PROFESSIONAL INFORMATION

SCHEDULING STATUS: **S5**

1. NAME OF THE MEDICINE

VEXALIN XR 75 mg (Extended release capsules)

VEXALIN XR 150 mg (Extended release capsules)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

VEXALIN XR 75 mg CAPSULES: Each extended release capsule contains venlafaxine hydrochloride equivalent to 75 mg venlafaxine. Sugar free.

VEXALIN XR 150 mg CAPSULES: Each extended release capsule contains venlafaxine hydrochloride equivalent to 150 mg venlafaxine. Sugar free.

Excipients:

For a full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

VEXALIN XR 75 mg (Extended release capsules).

Peach Cap/peach body, size ‘1’ capsules containing white to off white extended release beads with ‘L 87’ on cap and ‘75’ on body imprinted with red ink.

VEXALIN XR 150 mg (Extended release capsules).

Dark orange cap/dark orange body, size ‘0el’ capsules containing white to off white extended release beads with ‘L 88’ on cap and ‘150’ on body imprinted with white ink.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

VEXALIN 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 period of treatment.

- Prevention of recurrence in patients responding to 6 months of relapse prevention.

  The safety and efficacy of treatment beyond one year have not been demonstrated. When **VEXALIN XR** is used for long-term it should periodically be re-evaluated for the usefulness of the product in the individual patient.
- The treatment of generalised anxiety disorder.
- Treatment of Social Anxiety Disorder. The effectiveness of **VEXALIN XR** in the treatment of Social Anxiety Disorder for more than 12 weeks has not been demonstrated.

4.2 Posology and method of administration

Posology:

The usual recommended dose for **VEXALIN XR** is 75 mg, given once daily. If after several weeks further clinical improvement is required, the dose may be increased to 150 mg, given once daily. If needed, the dose can be further increased up to 225 mg given once daily. Dose increments should be made at intervals of approximately 2 weeks or more, but not less than 4 days. The dose for depressed patients may be further increased, if needed, up to 375 mg, given once daily.

VEXALIN XR should be administered once daily, at approximately the same time either in the morning or in the evening. The extended-release formulation contains spheroids, which release the medicine slowly into the digestive tract. The insoluble portion of these spheroids is eliminated and may be seen in stools.

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

Special populations

Patients with renal impairment:

Patients with renal impairment should receive lower doses of **VEXALIN XR**.

The total daily dose of **VEXALIN XR** should be reduced by 25 – 50 % for patients with renal impairment with a glomerular filtration rate (GFR) of 10 – 70 ml/min.

The total daily dose of **VEXALIN XR** should be reduced by 50 % in haemodialysis patients.

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

Patients with hepatic impairment:

The total daily dose of **VEXALIN XR** should be reduced by 50 % in patients with mild to moderate hepatic impairment. Patients with severe hepatic impairment have not been studied; therefore, caution should be used if considering treating these patients with **VEXALIN XR** and a further reduction should be considered. Since there is a variability in clearance between hepatically impaired patients, individualisation of dosing, including further dose reductions (> 50 %), may be desirable in some patients.

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

Elderly:

No dosage adjustment is recommended for elderly patients on the basis of age.

Pediatric population

See section 4.3.

Maintenance, continuation and extended treatment:

The need for long-term therapy with **VEXALIN XR** must be periodically reassessed. Whether the dose of antidepressant needed to induce remission is identical to the dose needed to maintain and/or sustain euthymia is unknown.

Discontinuing VEXALIN XR:

Dose tapering is recommended whenever possible when discontinuing **VEXALIN XR** therapy (see section 4.4). Tapering over at least a two-week period is recommended if **VEXALIN XR** has been used for more than 6 weeks. In clinical trials with venlafaxine extended-release capsules, tapering was achieved by reducing the daily dose by 75 mg at 1-week intervals. The period required for tapering may depend on the dose, duration of therapy and the individual patient. Patients should be advised to consult their doctor before abruptly discontinuing **VEXALIN XR** (see section 4.4).

Method of administration

For oral use.

It is recommended that **VEXALIN XR** be taken with food. Each capsule should be swallowed whole with fluid. Do not divide, crush, chew or place capsule in water.

