PROPOSED PROFESSIONAL INFORMATION FOR

VENLOR XR 37,5

VENLOR XR 75

VENLOR XR 150

SCHEDULING STATUS

S5

1. NAME OF THE MEDICINE

VENLOR XR 37,5; 37,5 mg, extended-release capsules

VENLOR XR 75; 75 mg, extended-release capsules

VENLOR XR 150; 150 mg, extended-release capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

VENLOR XR 37,5**:** Each extended-release capsule contains venlafaxine hydrochloride equivalent to 37,5 mg venlafaxine.

VENLOR XR 75**:** Each extended-release capsule contains venlafaxine hydrochloride equivalent to 75 mg venlafaxine.

VENLOR XR 150**:** Each extended-release capsule contains venlafaxine hydrochloride equivalent to 150 mg venlafaxine.

Contains sugar: sucrose.

VENLOR XR 37,5 mg: sucrose 50,61 mg per capsule.

VENLOR XR 75 mg: sucrose 101,21 mg per capsule.

VENLOR XR 150 mg: sucrose 202,42 mg per capsule.

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

3. PHARMACEUTICAL FORM

Extended-release capsules.

VENLOR XR 37,5: White to off-white pellets filled in hard gelatin capsule shell “size 3” with orange cap and clear transparent body.

VENLOR XR 75: White to off-white pellets filled in hard gelatin capsule shell “size 1” with yellow cap and clear transparent body**.**

VENLOR XR 150: White to off-white pellets filled in hard gelatin capsule shell “size 0” with buff cap and clear transparent body.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

VENLOR XR is indicated for the following:

- The treatment of depression, including depression with associated anxiety.
- Prevention of relapse of an episode of depression in patients that responded to an initial 6 to 8 weeks of treatment.
- Prevention of recurrence in patients responding to 6 months of relapse prevention. Clinical studies have not demonstrated the safety and efficacy of treatment beyond one year. Long-term use of VENLOR XR should be re-evaluated periodically for its usefulness in the individual patient.
- The treatment of generalised anxiety disorder.
- Treatment of social anxiety disorder. The effectiveness of VENLOR XR has not been demonstrated for longer than 12 weeks for this indication.

4.2 Posology and method of administration

Posology

The recommended daily dose for VENLOR XR is 75 mg once daily. The dose may be increased to 150 mg once daily after several weeks if further clinical improvement is required. If needed this dose can be further increased to 225 mg once daily. Intervals of 2 weeks or more, but not less than 4 days, should be allowed between dose increments. In depressed patients the dose may be increased to 375 mg once daily. The dose should then be gradually reduced, consistent with patient response and tolerance.

VENLOR XR should be taken once a day at more or less the same time, either in the mornings or at night. The active ingredient is released into the digestive system over an extended period of time.

Maintenance, continuation, and extended treatment

Periodic reassessment of the need for long-term therapy with VENLOR XR is recommended. It is unknown if the dose of antidepressant needed to induce remission is the same as the dose needed to maintain and/or sustain euthymia.

Discontinuing VENLOR XR

When discontinuation of VENLOR XR therapy is indicated, dose tapering is recommended. If venlafaxine has been used for more than 6 weeks, the tapering period should extend over at least two weeks (see **section 4.8**). The tapering period is influenced by the dose, duration of therapy and the individual patient. Patients should not discontinue VENLOR XR therapy abruptly without consulting with their doctor (see **section 4.4**).

Special populations

Patients with renal impairment

Lower doses of VENLOR XR is recommended in patients with renal impairment. In

patients with renal impairment with a glomerular filtration rate (GFR) of 10 to 70 mL/min, the total daily dose of VENLOR XR must be reduced by 25 to 50 %. In haemodialysis patients, the total daily dose of VENLOR XR must be reduced by 50 %. VENLOR XR administration must be withheld during dialysis and only given after completion thereof. Due to individual variability in clearance in these patients, individualisation of dosage may be desirable.

Patients with hepatic impairment:

In patients with mild to moderate hepatic impairment, the total daily dose of VENLOR XR must be reduced by 50 %. Caution is advised when treating patients with severe hepatic impairment. For these patients, reductions of more than 50 % may be appropriate. Individualisation of dosing, including further dose reductions (> 50 %), may be desirable in some patients since there is variability in clearance between hepatically impaired patients.

Elderly patients

No dosage adjustments of VENLOR XR are recommended solely based on age.

Paediatric population

VENLOR XR is contraindicated in children younger than 18 years (see **section 4.3**)

Method of administration

VENLOR XR should be taken with food. The capsule should be swallowed whole, with a glass of water. The capsule must not be chewed, crushed, divided or dissolved.

