR XR TABLET 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 VENLOR XR TABLET (see **section 4.4**).

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. These reactions have included tremor, myoclonus, diaphoresis, nausea, vomiting, flushing, dizziness, and hyperthermia with features resembling neuroleptic malignant syndrome, seizures, and death.

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 antiarrhythmics (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.

Medicines highly bound to plasma proteins

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

Medicines metabolised by cytochrome P450 isoenzymes

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

Potential for other medicines to affect VENLOR XR TABLET

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

CYP2D6 inhibitors

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

CYP3A4 inhibitors

Concomitant use of CYP3A4 inhibitors and VENLOR XR TABLET may increase levels of VENLOR XR TABLET and ODV. Therefore, caution is advised when combining VENLOR XR TABLET with a CYP3A4 inhibitor.

CYP2D6 and 3A4 inhibitors

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

Oral contraceptives

Unintended pregnancies have been reported in patients taking oral contraceptives while on venlafaxine. There is no clear evidence these pregnancies were a result of drug interaction with venlafaxine as in VENLOR XR TABLET. No interaction study with hormonal contraceptives has been performed.

4.6 Fertility, pregnancy, and lactation

Pregnancy

VENLOR XR TABLET must not be administered to pregnant women. Safety during human pregnancy has not been established (see **section 4.3**).

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

Observational data indicate an increased risk (less than 2-fold) of postpartum haemorrhage following SSRI/SNRI exposure within the month prior to birth (see **section 4.4** and **4.8**). Patients should be advised to notify their doctor if they become pregnant or intend to become pregnant during therapy.

Epidemiological data have suggested that the use of SSRIs in pregnancy, particularly in late pregnancy, may increase the risk of persistent pulmonary hypertension in the newborn (PPHN). Although no studies have investigated an association of PPHN to SNRI treatment, this

potential risk cannot be ruled out with VENLOR XR TABLET, taking into account the related mechanism of action (inhibition of the re-uptake of serotonin).

The following symptoms may be observed in neonates if the mother has used an SSRI/SNRI late in pregnancy: irritability, tremor, hypotonia, persistent crying, and difficulty in sucking or in sleeping. These symptoms may be due to either serotonergic effects or exposure symptoms. In the majority of cases, these complications are observed immediately or within 24 hours after partus.

Breastfeeding

Venlafaxine and ODV are excreted in human milk; therefore, mothers on treatment with VENLOR XR TABLET should not breastfeed.

Fertility

Reduced fertility was observed in a study in which both male and female rats were exposed to the major metabolite of VENLOR XR TABLET, ODV. This ODV exposure was approximately 2 to 3 times that of a human VENLOR XR TABLET dose of 225 mg/day**.** The human relevance of this finding is unknown**.**

4.7 Effects on ability to drive and use machines

VENLOR XR TABLET may impair judgement, thinking and motor skills. Therefore, patients should be cautioned about their ability to drive or operate hazardous machines. Patients (especially the elderly) should be warned of the risk of dizziness and unsteadiness due to orthostatic hypotension.

4.8 Undesirable effects

a. Summary of the safety profile

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

b. Tabulated list of adverse reactions

The following adverse effects have been classified as either being frequent, less frequent, or of an unknown frequency.

MedDRA system organ class	**Frequency**	**Side Effects**
Blood and lymphatic system disorders	*Less frequent*	Ecchymosis, haemorrhage including gastrointestinal bleeding.
	Frequency unknown	Mucous membrane bleeding*, prolonged bleeding time*, thrombocytopenia*, blood dyscrasias* (including agranulocytosis, aplastic anaemia, neutropenia, pancytopenia). *
Immune system disorders	*Frequency unknown*	Anaphylactic reaction. *
Metabolism and nutrition disorders	*Frequent*	Increased serum cholesterol (particularly with prolonged administration and possibly with higher doses), weight loss, decreased appetite.
	Less frequent	Altered taste, hyponatremia, weight gain.
Endocrine disorders	*Frequency unknown*	Syndrome of Inappropriate Antidiuretic Hormone (SIADH) secretion, increased prolactin.*

Psychiatric disorders	*Frequent*	Abnormal dreams, nervousness, insomnia, decreased libido, anxiety, agitation, depersonalisation.
	Less frequent	Apathy, hallucinations, manic reaction, activation of mania or hypomania, derealisation.
	Frequency unknown	Delirium*, abnormal thinking, aggression, amnesia, depression*, emotional lability*, confusional state*, suicidal ideation, and behaviours.
Nervous system disorders	*Frequent*	Dizziness, hypertonia, paraesthesia, tremor, headache, somnolence, sedation, akathisia, dysgeusia.
	Less frequent	Myoclonus, convulsion, dysarthria, syncope, balance disorder, abnormal co-ordination.
	Frequency unknown	Neuroleptic Malignant Syndrome (NMS) *, serotonin syndrome*, tardive dyskinesia*, hypoaesthesia*, trismus*, dyskinesia*, dystonia.*
Eye disorders	*Frequent*	Abnormality of accommodation, mydriasis, visual disturbances.
	Frequency unknown	Angle closure glaucoma. *
Ear and labyrinth disorders	*Frequent*	Tinnitus.
	Frequency unknown	Vertigo.
Cardiac disorders	*Frequent*	Palpitations, tachycardia.