4.3 Contraindications

VEXALIN XR is contraindicated in:

- Patients with hypersensitivity to venlafaxine hydrochloride, or to any of the inactive ingredients of **VEXALIN XR** listed in section 6.1.
- Concomitant use of monoamine oxidase inhibitors (MAOIs). **VEXALIN XR** must not be initiated for at least 14 days after discontinuation of treatment with a MAOI. **VEXALIN XR** must be discontinued for at least 7 days before starting treatment with any MAOI. Severe adverse reactions have been reported when **VEXALIN XR** therapy is initiated soon after discontinuation of an MAOI and when an MAOI is initiated soon after discontinuation of **VEXALIN XR**. These reactions have included tremor, myoclonus, diaphoresis, nausea, vomiting, flushing, dizziness, hyperthermia with features resembling neuroleptic malignant syndrome, seizures and death (see section 4.5).
- Pregnancy and lactation (see section 4.6).
- Children under 18 years (see section 4.4).

4.4 Special warnings and precautions for use

Suicide:

All patients treated with **VEXALIN XR** should be monitored appropriately and observed closely for clinical worsening and suicidality. Patients, their families, and their caregivers should be encouraged to be alert to the emergence of anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restless), hypomania, mania, other unusual changes in behaviour, worsening of depression, and suicidal ideation, especially when initiating therapy or during any change in dose or dosage regimen. The risk of suicide attempt must be considered especially in depressed patients, and the smallest quantity of medicine, consistent with

good patient management, should be provided to reduce the risk of overdose. Risk assessment for suicide should be performed regularly.

Suicide is a known risk of depression and certain other psychiatric disorders, and these disorders themselves are strong predictors of suicide. Pooled analyses of short-term placebo-controlled trials of antidepressant medicines (SSRIs and others) showed that these medicines increase the risk of suicidality in children, adolescents, and young adults (aged 18 – 24 years) with major depression and other psychiatric disorders.

Patients with major depressive disorder may experience worsening of their depression and/or emergence of suicidal ideation and behaviour, whether or not they are taking antidepressant medicine. This risk may persist until significant remission occurs. A causal role, however, for antidepressant medicines in inducing such behaviour has not been established. Patients being treated with **VEXALIN XR** should nevertheless, be observed closely for clinical worsening and suicidality, especially at the beginning of a course of therapy, or at any time of dose changes, either increases or decreases.

Because of the possibility of co-morbidity between major depressive disorder and other psychiatric and non-psychiatric disorders, the same precautions observed when treating patients with major depressive disorder should be observed when treating patients with other psychiatric and non-psychiatric disorders.

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

Serotonin syndrome:

Serotonin syndrome, a potentially life-threatening condition may occur with **VEXALIN XR** treatment, particularly with concomitant use of other medicines that may affect the serotonergic neurotransmitter

system (including triptans, SSRIs, SNRIs, amphetamines, lithium, sibutramine, St. John's Wort [*Hypericum perforatum*], fentanyl and its analogues, tramadol, dextromethorphan, tapentadol, pethidine, methadone and pentazocine), with medicines that impair metabolism of serotonin (such as MAOIs e.g. methylene blue), with serotonin precursors (such as tryptophan supplements) or with antipsychotics or other dopamine antagonists (see sections 4.3 and 4.5).

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

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

Mydriasis:

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

Heart rate:

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

Cardiac disease and risk of dysrhythmia:

VEXALIN XR has not been evaluated in patients with a recent history of myocardial infarction or unstable heart disease. Therefore, it should be used with caution in these patients.

In postmarketing experience, cases of QTc prolongation, Torsade de Pointes (TdP), ventricular tachycardia, and fatal cardiac dysrhythmias have been reported with the use of venlafaxine, especially in overdose or in patients with other risk factors for QTc prolongation/TdP. The balance of risks and benefits should be considered before prescribing **VEXALIN XR** to patients at high risk of serious cardiac dysrhythmia or QTc prolongation (see section 5.1).