4.3 Contraindications

VENLOR XR is contraindicated in:

- Hypersensitivity to venlafaxine or any of the inactive ingredients of VENLOR XR (see **section 6.1**).
- Children younger than 18 years.
- Pregnancy and lactation (see **section 4.6)**
- Patients using monoamine oxidase inhibitors (MAOI's) concomitantly (see **section 4.4**) due to the risk of serotonin syndrome with symptoms such as tremor, agitation and hyperthermia.

  Initiation of VENLOR XR therapy soon after discontinuation of a MAOI and initiation of MAOI therapy soon after discontinuation of VENLOR XR have resulted in severe adverse reactions. These reactions have included nausea, vomiting, tremor, myoclonus, dizziness, diaphoresis, flushing and hyperthermia with features apparently similar to neuroleptic malignant syndrome, seizures and death. VENLOR XR therapy should not commence within 14 days of discontinuing MAOI therapy. At least 7 days should be allowed between starting MAOI therapy and discontinuing treatment with VENLOR XR (see **section 4.5**).

4.4 Special warnings and precautions for use

Suicide, suicidal thoughts or clinical worsening

All patients treated with VENLOR XR, should be monitored appropriately, and observed closely for clinical worsening and suicidality. Patients, their families, and caregivers should be encouraged to be alert to the development of the following symptoms: agitation, anxiety, insomnia, irritability, panic attacks, 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 dose regimen. The risk of suicide attempt must be considered particularly in depressed patients. To

reduce the possibility of overdose, the smallest quantity of medicine, consistent with good patient management should be provided.

Depression is associated with an increased risk of self-harm, suicidal thoughts, and suicide. Antidepressant medicines (Selective Serotonin Reuptake Inhibitors (SSRIs) and others) may increase the risk of suicidality in children, adolescents and young adults aged between 18 to 24 years, with major depression and other psychiatric disorders.

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 causal role, however, for antidepressant medicine in inducing such behaviour has not been established.

Patients being treated with VENLOR XR should, nevertheless, be observed closely for clinical worsening and suicidality, especially at the beginning of a course of therapy or at any time of dose changes, either increases or decreases.

Because of the possibility of co-morbidity between major depressive disorder and other psychiatric and non-psychiatric disorders, the same precautions observed when treating patients with major depressive 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 VENLOR XR, in patients for whom such symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms.

If the decision is made to discontinue treatment, VENLOR XR should be tapered (see **section 4.2**).

Serotonin syndrome

Serotonin syndrome, a potentially life threatening condition, may occur with concomitant use of VENLOR XR and other agents that affect the serotonergic neurotransmitter systems (including triptans, SSRIs, Serotonin and Norepinephrine Reuptake Inhibitors (SNRIs), sibutramine, lithium, St. John's Wort [*Hypericum perforatum*], fentanyl and its analogues, tramadol, tapentadol, dextromethorphan, pethidine, methadone and pentazocine), with medicinal agents 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.

Serotonin syndrome symptoms may include mental status changes (e.g., agitation, hallucinations, coma), autonomic instability (e.g., labile blood pressure, hyperthermia, and tachycardia), neuromuscular aberrations (e.g., incoordination and hyperreflexia) and/or gastrointestinal symptoms (e.g., nausea, vomiting and diarrhoea). In its most severe form, serotonin syndrome can resemble neuroleptic malignant syndrome (NMS), which includes muscle rigidity, hyperthermia, autonomic instability with possible rapid fluctuation of vital signs and mental status changes.

Careful observation of the patient is advised if concomitant treatment with VENLOR XR and other agents that may affect the serotonergic and/or dopaminergic neurotransmitter systems is clinically warranted, particularly during treatment initiation and dose increases. The concomitant use of VENLOR XR with serotonin precursors such as tryptophan supplements is not recommended.

Narrow-angle glaucoma

Mydriasis may occur in association with VENLOR XR. Patients with raised intraocular pressure or patients at risk for acute narrow-angle glaucoma (angle-closure glaucoma) must be closely monitored.

Blood pressure

In some patients, VENLOR XR treatment may result in dose-related increases in blood pressure post-marketing. Patients should be screened for high blood pressure and pre-existing hypertension should be controlled before initiation of treatment. Regular blood pressure monitoring is recommended for patients receiving VENLOR XR. Caution should be exercised in patients whose underlying conditions might be compromised by increases in blood pressure.

Heart rate

Treatment with VENLOR XR especially at higher doses, is associated with an approximate increase in mean heart rate of 4 beats/minute. Care should therefore be taken when VENLOR XR is prescribed to patients whose underlying medical conditions might be compromised by increases in heart rate (e.g. patients with hyperthyroidism, heart failure, or recent myocardial infarction).

Cardiac disease and risk of dysrhythmia

The effects of VENLOR XR in patients with a recent history of myocardial infarction or unstable heart disease have not been evaluated to any appreciable extent, 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 or TdP. The balance of risks and benefits should be considered before

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

Convulsions

Caution is advised when VENLOR XR is introduced in patients with a history of seizures. Convulsions may occur with VENLOR XR therapy. VENLOR XR should be discontinued in any patient developing a seizure.

