PROFESSIONAL INFORMATION

SCHEDULING STATUS: S5

1. NAME OF THE MEDICINE

VENLAFAXINE XR 37,5 BIOTECH hard prolonged-release capsules

VENLAFAXINE XR 75 BIOTECH hard prolonged-release capsules

VENLAFAXINE XR 150 BIOTECH hard prolonged-release capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

VENLAFAXINE XR BIOTECH are hard gelatine capsules, filled with extended-release mini film coated tablets.

Each extended-release mini film coated tablet contains venlafaxine hydrochloride equivalent to 12,5 mg venlafaxine.

VENLAFAXINE XR 37,5 BIOTECH: Each hard prolonged-release capsule contains venlafaxine hydrochloride equivalent to 37,5 mg venlafaxine.

VENLAFAXINE XR 37,5 BIOTECH capsules are filled with 3 extended-release mini film coated tablets (3 x 12,5 mg venlafaxine).

VENLAFAXINE XR 75 BIOTECH: Each hard prolonged-release capsule contains venlafaxine hydrochloride equivalent to 75 mg venlafaxine.

VENLAFAXINE XR 75 BIOTECH capsules are filled with 6 extended- release mini film coated tablets (6 x 12,5 mg venlafaxine).

VENLAFAXINE XR 150 BIOTECH: Each hard prolonged-release capsule contains venlafaxine hydrochloride equivalent to 150 mg venlafaxine.

VENLAFAXINE XR 150 BIOTECH capsules are filled with 12 extended-release mini film coated tablets (12 x 12,5 mg venlafaxine).

Signed: _____ Date of submission: 23 April 2024

Sugar free.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard prolonged-release capsules.

VENLAFAXINE XR 37,5 BIOTECH: Light grey opaque / peach opaque, size ‘3’ hard gelatine capsules having thick and thin radial circular bands on the body in red ink and thick and thin radial circular bands on the cap in red ink. The capsule is filled with white to off-white, round, biconvex, film coated mini tablets.

VENLAFAXINE XR 75 BIOTECH: Peach opaque / peach opaque, size ‘1’ hard gelatine capsules having thick and thin radial circular bands on the body in red ink and thick and thin radial circular bands on the cap in red ink. The capsule is filled with white to off-white, round, biconvex, film coated mini tablets.

VENLAFAXINE XR 150 BIOTECH: Dark orange / dark orange opaque, size ‘0’ hard gelatine capsules having thick and thin radial circular bands on the body in white ink and thick and thin radial circular bands on the cap in white ink. The capsule is filled with white to off-white, round, biconvex, film coated mini tablets.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

VENLAFAXINE XR BIOTECH is indicated for the treatment of depression, including depression with associated anxiety. VENLAFAXINE XR BIOTECH is indicated for the prevention of relapses of an episode of depression in patients responding to an initial six to eight weeks of treatment. In patients responding to six months of relapse prevention, VENLAFAXINE XR BIOTECH may be used to prevent recurrence. Safety and efficacy beyond one year have not been demonstrated. When VENLAFAXINE XR BIOTECH is used for long-term treatment it should periodically be re-evaluated for the usefulness of the product in the individual patient.

VENLAFAXINE XR BIOTECH is indicated for the treatment of generalised anxiety disorder and for the treatment of social anxiety disorder. The effectiveness of VENLAFAXINE XR BIOTECH in the treatment of social anxiety disorder for more than 12 weeks has not been demonstrated.

4.2 Posology and method of administration

Posology

The usual recommended dose for VENLAFAXINE XR BIOTECH 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.

Patients with renal impairment

Patients with renal impairment should receive lower doses of VENLAFAXINE XR BIOTECH.
The total daily dose of VENLAFAXINE XR BIOTECH 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 VENLAFAXINE XR BIOTECH should be reduced by 50 % in haemodialysis patients.

Because of individual variability in clearance in these patients, individualisation of dosage may be desirable (see section 5.2).

Patients with hepatic impairment

The total daily dose of VENLAFAXINE XR BIOTECH should be reduced by 50 % in patients with mild to moderate hepatic impairment. Patients with severe hepatic impairment have not been

studied; therefore, caution should be used if considering treating these patients with VENLAFAXINE XR BIOTECH 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 (see section 5.2).

Children

See section 4.3.

Elderly patients

No specific dosage adjustments of VENLAFAXINE XR BIOTECH are recommended based on patient age.