Blood pressure:

Dose-related increases in blood pressure have been frequently reported with venlafaxine. In some cases, severely elevated blood pressure requiring immediate treatment has been reported in postmarketing experience. Regular blood pressure monitoring is recommended for patients receiving **VEXALIN XR**. Pre-existing hypertension should be controlled before treatment with **VEXALIN XR**. Caution should be exercised in patients whose underlying conditions might be compromised by increases in blood pressure.

Convulsions:

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

Activation of mania/hypomania:

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

Aggression:

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

Hyponatraemia and/or the Syndrome of Inappropriate Antidiuretic Hormone (SIADH):

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

Abnormal bleeding:

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

Allergic reaction:

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

Cholesterol:

Clinically relevant increases in serum cholesterol were recorded in 5,3 % of venlafaxine-treated patients and 0 % of placebo-treated patients treated for at least 3 months in placebo-controlled clinical trials. Measurement of serum cholesterol levels should be considered during long-term treatment.

Discontinuation of treatment:

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

The following symptoms have been reported in association with abrupt discontinuation or dose-reduction, or tapering of venlafaxine treatment: Hypomania, anxiety, agitation, nervousness, confusion, insomnia or other sleep disturbances, fatigue, somnolence, paraesthesia, dizziness, convulsion, vertigo, headache, flu-like symptoms, tinnitus, impaired coordination and balance, tremor, sweating, dry mouth, anorexia, diarrhoea, nausea and vomiting. In premarketing studies, the majority of discontinuation reactions were mild and resolved without treatment.

Sexual dysfunction:

Serotonin-norepinephrine reuptake inhibitors (SNRIs) including **VEXALIN XR** 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 **VEXALIN XR** may alter glycaemic control. Insulin and/or oral antidiabetic dosage may need to be adjusted.

Post-partum haemorrhage

There has been evidence of an association between antidepressants [particularly selective serotonin reuptake inhibitors (SSRIs) and serotonin non-selective reuptake inhibitors (SNRIs)] and post-partum haemorrhage (PPH). Observational data indicate an increased risk (less than 2-fold) of postpartum haemorrhage PPH following SSRI/SNRI exposure within the month prior to birth.

Healthcare professionals should be aware of the potential risk of PPH while making treatment decisions for prescribing SSRI/SNRI towards the end of pregnancy.

Patients should be advised to inform their doctors before taking SSRI/SNRI if they have history of bleeding disorders, such as von Willebrand disease (VWD) or haemophilia or if they are pregnant.

Paediatric use:

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

Use in elderly patients:

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

Abuse and dependence:

Clinical studies did not show evidence of drug-seeking behaviour, development of tolerance, or dose escalation over time. *In vitro* studies revealed that venlafaxine has virtually no affinity for opiate, benzodiazepine, phencyclidine (PCP) or N-methyl-D-aspartic acid (NMDA) receptors. Venlafaxine was not found to have any significant CNS stimulant activity in rodents. In primate medicine discrimination studies, venlafaxine showed no significant stimulant or depressant abuse liability.

4.5 Interaction with other medicines and other forms of interaction

Monoamine oxidase inhibitors (MAOIs):

Severe adverse reactions have been reported in patients who have recently been discontinued from a MAOI and started on venlafaxine or have recently had venlafaxine 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 venlafaxine in combination with other CNS-active medicines has not been systematically evaluated. Consequently, caution is advised when **VEXALIN XR** is taken in combination with other CNS-active medicines.

Serotonin syndrome, a potentially life threatening condition which may occur with **VEXALIN XR** 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 4.4).

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

Indinavir:

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

Ethanol:

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

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 **VEXALIN XR** concomitantly.

Cimetidine:

At steady-state, cimetidine has been shown to inhibit first-pass metabolism of venlafaxine; however, cimetidine had no effect on the pharmacokinetics of O-desmethylvenlafaxine. The overall pharmacological activity of venlafaxine plus O-desmethylvenlafaxine is expected to increase only slightly in most patients. In the elderly and in patients with hepatic or renal dysfunction this interaction may be more pronounced.

Imipramine:

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

Ketoconazole:

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

Metoprolol:

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

Venlafaxine appeared to reduce the blood pressure lowering effect of metoprolol in this study of healthy volunteers. The clinical relevance of this finding in hypertensive patients is unknown.