Hyponatraemia

Hyponatraemia and/or the syndrome of inappropriate antidiuretic hormone (SIADH) secretion have been reported with VENLOR XR. These adverse reactions usually occurred in dehydrated or elderly patients or those on diuretics.

Abnormal bleeding

Medicines that inhibit serotonin uptake may lead to reduced platelet function. Bleeding events related to SSRI and SNRI use have ranged from hematomas, ecchymoses, epistaxis and petechiae to gastrointestinal and life-threatening haemorrhages. The risk of bleeding may be increased. VENLOR XR should therefore be used with care in patients predisposed to bleeding including patients on anticoagulants and platelet inhibitors.

Haemorrhage

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

Serum cholesterol

Serum cholesterol increases have been reported in patients treated for at least 3

months. During long-term treatment, serum cholesterol measurement should be considered.

Co-administration with weight loss agents

Venlafaxine treatment is frequently associated with loss of appetite. Dose-related weight loss has also been reported. Therefore, a significant decrease in body weight, especially in already underweight depressed patients, may be an unwanted effect of treatment with VENLOR XR· The safety and efficacy of VENLOR XR in combination with weight loss agents, including phentermine, have not been established. VENLOR XR is not indicated for weight loss alone or in combination with other products. Co-administration of VENLOR XR and other weight loss agents is not recommended. Weight gain is less frequently associated with VENLOR XR treatment.

Mania/hypomania

Mania/hypomania activation has been reported in patients with mood disorders. VENLOR XR should be used cautiously in patients with a history or family history of mania and bipolar disorder.

Aggression

Aggression may occur in patients who receive VENLOR XR treatment dose reduction or discontinuation. VENLOR XR should be used with caution in patients with a history of aggression.

Discontinuation of treatment

Withdrawal symptoms when treatment is discontinued occur frequently. Dizziness, sensory disturbances (including paraesthesia), sleep disturbances (including insomnia and intense dreams), agitation or anxiety, nausea and vomiting, tremor, headache,

hypomania, nervousness, confusion, somnolence, convulsion, vertigo, flu-like symptoms, tinnitus, impaired coordination and balance, sweating, dry mouth, anorexia, and diarrhoea are the most frequently reported reactions. They usually occur within the first few days of treatment discontinuation, but there have been reports of such symptoms in patients who have inadvertently missed a dose. Generally, these symptoms are self-limiting and resolve within 2 weeks. It is recommended that VENLOR XR be tapered gradually, and the patient be monitored over a period of several weeks, according to the patient's need to reduce discontinuation effects (see **section 4.2** and **4.8**).

Akathisia/psychomotor restlessness

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

Skin reactions

Should a rash, urticaria, or a related allergic phenomenon develop, the patient should notify their doctor thereof.

Renal and hepatic impairment

Care should be taken when VENLOR XR is administered to patients with moderate to severe renal impairment or cirrhosis of the liver. A lower dose or the frequency of dosing may be considered (see **section 4.2**).

Dry mouth

Dry mouth has been reported, which may increase the risk of caries. Patients should be advised upon the importance of dental hygiene.

Diabetes

Treatment with VENLOR XR in diabetic patients may alter glycaemic control. Insulin and oral antidiabetic dosage may need to be adjusted.

Laboratory test interactions

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

Use in elderly patients

The use of VENLOR XR in healthy elderly patients does not pose exceptional safety problems. Although age-related clinical circumstances, such as renal impairment, may warrant a dose reduction in the elderly, advanced age is not an indication for dosage adjustments.

Carcinogenesis, mutagenesis, impairment of fertility

Non-clinical toxicology studies have shown no evidence of carcinogenesis or mutagenesis or impairment of fertility.

Abuse and dependence

Patients taking VENLOR XR over long periods of time show no signs of drug-seeking

behaviour, development of tolerance, or dose escalation. Doctors are nevertheless advised to carefully evaluate patients for a history of drug abuse, to monitor such patients closely and screen them for signs of misuse or abuse of VENLOR XR (e.g. drug-seeking behaviour, increase in dose or development of tolerance).

Sexual dysfunction

Serotonin-norepinephrine reuptake inhibitors (SNRIs) can lead to 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.

Paediatric population

VENLOR XR should not be used in the treatment of children and adolescents under the age of 18 years as the safety and efficacy have not been established. Clinical trials in major depressive disorder show increases in hostility and suicide-related events such as suicidal ideation and self-harm (see **section 4.3**).

Sucrose

VENLOR XR contains sucrose. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

Sunset yellow

VENLOR XR contains Sunset yellow which may cause allergic reactions.