Maintenance, continuation and extended treatment

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

Discontinuing VENLAFAXINE XR BIOTECH

Dose tapering is recommended whenever possible when discontinuing VENLAFAXINE XR BIOTECH therapy (see section 4.4). The period required for tapering may depend on the dose, duration of therapy and the individual patient. Patients should be advised to consult their medical practioner before abruptly discontinuing VENLAFAXINE XR BIOTECH (see section 4.4).

Method of administration

For oral use.

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

VENLAFAXINE XR BIOTECH capsules should be administered once daily, at approximately the same time either in the morning or in the evening.

VENLAFAXINE XR BIOTECH prolonged-release capsules contain extended-release mini film coated tablets, which release the active ingredient, venlafaxine, slowly into the digestive tract. The insoluble portion of these mini film coated tablets is eliminated and may be seen in stools.

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

4.3 Contraindications

- Hypersensitivity to venlafaxine or any excipients of VENLAFAXINE XR BIOTECH (see section 6.1).
- Concomitant use in patients taking monoamine oxidase inhibitors (MAOIs). VENLAFAXINE XR BIOTECH must not be initiated for at least 14 days after discontinuation of treatment with an MAOI. VENLAFAXINE XR BIOTECH must be discontinued for at least 7 days before starting treatment with any MAOI (see section 4.5). Severe adverse reactions have been reported when VENLAFAXINE XR BIOTECH therapy is initiated soon after discontinuation of an MAOI and when an MAOI is initiated soon after discontinuation of VENLAFAXINE XR BIOTECH. These reactions have included tremor, myoclonus, diaphoresis, nausea, vomiting, flushing, dizziness, hyperthermia with features resembling neuroleptic malignant syndrome, seizures and death (see section 4.5).
- Children under 18 years (see sections 4.4 and 4.8).
- Pregnancy and lactation (see section 4.6).

4.4 Special warnings and precautions for use

Suicide/suicidal thoughts or clinical worsening

Patients with major depressive disorder 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 VENLAFAXINE XR BIOTECH should, nevertheless, be observed closely for clinical worsening and suicidality, especially at the beginning of a course of therapy or at any time of dose changes, either increases or decreases. Because of the possibility of co- morbidity between major depressive disorder and other psychiatric and non-psychiatric disorders, the same precautions observed when treating patients with major depressive disorders should be observed when treating patients with other psychiatric and non-psychiatric disorders. The following symptoms have been reported in patients being treated with antidepressants for major depressive disorder as well as for other indications, both psychiatric and non-psychiatric: anxiety, agitation, panic attacks, insomnia, irritability, hostility (aggressiveness, impulsivity, akathisia, hypomania, and mania). Although a causal link between the emergence of suicidal impulses has not been established, consideration should be given to changing the therapeutic regimen, including possibly discontinuing VENLAFAXINE XR BIOTECH, in patients for whom such symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms. If the decision is made to discontinue treatment, VENLAFAXINE XR BIOTECH should be tapered (see section 4.2).

Close supervision of patients, and in particular those at high risk, should accompany therapy, especially in early treatment and following dose changes. Patients (and caregivers of patients) should be alerted about the need to monitor for any clinical worsening, suicidal behaviour or

thoughts and unusual changes in behaviour, and to seek medical advice immediately if these symptoms present.

Paediatric population

Safety and efficacy in children under 18 years of age have not been established. In clinical trials in major depressive disorder, there were increased reports of hostility (predominantly aggression, oppositional behaviour, and anger) and suicide-related adverse events such as suicidal ideation, suicide, and self-harm (see sections 4.3 and 4.8). In addition, long-term safety data in children and adolescents concerning growth, maturation and cognitive and behavioural development are lacking.

Serotonin syndrome

Serotonin syndrome, a potentially life-threatening condition, may occur with VENLAFAXINE XR BIOTECH treatment, particularly with concomitant use of other medicines that may affect the serotonergic neurotransmitter system (including triptans, SSRIs, SNRIs, amphetamines, lithium, sibutramine, St John's wort [*Hypericum perforatum*], fentanyl and its analogues, tramadol, dextromethorphan, tapentadol, pethidine, methadone and pentazocine), with medicines that impair metabolism of serotonin (such as MAOIs, e.g. methylene blue), with serotonin precursors (such as tryptophan supplements) or with antipsychotics or other dopamine antagonists (see sections 4.3 and 4.5).

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

If concomitant treatment with VENLAFAXINE XR BIOTECH and other medicines that may affect the serotonergic and/or dopaminergic neurotransmitter systems is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases. The concomitant use of VENLAFAXINE XR BIOTECH with serotonin precursors (such as tryptophan supplements) is not recommended.