	Less frequent	Dysrhythmias, electrocardiogram QT prolongation, ventricular fibrillation, ventricular tachycardia (including torsade de pointes).
	Frequency unknown	Stress cardiomyopathy* (takotsubo cardiomyopathy).*
Vascular disorders	*Frequent*	Hypertension, vasodilation (hot flushes/flashes), dose related increases in blood pressure.
	Less frequent	Orthostatic or postural hypotension, syncope.
	Frequency unknown	Hypotension.*
Respiratory, thoracic and mediastinal disorders	*Frequent*	Dyspnoea, yawning.
	Less frequent	Interstitial lung disease, pulmonary eosinophilia.
	Frequency unknown	Pharyngitis, rhinitis.
Gastrointestinal disorders	*Frequent*	Decreased appetite, constipation, nausea, vomiting, anorexia, diarrhoea, dyspepsia, abdominal pain, dry mouth.
	Less frequent	Bruxism, pancreatitis, gastrointestinal Haemorrhage (see **blood and lymphatic disorders**).
	Frequency unknown	Increased appetite*, eructation*, flatulence.*

Hepatobiliary disorders	*Less frequent*	Reversible increases in liver enzymes, hepatitis.
	Frequency unknown	Abnormal liver function test. *
Skin and subcutaneous tissue disorders	*Frequent*	Sweating, pruritus, hyperhidrosis (including night sweats), rash.
	Less frequent	Angioedema, alopecia, erythema multiforme, Stevens-Johnson syndrome, urticaria, photosensitivity reaction (see **general disorders and administrative site conditions**), toxic epidermal necrolysis, ecchymosis (see **blood and lymphatic system disorders**).
Musculoskeletal, connective tissue and bone disorders	*Frequent*	Arthralgia, hypertonia, paraesthesia, myalgia.
	Less frequent	Ataxia, muscle spasm, rhabdomyolysis.
Renal and urinary disorders	*Frequent*	Urinary hesitation, urinary frequency, pollakiuria, urinary retention.
	Less frequent	Urinary incontinence.
Reproductive system and breast disorders	*Frequent*	Abnormal ejaculation/orgasms (male), anorgasmia, erectile dysfunction, sexual dysfunction.
	Less frequent	Abnormal orgasm (female), galactorrhoea, menstrual changes, menorrhagia.

	Frequency unknown	Menstrual disorders associated with increased bleeding or increased irregular bleeding* (e.g. menorrhagia, metrorrhagia*), post-partum haemorrhage.*
General disorders and administrative site conditions	*Frequent*	Asthenia/fatigue, headache, pain, abdominal pain, back pain, chest pain, chills, fever.
	Frequency unknown	Photosensitivity reactions, anaphylaxis, mucosal haemorrhage*, angioedema.
Investigations	*Frequent*	Increased blood cholesterol.

*Post marketing

c. Description of selected adverse reactions

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

d. Paediatric population

Children and adolescents up to 18 years

The side effect profile of venlafaxine in children and adolescents was similar to that seen in adults. In paediatric clinical trials, there were increased reports of hostility and, especially in Major Depressive Disorders, suicide-related adverse events such as suicidal ideation and self-harm.
As with adults, decreased appetite, weight loss, increased blood pressure, and increased serum cholesterol were observed. Particularly, the following adverse reactions were observed: abdominal pain, agitation, dyspepsia, ecchymosis, epistaxis, and myalgia. (see **section 4.3** and **4.4**).

Discontinuation of treatment

Discontinuation of venlafaxine as in VENLOR XR TABLET (particularly when abrupt) commonly leads to withdrawal symptoms. Fatigue, somnolence, anorexia, palpitations, dizziness, dry mouth,

diarrhoea, sensory disturbances (including paraesthesia), sleep disturbances (including insomnia and intense dreams), agitation or anxiety, nervousness, confusion, hypomania, nausea and/or vomiting, tremor, vertigo, headache, flu syndrome, visual impairment and hypertension 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 prolonged. It is therefore advised that when venlafaxine as in VENLOR XR TABLET treatment is no longer required, gradual discontinuation by dose tapering should be carried out. However, in some patient's, severe aggression, and suicidal ideation occurred when the dose was reduced or during discontinuation (see **section 4.2** and **section 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. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) or to Cipla Medpro (Pty) Ltd. by email: drugsafetysa@cipla.com or telephone: 080 222 6662 (toll free).

4.9 Overdose

VENLOR XR TABLET overdose is reported predominantly in combination with alcohol and/or other medicines. The most frequent events in overdose include tachycardia, changes in level of consciousness (ranging from somnolence to coma), mydriasis, convulsion, and vomiting. Other events reported include electrocardiographic changes (e.g., prolongation of QT interval, bundle branch block, QRS prolongation), ventricular tachycardia, bradycardia, hypotension, hypoglycaemia**,** vertigo, and death.