Ponceau 4R

VENLOR XR contains Ponceau 4R which may cause allergic reactions.

4.5 Interaction with other medicines and other forms of interaction

Monoamine oxidase inhibitors: (see **section 4.3** and **4.4**)

Irreversible non-selective MAOIs

VENLOR XR must not be used in combination with irreversible non-selective MAOIs. VENLOR XR must not be initiated for at least 14 days after discontinuation of treatment with an irreversible non-selective MAOI. VENLOR XR must be discontinued for at least 7 days before starting treatment with an irreversible non-selective MAOI.

Reversible, selective MAO-A inhibitor (moclobemide)

The combination of VENLOR XR with a reversible and selective MAOI, such as moclobemide, is not recommended due to the risk of serotonin syndrome. A shorter withdrawal period than 14 days following treatment with a reversible MAO-inhibitor may be used before initiation of VENLOR XR treatment. Treatment with VENLOR XR should be discontinued for at least 7 days before starting treatment with a reversible MAOI.

Reversible, non-selective MAOI (linezolid)

Patients treated with VENLOR XR should not receive the weak reversible and non-selective MAOI antibiotic, linezolid.

Recent discontinuation from a MAOI followed by initiation of VENLOR XR, or recent discontinuation from VENLOR XR, prior to initiation of MAOI may result in emergence of severe adverse reactions (see **section 4.3**)**.** These reactions include nausea, vomiting, dizziness, tremor, myoclonus, diaphoresis, flushing, hyperthermia with features resembling neuroleptic malignant syndrome, seizure and death.

CNS active medicines

Serotonin syndrome, a potentially life threatening condition, may occur with concomitant use of VENLOR XR and other agents that affect the serotonergic neurotransmitter systems (including triptans, SSRIs, SNRIs, sibutramine, lithium, St. John's Wort [*Hypericum perforatum*], fentanyl and its analogues, tramadol, tapentadol, dextromethorphan, pethidine, methadone and pentazocine), with medicinal agents 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. Serotonin syndrome symptoms may include mental status changes (e.g., agitation, hallucinations, coma), autonomic instability (e.g., labile blood pressure, hyperthermia, and tachycardia), neuromuscular aberrations (e.g., incoordination and hyperreflexia) and/or gastrointestinal symptoms (e.g., nausea, vomiting and diarrhoea). In its most severe form, serotonin syndrome can resemble NMS, which includes muscle rigidity, hyperthermia, autonomic instability with possible rapid fluctuation of vital signs and mental status changes (see **section 4.3** and **4.4**).

Careful observation of the patient is advised if concomitant treatment with VENLOR XR and other agents that may affect the serotonergic and/or dopaminergic neurotransmitter systems is clinically warranted, particularly during treatment initiation and dose increases. The concomitant use of VENLOR XR with serotonin precursors such as tryptophan supplements is not recommended.

Indinavir

When venlafaxine and indinavir are co-administered, a decrease of 28 % in the AUC and a decrease of 36 % in C_{max} for indinavir are reported. The pharmacokinetics of VENLOR XR and O-desmethylvenlafaxine is not affected by indinavir. It is unknown what the clinical significance of this interaction is.

Warfarin

VENLOR XR may result in increased anticoagulant effects in patients taking warfarin.

Ethanol

VENLOR XR does not increase the impairment of mental and motor skills caused by ethanol. However the consumption of alcohol during VENLOR XR treatment should be discouraged.

Haloperidol

Changes in the pharmacokinetics of oral haloperidol include a possible decrease of 42 % in total clearance, a 70 % increase in AUC, and an 88 % increase in the $C_{max.}$ The half-life is not affected. This should be considered in the co-administration of haloperidol and VENLOR XR.

Cimetidine

The first-pass metabolism of VENLOR XR is inhibited by cimetidine. It does not affect the formation or elimination of O-desmethylvenlafaxine, which has a much higher blood concentration. Therefore, the combined pharmacologic activity of VENLOR XR and O-desmethylvenlafaxine is not expected to increase much.

The co-administration of VENLOR XR and cimetidine does not require any dosage adjustments. The extent of the interaction between VENLOR XR and cimetidine in the elderly and in patients with hepatic dysfunction is not known. Since the interaction can potentially be more pronounced in such patients, clinical monitoring is indicated.

Risperidone

The AUC of risperidone may be increased by 50 %, but the pharmacokinetic profile of

the total active moiety (risperidone plus 9-hydroxyrisperidone) is not significantly altered by VENLOR XR.

Diazepam

The pharmacokinetics of VENLOR XR and O-desmethylvenlafaxine is seemingly not affected by diazepam. The pharmacokinetics and pharmacodynamics of diazepam and its active metabolite, desmethyldiazepam, is also not affected by VENLOR XR. Whether a pharmacokinetic and/or pharmacodynamic interaction exist with other benzodiazepines is unknown.