Metoprolol did not alter the pharmacokinetic profile of venlafaxine or its active metabolite, O-desmethylvenlafaxine. Caution should be exercised with co-administration of **VEXALIN XR** and metoprolol.

Risperidone:

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

Diazepam:

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

Lithium:

The steady-state pharmacokinetics of venlafaxine and O-desmethylvenlafaxine are not affected when lithium is co-administered. Venlafaxine also has no effects on the pharmacokinetics of lithium.

Medicines highly bound to plasma proteins:

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

Medicines metabolised by cytochrome P450 isoenzymes:

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

Potential for other medicines to affect VEXALIN XR:

The metabolic pathways for **VEXALIN XR** include CYP2D6 and CYP3A4. **VEXALIN XR** is primarily metabolised to its active metabolite, O-desmethylvenlafaxine, by the cytochrome P450 enzyme CYP2D6. CYP3A4 is a minor pathway relative to CYP2D6 in the metabolism of **VEXALIN XR**.

CYP2D6 inhibitors:

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

CYP3A4 inhibitors:

Concomitant use of CYP3A4 inhibitors and **VEXALIN XR** may increase levels of **VEXALIN XR** and O-desmethylvenlafaxine. Therefore, caution is advised when combining **VEXALIN XR** with a CYP3A4 inhibitor.

CYP2D6 and 3A4 inhibitors:

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

Medicines that Prolong the QT Interval

The risk of QTc prolongation and/or ventricular arrhythmias (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.

Drug-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 **VEXALIN XR** therapy. Confirmatory tests, such as gas chromatography/mass spectrometry, will distinguish venlafaxine from PCP and amphetamine.

4.6 Fertility, pregnancy and lactation

Pregnancy

VEXALIN XR must not be administered to pregnant or lactating women. Safety during human pregnancy and lactation has not been established (see section 4.3). Some neonates exposed to venlafaxine late in the third trimester have developed complications requiring tube-feeding, respiratory support or prolonged hospitalization. Such complications can arise immediately upon delivery. Patients should be advised to notify their doctor if they become pregnant or intend to become pregnant during therapy.

Breastfeeding

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

4.7 Effects on ability to drive and use machines

VEXALIN XR causes dizziness and sedation; it may therefore impair judgement, thinking and motor skills. Therefore, patients receiving **VEXALIN XR** should be cautioned about their ability to drive or operate hazardous machinery.

4.8 Undesirable effects

The most frequently observed adverse events associated with the use of **VEXALIN XR** are nausea, dry mouth, headache and sweating (including night sweats). The occurrence of many frequently observed adverse events is dose related.

The following adverse reactions have been reported in association with **VEXALIN XR**:

System Organ Class	**Frequency**	**Undesirable effects**

System Organ Class	**Frequency**	**Undesirable effects**
Blood and lymphatic system disorders	Less frequent	Ecchymosis
	Frequency unknown	Mucous membrane bleeding, prolonged bleeding time, thrombocytopenia*, blood dyscrasias (including agranulocytosis*, aplastic anaemia*, neutropenia* and pancytopenia*)
Immune system disorders	Frequency unknown	Anaphylactic reaction*, angioedema
Endocrine disorders	Frequency unknown	Increased prolactin*, Syndrome of Inappropriate Antidiuretic Hormone Secretion (SIADH)*.
Metabolism and nutrition disorders	Frequent	Increased serum cholesterol (dose related and after prolonged use), weight loss, decreased appetite
	Frequency unknown	Hyponatraemia*
Psychiatric disorders	Frequent	Abnormal dreams, decreased libido, insomnia, nervousness
	Less frequent	Apathy, hallucinations, manic reaction
	Frequency unknown	Confusion*, depersonalization*, agitation*, delirium*, aggression, amnesia, anxiety, depression, emotional lability, abnormal thinking, suicidal ideation and suicidal behaviours.
Nervous system disorders	Frequent	Dizziness, dry mouth, hypertonia, paraesthesia, sedation, tremor,