VENLOR XR TABLET overdosage may be associated with an increased risk of fatal outcomes compared to that observed with SSRI antidepressant medicines, but lower than that for tricyclic antidepressants. Epidemiological studies have shown that 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 VENLOR XR TABLET should be written for the smallest quantity of medicine consistent with good patient management, in order to reduce the risk of overdose.

Management of overdose

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 VENLOR XR TABLET are known.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacological classification: A 1.2 Psychoanaleptics (antidepressants)

Pharmacotherapeutic group: Other antidepressants

ATC code: N06AX16

Mechanism of action

Studies have shown that venlafaxine and its major metabolite, ODV are inhibitors of serotonin and norepinephrine re-uptake and also weakly inhibit dopamine re-uptake. Venlafaxine and ODV reduce beta-adrenergic responsiveness after both acute (single dose) and chronic administration. Venlafaxine and its major metabolite appear to be equipotent with respect to their overall action on neurotransmitter re-uptake and receptor binding.

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

5.2 Pharmacokinetics properties

Absorption

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

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

Effects of food

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

Distribution

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

Plasma concentrations of venlafaxine and ODV generally correlate well with dose levels.

Venlafaxine and ODV are less than 35 % bound to plasma proteins (Venlafaxine and ODV are 27 % and 30 % bound to plasma proteins respectively).

Biotransformation

Venlafaxine is extensively metabolised in the liver. ODV is the major active metabolite of venlafaxine.

Elimination

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

Linearity/non-linearity

Venlafaxine and O-desmethylvenlafaxine exhibit linear kinetics over the dose range of 75 mg to 450 mg/day.

Special populations

Elderly

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

Renal impairment

In patients with moderate to severe impairment of renal function, the total clearance of both venlafaxine and ODV was reduced, and t½ was prolonged. The reduction in total clearance was most pronounced in subjects with creatinine clearance less than 30 mL/min. Dosage adjustment is recommended for these patients (see **section 4.2**).

Patients with hepatic impairment

In patients with compensated hepatic cirrhosis (mild to moderate hepatic impairment), the pharmacokinetic disposition of both venlafaxine and ODV was significantly altered.
The reduction in both the metabolism of venlafaxine and elimination of ODV resulted in significantly higher plasma concentrations of both. Dosage adjustment is recommended in these patients (see **section 4.2***)*.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

- Cellulose acetate 320S
- Cellulose acetate 398-10

- Macrogol 400
- Magnesium stearate
- Mannitol
- Microcrystalline cellulose
- Opadry® Y-30-18037 white
- Povidone K 90
- Silica colloidal anhydrous

Composition of the Opadry® Y-30-18037 white

- Hypromellose
- Lactose monohydrate
- Titanium dioxide
- Triacetin

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months (37,5 mg, 75 mg, 150 mg, and 225 mg).

24 months (300 mg).

6.4 Special precautions for storage

Store at or below 25 ºC.

Store in the original package. This medicine does not require any special temperature storage conditions.

6.5 Nature and contents of container

VENLOR XR TABLET prolonged-release tablets are packaged in blisters composed of PVC-PCTFE/Aluminium.

VENLOR XR TABLET is packed in the following pack sizes:

VENLOR XR 37,5 mg TABLET, prolonged-release tablets:
PVC-Polychlorotrifluoroethylene/Aluminium Blister: 10, 14, 20, 28, 30, 50, 56, 60, 100 and 500 (only for hospital use) prolonged-release tablets.

VENLOR XR 75 mg TABLET, prolonged-release tablets:
PVC-PCTFE/Aluminium Blister: 10, 14, 20, 28, 30, 50, 56, 60, 70, 98, 100 and 500 (only for hospital use) prolonged-release tablets.

VENLOR XR 150 mg TABLET, prolonged-release tablets:
PVC-PCTFE/Aluminium Blister: 10, 14, 20, 28, 30, 50, 56, 60, 70, 98, 100 and 500 (only for hospital use) prolonged-release tablets.

VENLOR XR 225 mg TABLET, prolonged-release tablets:
PVC-PCTFE/Aluminium Blister: 10, 14, 20, 28, 30, 50, 56, 60, 70, 98, 100 and 500 (only for hospital use) prolonged-release tablets.

VENLOR XR 300 mg TABLET, prolonged-release tablets:
PVC-PCTFE/Aluminium Blister: 10, 14, 20, 28, 30, 50, 56, 60, 70, 98, 100 and 500 (only for hospital use) prolonged-release tablets.

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

CIPLA MEDPRO (PTY) LTD.

Building 9

Parc du Cap

Mispel street

Bellville

7530

Customer Care: 080 222 6662

8. REGISTRATION NUMBERS

VENLOR XR 37,5 mg TABLET: 56/1.2/0037

VENLOR XR 75 mg TABLET: 56/1.2/0038

VENLOR XR 150 mg TABLET: 56/1.2/0039

VENLOR XR 225 mg TABLET: 56/1.2/0035

VENLOR XR 300 mg TABLET: 56/1.2/0036

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

First authorisation: 08 August 2023

Latest renewal: Not applicable.

10. DATE OF REVISION OF THE TEXT

To be allocated.