Lithium

Lithium does not affect the steady state pharmacokinetics of VENLOR XR and O-desmethylvenlafaxine. The pharmacokinetics of lithium is also not affected by VENLOR XR. Concomitant use of VENLOR XR and lithium may cause serotonin syndrome.

Imipramine

The pharmacokinetics of imipramine and 2-OH-imipramine is not affected by VENLOR XR. However, the AUC, C_{max} and C_{min} of desipramine is increased by about 35 % when VENLOR XR is co-administered. The pharmacokinetics of venlafaxine and O-desmethylvenlafaxine are not affected by imipramine. This should be considered when imipramine and VENLOR XR are co-administered.

Metoprolol

An increase of plasma concentrations of metoprolol by approximately 30 to 40 % without altering the plasma concentrations of its active metabolite, α-hydroxymetoprolol was found with concomitant administration of venlafaxine (50 mg every 8 hours for 5 days) and metoprolol (100 mg every 24 hours for 5 days). The

clinical relevance of this finding in hypertensive patients is unknown. Metoprolol does not alter the pharmacokinetic profile of VENLOR XR or its active metabolite, O-desmethylvenlafaxine. Caution is advised with co-administration of VENLOR XR and metoprolol.

Medicines that prolong the QT interval

Concomitant use of VENLOR XR with other medicines which prolong the QTc interval increases the risk of QTc prolongation and/or ventricular dysrhythmias. Co-administration of such medicines should be avoided. Relevant classes include class Ia and III antidysrhythmics (e.g. quinidine, amiodarone, dofetilide and sotalol), some antipsychotics (e.g. thioridazine), some macrolides (e.g. erythromycin), some antihistamines, and 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

Since only 27 % of VENLOR XR is plasma protein bound, the concomitant administration of VENLOR XR and other highly protein bound medicines is not expected to result in increased free concentration of the medicine due to displacement.

Medicines metabolised by cytochrome P450 isoenzymes

VENLOR XR only weakly inhibits CYP2D6. VENLOR XR has no inhibitory effect on CYP3A4, CYP1A2 and CYP2C9 *in vitro.*

Potential for other medicines to affect VENLOR XR

Metabolic pathways for VENLOR XR include CYP2D6 and CYP3A4. VENLOR XR is

mainly metabolised to its active metabolite, O-desmethylvenlafaxine, by the cytochrome P450 enzyme CYP2D6. CYP3A4 is a minor pathway relative to CYP2D6 in the metabolism of VENLOR XR.

CYP2D6 inhibitors

The metabolism of venlafaxine, as in VENLOR XR to O-desmethylvenlafaxine may be reduced with the concomitant use of CYP2D6 inhibitors, resulting in increased plasma concentrations of venlafaxine and decreased concentrations of O-desmethylvenlafaxine. No dosage adjustment is required when VENLOR XR is co-administered with a CYP2D6 inhibitor as venlafaxine and O-desmethylvenlafaxine are both pharmacologically active.

CYP3A4 inhibitors

Caution is advised when combining VENLOR XR with a CYP3A4 inhibitor as concomitant use of CYP3A4 inhibitors and VENLOR XR may increase levels of venlafaxine and O-desmethylvenlafaxine.

CYP2D6 and *CYP3A4* inhibitors

Concomitant use of VENLOR XR with medicines that potentially inhibit both CYP2D6 and CYP3A4 has not been studied, however concomitant use would be expected to increase VENLOR XR plasma concentrations. Caution is advised when combining VENLOR XR with any agents that produce simultaneous inhibition of these two enzyme systems.

Ketoconazole (CYP3A4 inhibitor)

In poor and extensive metabolisers of CYP2D6, higher AUC values of venlafaxine (70 % and 21 %, respectively) and O-desmethylvenlafaxine (33 % and 23 %, respectively)

following administration of ketoconazole were found. Concomitant use of CYP3A4 inhibitors (e.g., clarithromycin, atazanavir, itraconazole, indinavir, voriconazole, ketoconazole, posaconazole, nelfinavir, saquinavir, ritonavir and telithromycin) and VENLOR XR may increase levels of venlafaxine and O-desmethylvenlafaxine. Caution is advised if a patient's therapy includes VENLOR XR and a CYP3A4 inhibitor concomitantly.

4.6 Fertility, pregnancy, and lactation

Women of childbearing potential

Patients falling pregnant or planning a pregnancy during therapy should inform their doctor.