System Organ Class	**Frequency**	**Undesirable effects**
		Dysgeusia
	Less frequent	Myoclonus, convulsion,
	Frequency unknown	Headache*, impaired coordination and balance*, akathisia*/psychomotor restlessness, neuroleptic malignant syndrome (NMS)*, serotonergic syndrome*, extrapyramidal reactions (including dystonia* and dyskinesia), tardive dyskinesia*, hypoaesthesia, somnolence, trismus
Eye disorders	Frequent	Abnormality of accommodation, mydriasis, visual disturbance
	Frequency unknown	Angle-closure glaucoma*
Ear and labyrinth disorders	Frequent	Tinnitus*
	Frequency unknown	Vertigo
Cardiac disorders	Less frequent	Tachycardia
	Frequency unknown	Palpitations*, QT prolongation*, ventricular tachycardia* and fibrillation (including Torsade de Pointes)*
Vascular disorders	Frequent	Hypertension, vasodilation (mostly flushes) and hypertension
	Less frequent	Postural hypotension, syncope

System Organ Class	**Frequency**	**Undesirable effects**
	Frequency unknown	Hypotension*
Respiratory, thoracic and mediastinal disorders	Frequent	Yawning Dyspnoea*
	Frequency unknown	Pulmonary eosinophilia*, pharyngitis and rhinitis
Gastrointestinal disorders	Frequent	Decreased appetite, constipation, nausea, vomiting
	Frequency not known	Bruxism*, diarrhoea*, gastrointestinal haemorrhage*, pancreatitis*, anorexia, increased appetite, dyspepsia, eructation, flatulence
Hepatobiliary disorders	Frequency not known	Abnormal liver function tests*, hepatitis*
Skin and subcutaneous tissue disorders	Less frequent	Rash, photosensitivity reaction
	Frequency not known	Sweating* (including night sweats*), alopecia*, Stevens-Johnson syndrome*, erythema multiforme*, pruritus*, urticaria*, toxic epidermal necrolysis*
Musculoskeletal and connective tissue disorders	Frequency not known	Myalgia, rhabdomyolysis*
Renal and urinary disorders	Frequent	Impaired urination (mostly hesitancy)
	Less frequent	Urinary retention
	Frequency not known	Increased urinary frequency*, urinary incontinence

System Organ Class	Frequency	Undesirable effects
Reproductive system and breast disorders	Frequent	Abnormal ejaculation / orgasm(males), erectile dysfunction, anorgasmia
	Less frequent	Abnormal orgasm (females)
	Frequency unknown	Menstrual disorders associated with increased bleeding* or increased irregular bleeding* (e.g. menorrhagia*, metrorrhagia*), post-partum haemorrhage**.
General disorders and administration site conditions	Frequent	Asthenia, fatigue, pain, abdominal pain, back pain, chest pain
	Frequency not known	Chills*
Investigations	Frequent	Weight decrease Weight increased Blood cholesterol increased
	Less frequent	Bleeding time prolonged*

*ADR identified during post-marketing

** There has been evidence of an association between antidepressants [particularly selective serotonin reuptake inhibitors (SSRIs) and serotonin non-selective reuptake inhibitors (SNRIs)] and post-partum haemorrhage (PPH). Observational data indicate an increased risk (less than 2-fold) of postpartum haemorrhage PPH following SSRI/SNRI exposure within the month prior to birth. Healthcare professionals should be aware of the potential risk of PPH while making treatment decisions for prescribing SSRI/SNRI towards the end of pregnancy.

Patients should be advised to inform their doctors before taking SSRI/SNRI if they have history of bleeding disorders, such as von Willebrand disease (VWD) or haemophilia or if they are pregnant.

Discontinuation of treatment

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

Reporting of suspected adverse reactions

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

4.9 Overdose

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

Published retrospective studies report that venlafaxine overdosage may be associated with an increased risk of fatal outcomes compared to that observed with SSRI antidepressant products, but lower than that for tricyclic antidepressants. Epidemiological studies have shown that venlafaxine-treated patients have a higher burden of suicide risk factors than SSRI 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 **VEXALIN XR** should be written for the smallest quantity of medicine consistent with good patient management, in order to reduce the risk of overdose.