Pregnancy

VENLOR XR must not be administered to pregnant women as the safety of VENLOR XR in pregnancy has not been established (see **section 4.3**). If VENLOR XR is used up to shortly before birth, discontinuation effects should be considered in the newborn. VENLOR XR use late in the third trimester has led to neonatal complications requiring respiratory support, tube feeding or prolonged hospitalisation. Such complications can arise immediately upon delivery. If a mother has used an SSRI/SNRI late in pregnancy the following symptoms may be observed in neonates: tremor, irritability, persistent crying, hypotonia, difficulty in sucking or difficulty in sleeping, these symptoms may be due to either serotonergic effect or exposure symptoms and are observed immediately or within 24 hours after partus.

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**).

Breastfeeding

VENLOR XR must not be administered to lactating women as the safety of VENLOR XR in lactation has not been established (see **section 4.3**). Both venlafaxine and O-desmethylvenlafaxine are excreted in breast milk. There have been post-marketing reports of breastfed infants who experienced crying, abnormal sleep patterns and irritability. Symptoms consistent with velanfaxine discontinuation have also been reported after stopping breastfeeding. The risk to the suckling child cannot be excluded, therefore a decision should be made as to whether VENLOR XR should be discontinued, or whether the patient should stop breastfeeding, taking into account the benefit of breastfeeding the infant and the benefit of VENLOR XR therapy to the mother.

Fertility

A reduction in fertility was observed in a study in which both male and female rats were exposed to O-desmethylvenlafaxine. The human relevance of this finding is not known.

4.7 Effects on ability to drive and use machines

The use of VENLOR XR may be associated with impairment of judgment, thinking or motor skills. Until the adverse effect profile of VENLOR XR has been established in a patient, patients should be advised not to operate hazardous machinery or not to drive.

4.8 Undesirable effects

a. Summary of the safety profile

The adverse events most frequently associated with VENLOR XR administration are nervous system complaints, such as headache, dizziness, insomnia, somnolence, nervousness, and dry mouth; gastrointestinal complaints, including anorexia, nausea and constipation; and abnormal ejaculation/orgasm, sweating and asthenia. Many of

the frequently observed adverse events are dose related. With continued therapy, these adverse events generally decrease in frequency and intensity, and in general do not require discontinuation of treatment.

b. Tabulated list of adverse reactions

MedDRA system organ class	**Frequency**	**Side effects**
Blood and lymphatic system disorders	*Less frequent*	Ecchymosis.
	Frequency unknown	Thrombocytopaenia, blood disorder including agranulocytosis, aplastic anaemia, neutropaenia and pancytopaenia.
Immune system disorders	*Less frequent*	Angioedema.
	Frequency unknown	Anaphylactic reaction.
Endocrine disorders	*Frequency unknown*	Syndrome of Inappropriate Antidiuretic Hormone Secretion (SAIDH)
Metabolism and nutrition disorders	*Frequent*	Decreased appetite.
	Less frequent	Hyponatraemia.
Psychiatric disorders	*Frequent*	Nervousness, confusion,

		depersonalisation, insomnia, abnormal dreams, decreased libido, sedation, anxiety, amnesia, abnormal thinking, depression, emotional lability and anorgasmia.
	Less frequent	Apathy, hallucinations, derealisation, agitation, abnormal orgasm (female), hypomania, bruxism and manic reactions.
	Frequency unknown	Suicidal ideation and suicidal behaviours, delirium, aggression.
Nervous system disorders	*Frequent*	Dizziness, headache, somnolence, tremor, paraesthesia, hypertonia, hyperaesthesia and trismus.
	Less frequent	Akathisia/psychomotor restlessness, syncope, myoclonus, abnormal coordination, balance disorder, dysgeusia, convulsion and migraine.
	Frequency unknown	Neuroleptic malignant syndrome (NMS), Serotonergic syndrome, extrapyramidal disorder, including dystonia and dyskinesia, tardive

		dyskinesia.
Eye disorders	*Frequent* *Frequency unknown*	Abnormality of accommodation, visual impairment including blurred vision, and mydriasis. Angle-closure glaucoma.
Ear and labyrinth disorders	*Frequent* *Frequency unknown*	Tinnitus. Vertigo.
Cardiac disorders	*Frequent* *Less frequent* *Frequency unknown*	Palpitations. Tachycardia. Ventricular fibrillation, ventricular tachycardia (including Torsade de Pointes), QT prolongation.
Vascular disorders	*Frequent* *Less frequent* *Frequency unknown*	Vasodilation (mostly flushes) and hypertension. Orthostatic hypotension, oedema. Hypotension, bleeding (mucous membrane bleeding).

Respiratory, thoracic and mediastinal disorders	*Frequent* *Less frequent* *Frequency unknown*	Yawning, rhinitis, pharyngitis, and bronchitis. Dyspnoea. Pulmonary eosinophilia.
Gastrointestinal disorders	*Frequent* *Less frequent* *Frequency unknown*	Dry mouth, diarrhoea, constipation, nausea and vomiting, abdominal pain, anorexia, eructation, dyspepsia, flatulence and taste perversion. Gastrointestinal haemorrhage, increased appetite. Pancreatitis.
Hepatobiliary disorders	*Frequency unknown*	Hepatitis, abnormal liver function test.
Skin and subcutaneous tissue disorders	*Frequent* *Less frequent* *Frequency*	Hyperhidrosis (including night sweats). Photosensitivity reaction, ecchymosis, rash, alopecia. Erythema multiforme, toxic

	unknown	epidermal necrolysis, Stevens-Johnson syndrome, pruritus, urticaria.
Musculoskeletal, connective tissue and bone disorders	*Frequent* *Frequency unknown*	Arthralgia and myalgia. Rhabdomyolysis.
Renal and urinary disorders	*Frequent* *Less frequent*	Dysuria (mostly urinary hesitation), pollakiuria. Urinary retention and urinary incontinence.
Reproductive system and breast disorders	*Frequent* *Frequency unknown*	Menstrual disorders associated with increased bleeding or irregular bleeding (e.g., menorrhagia, metrorrhagia), ejaculation disorder, and erectile dysfunction. Postpartum haemorrhage*. * This event has been reported for the therapeutic class of SSRI/SNRIs (see **section 4.4** and **4.6**.)
General disorders and	*Frequent*	Asthenia, chills and fatigue, chest

administrative site conditions		pain, neck pain, back pain.
Investigations	*Frequent* *Less frequent* *Frequency unknown*	Increased blood cholesterol. Increased weight, decreased weight. Prolonged electrocardiogram QT, prolonged bleeding time, increased blood prolactin.

Discontinuation of VENLOR XR

As discontinuation effects are known to occur with some antidepressants, it is recommended to taper the dosage of VENLOR XR gradually and to monitor the patient (see **section 4.2**). The following adverse effects have been reported after abrupt discontinuation, rapid dose reduction or tapering of treatment: nervousness, confusion, fatigue, insomnia, somnolence or other sleep disturbances, dizziness, paraesthesia, convulsion, headache, vertigo, sweating, tinnitus, dry mouth, anorexia, nausea, vomiting, diarrhoea, agitation, anxiety, and hypomania. The majority of these reactions are mild and resolved without intervention.

c. Paediatric population

The adverse events profile of VENLOR XR in children and adolescents are similar to that seen in adults in general. Increased reports of hostility, suicidal ideation and self-harm were observed. Decreased appetite, weight loss, increased blood pressure and increased serum cholesterol similar to adult patients were observed. The following adverse reactions were also observed: abdominal pain, agitation, dyspepsia, ecchymosis, epistaxis, and myalgia.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website or to Cipla Medpro (Pty) Ltd. by email: drugsafetysa@cipla.com or telephone: 080 222 6662 (toll free).

4.9 Overdose

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

VENLOR XR overdose may be associated with an increased risk of fatal outcomes compared to that observed with SSRI antidepressants, but lower than that for tricyclic antidepressants according to published retrospective study reports. 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 VENLOR XR in overdosage, as opposed to some characteristics of venlafaxine-treated patients, is not clear. To reduce the risk of overdose, prescription for VENLOR XR should be written for the smallest quantity of medicine consistent with good patient management.

Recommended treatment

General supportive and symptomatic measures are recommended. Vital signs and cardiac rhythm must be monitored. Induction of emesis is not recommended when there is a risk of aspiration. Gastric lavage may be indicated if performed soon after ingestion or in symptomatic patients. Absorption of the active substances may be limited by administrating active charcoal. Forced diuresis, dialysis, hemoperfusion and exchange transfusion are unlikely to be of benefit. No specific antidotes for VENLOR XR are known.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacological classification: A 1.2 Psychoanaleptics (antidepressants).

Pharmacotherapeutic group: Other antidepressants

ATC code: N06AX16

Venlafaxine and its major metabolite, O-desmethylvenlafaxine, are both serotonin and noradrenaline re-uptake inhibitors. Both also weakly inhibit the re-uptake of dopamine. This effectively potentiates neurotransmitter activity in the central nervous system (CNS). Following both acute (single dose) and chronic administration, venlafaxine and O-desmethylvenlafaxine reduce responsiveness to beta-adrenergic stimulation. With respect to their overall action on receptor binding and the re-uptake of neurotransmitters, venlafaxine and O-desmethylvenlafaxine appear to be equipotent.

Venlafaxine does not have monoamine oxidase (MAO) inhibitory activity. *In vitro* studies revealed that venlafaxine has practically no affinity for opiate or benzodiazepine sensitive receptors.

5.2 Pharmacokinetic properties

Absorption

Venlafaxine is well absorbed from the gut. After absorption it is extensively metabolised by first-pass mechanisms. Following venlafaxine administration, peak plasma concentrations of venlafaxine and O-desmethylvenlafaxine are reached after 6,0 ± 1,5 and 8,8 ± 2,2 hours, respectively.