Recommended treatment:

General supportive and symptomatic measures are recommended; cardiac rhythm and vital signs must be monitored.

When there is a risk of aspiration, induction of emesis is not recommended.

Administration of activated charcoal may also limit medicine absorption.

Forced diuresis, dialysis, haemoperfusion and exchange transfusion are unlikely to be of benefit. No specific antidotes for **VEXALIN XR** are known.

5. PHARMACOLOGICAL PROPERTIES

ATC code: N06AX21

A1.2 Psychoanaleptics (antidepressants)

5.1 Pharmacodynamic properties

Studies have shown that venlafaxine and its major metabolite, O-desmethylvenlafaxine are inhibitors of serotonin and norepinephrine re-uptake and also weakly inhibit dopamine re-uptake.

Venlafaxine and O-desmethylvenlafaxine reduce beta-adrenergic responsiveness after both acute (single dose) and chronic administration. Venlafaxine and its major metabolite appear to be equipotent with respect to their overall action on neurotransmitter re-uptake and receptor binding.

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

5.2 Pharmacokinetic properties

Absorption:

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

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

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

Metabolism:

Venlafaxine is extensively metabolised in the liver. O-desmethylvenlafaxine is the major active metabolite of venlafaxine.

Distribution:

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

Plasma concentrations of venlafaxine and O-desmethylvenlafaxine generally correlated well with dose levels. Venlafaxine and O-desmethylvenlafaxine are less than 35 % bound to plasma proteins. (Venlafaxine and O-desmethylvenlafaxine are 27 % and 30 % bound to plasma proteins respectively).

Elimination:

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

Special populations

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

Renal impairment: In patients with moderate to severe impairment of renal function, the total clearance of both venlafaxine and O-desmethylvenlafaxine was reduced, and $t_{½}$ 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).

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Low substituted hydroxy propyl cellulose, corn starch, microcrystalline cellulose, ethyl cellulose, hydroxypropyl methyl cellulose, purified talc, hard gelatine capsules containing titanium dioxide, iron oxide red, gelatine and sodium lauryl sulfate. In addition **VEXALIN XR 75 mg CAPSULES** contain iron oxide yellow.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months from the date of manufacturing.

6.4 Special precautions for storage

Store at or below 25 °C.

Protect from light and moisture.

Keep the blisters in the carton until required for use.

Keep HDPE containers tightly closed.

KEEP OUT OF REACH OF CHILDREN

6.5 Nature and contents of container

Blister pack:

Plain, silver coloured, 25 µ aluminium foil/ 6-8 gsm HSL as the lidding material and clear, transparent PVC/PE/PVdC, 250 µ/25 µ/90 gsm, as the forming material, packed in a pre-printed unit carton with 10, 28 or 30 capsules.

HDPE container pack:

Capsules are packed in white, opaque, round 40 ml or 60 ml HDPE container for **VEXALIN XR** 75 mg and 60 ml HDPE container for **VEXALIN XR** 150 mg with 33 mm neck finish closed with 33 mm white polypropylene closure with wad having induction sealing liner. Each container contains 28 or 30

capsules with a silica gel. The containers are placed in a pre-printed outer carton with a package insert.

Not all packs and pack sizes are necessarily marketed.

6.6 Special precautions for disposal of a used medicine or waste materials derived from such medicine and other handling of the product

No special requirements.

Any unused product or waste material should be disposed of in accordance with local requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

MACLEODS PHARMACEUTICALS SA (PTY) LTD

Office block 1, Bassonia Estate Office Park (East),

1 Cussonia Drive, Bassonia Rock, Ext. 12,

Alberton, South Africa.

8. REGISTRATION NUMBER(S)

VEXALIN XR 75 mg (Extended release capsules): 51/1.2/0059.057

VEXALIN XR 150 mg (Extended release capsules): 51/1.2/0060.058

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

20 April 2021

10. DATE OF REVISION OF THE TEXT

04 August 2023

PM0095-01

Vanita Rajool

Digitally signed by Vanita Rajool
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Date: 2024.08.06 10:32:04 +02'00'