Metabolism

Extensive hepatic metabolism of venlafaxine results in the release of the major active metabolite, O-desmethylvenlafaxine.

Distribution

Venlafaxine and O-desmethylvenlafaxine have mean disposition half-lives of approximately 5 and 11 hours, respectively. The doses and plasma concentrations of venlafaxine and O-desmethylvenlafaxine generally correlate well. Less than 35 % of venlafaxine and O-desmethylvenlafaxine are bound to plasma proteins (27 % venlafaxine and 30 % O-desmethylvenlafaxine are plasma protein bound, respectively).

Elimination

The kidneys are the major route of excretion for both venlafaxine and its metabolites. Within 48 hours of administration, approximately 87 % of a venlafaxine dose is recovered in the urine as unchanged venlafaxine, unconjugated O-desmethylvenlafaxine, conjugated O-desmethylvenlafaxine, or other minor metabolites.

Food

The extent of absorption of venlafaxine is not altered by food. Food also does not affect the formation of O-desmethylvenlafaxine.

Special populations

Elderly

In subjects over 60 years of age, a 20 % reduction in clearance of O-desmethylvenlafaxine is noted.

Renal impairment

The total clearance of both venlafaxine and O-desmethylvenlafaxine is reduced, and t½ prolonged, in patients with moderate to severe renal impairment and in patients that require haemodialyis. This reduction in total clearance is most prominent in patients with creatinine clearance < 30 mL/min. Dosages should be adjusted in this patient group (see **section 4.2**).

Hepatic impairment:

The pharmacokinetic disposition of both venlafaxine and O-desmethylvenlafaxine is significantly altered in patients with compensated hepatic cirrhosis. As both the metabolism of venlafaxine and the elimination of O-desmethylvenlafaxine are reduced, higher plasma concentrations of both molecules are encountered. Dosages should be adjusted in this patient group (see **section 4.2**).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

- Sugar Spheres
- Hydroxy propyl cellulose
- Isopropyl alcohol

- Purified water

Composition of the seal coating

- Hydroxy propyl methyl cellulose
- Purified talc
- Isopropyl alcohol
- Purified water

Blending

- Purified talc
- EHG capsule shell

Composition of the sustained release coating

- Hydroxy propyl methyl cellulose (E-15)
- Ethyl cellulose aqueous dispersion Type B
- Purified water

Composition of Surelease E-7-19030 clear

- Ammonium hydroxide 28%
- Colloidal anhydrous silica
- Dibutyl sebacate
- Ethyl cellulose 20 cp
- Oleic acid
- Purified water

Composition of Capsule Shell for VENLOR XR 37,5 mg:

- Hard gelatin capsule body (clear)

    - Sodium lauryl sulphate
    - Gelatin
- Hard gelatin capsule cap (orange)
    - Ponceau 4R
    - Quinoline yellow
    - Titanium dioxide
    - Sodium lauryl sulphate
    - Gelatin

Composition of Capsule Shell for VENLOR XR 75 mg:

- Hard gelatin capsule body (clear)
    - Sodium lauryl sulphate
    - Gelatin
- Hard gelatin capsule cap (yellow)
    - Sunset yellow
    - Quinoline yellow
    - Titanium dioxide
    - Sodium lauryl sulphate
    - Gelatin

Composition of Capsule Shell for VENLOR XR 150 mg:

- Hard gelatin capsule body (clear)
    - Sodium lauryl sulphate
    - Gelatin
- Hard gelatin capsule cap (yellow)
    - Sunset yellow
    - Quinoline yellow

- Patent Blue
- Titanium dioxide
- Sodium lauryl sulphate
- Gelatin

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months.

6.4 Special precautions for storage

Store at or below 25 º C. Keep the blister strips in the outer carton until required for use.

6.5 Nature and contents of container

VENLOR XR 37,5: packed in PVC film/aluminium foil blister strips of 10 capsules, packed in 30's.

VENLOR XR 75: packed in PVC film/aluminium foil blister strips of 10 capsules, packed in 30's.

VENLOR XR 150: packed in PVC film/aluminium foil blister strips of 10 capsules, packed in 30's.

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 NUMBER(S)

VENLOR XR 37,5: A40/1.2/0032

VENLOR XR 75: A40/1.2/0033

VENLOR XR 150: A40/1.2/0034

VENLOR XR 37,5

Botswana: S2 BOT1302381

Namibia: NS2 06/1.2/0299

VENLOR XR 75

Botswana: S2 BOT0801423

Namibia: NS2 06/1.2/0300

VENLOR XR 150

Botswana: S2 BOT0801424

Namibia: NS2 06/1.2/0301

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

First authorisation: 07 April 2006

Latest renewal: Not applicable.

10. DATE OF REVISION OF THE TEXT

07 November 2024