Narrow-angle glaucoma

Mydriasis may occur in association with venlafaxine. It is recommended that patients with raised intraocular pressure or patients at risk for acute narrow-angle glaucoma (angle-closure glaucoma) be closely monitored (see section 4.8).

Blood pressure

Dose-related increases in blood pressure have been commonly reported with venlafaxine. In some cases, severely elevated blood pressure requiring immediate treatment has been reported in post-marketing experience. All patients should be carefully screened for high blood pressure and pre-existing hypertension should be controlled before initiation of treatment. Blood pressure should be reviewed periodically, after initiation of treatment and after dose increases. Caution should be exercised in patients whose underlying conditions might be compromised by increases in blood pressure, e.g. those with impaired cardiac function (see section 4.8).

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 (see section 4.8).

Cardiac disease and risk of dysrhythmia

Venlafaxine has not been evaluated in patients with a recent history of myocardial infarction or unstable heart disease. Therefore, it should be used with caution in these patients.
In post-marketing experience, cases of QTc prolongation, torsades de pointes (TdP), ventricular tachycardia, and fatal cardiac dysrhythmias have been reported with the use of venlafaxine, especially in overdose or in patients with other risk factors for QTc prolongation/TdP. The balance of risks and benefits should be considered before prescribing VENLAFAXINE XR BIOTECH to patients at high risk of serious cardiac dysrhythmia or QTc prolongation (see section 5.1).

Convulsions

Convulsions may occur with VENLAFAXINE XR BIOTECH therapy. As with all antidepressants, VENLAFAXINE XR BIOTECH should be introduced with caution in patients with a history of convulsions and concerned patients should be closely monitored.
Treatment should be discontinued in any patient who develops seizures (see section 4.8).

Hyponatraemia

Cases of hyponatraemia and/or the syndrome of inappropriate antidiuretic hormone (SIADH) secretion may occur with venlafaxine. This has most frequently been reported in volume-depleted or dehydrated patients. Elderly patients, patients taking diuretics, and patients who are otherwise volume-depleted, may be at greater risk for this event (see section 4.8).

Abnormal bleeding

Medicines that inhibit serotonin uptake may lead to reduced platelet function. Bleeding events related to SSRI and SNRI use have ranged from ecchymoses, haematomas, epistaxis and petechiae to gastrointestinal and life-threatening haemorrhages. The risk of haemorrhage may be increased in patients taking VENLAFAXINE XR BIOTECH. As with other serotonin-reuptake inhibitors, VENLAFAXINE XR BIOTECH should be used cautiously in patients predisposed to bleeding, including patients on anticoagulants and platelet inhibitors.

Serum cholesterol

Clinically relevant increases in serum cholesterol were recorded in 5,3 % of venlafaxine-treated patients and 0,0 % of placebo-treated patients treated for at least 3 months in placebo-controlled clinical trials. Measurement of serum cholesterol levels should be considered during long-term treatment (see section 4.8).

Co-administration with weight loss medicines

The safety and efficacy of VENLAFAXINE XR BIOTECH therapy in combination with weight loss medicines, including phentermine, have not been established. Co-administration of VENLAFAXINE XR BIOTECH and weight loss medicines are not recommended. VENLAFAXINE XR BIOTECH is not indicated for weight loss alone or in combination with other medicines.

Mania/hypomania

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

Aggression

Aggression may occur in a small number of patients who have received antidepressants, including VENLAFAXINE XR BIOTECH. This has been reported with initiation, dose changes and discontinuation of treatment. As with other antidepressants, VENLAFAXINE XR BIOTECH should be used cautiously in patients with a history of aggression (see section 4.8).

Discontinuation of treatment

Withdrawal symptoms, when treatment is discontinued, are common, particularly if discontinuation is abrupt (see section 4.8).

The risk of withdrawal symptoms may be dependent on several factors, including the duration and dose of therapy and the rate of dose reduction. Dizziness, sensory disturbances (including paraesthesia), sleep disturbances (including insomnia and intense dreams), agitation or anxiety, nausea and/or vomiting, tremor and headache are the most commonly reported reactions. Generally, these symptoms are mild to moderate; however, in some patients they may be severe in intensity. They usually occur within the first few days of discontinuing treatment, but there have been very rare 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 – 3 months or more). It is therefore advised that VENLAFAXINE XR BIOTECH should be gradually tapered when discontinuing treatment over a period of several weeks or months, according to the patient's needs (see section 4.2).

Sexual dysfunction

Serotonin-norepinephrine reuptake inhibitors (SNRIs) may cause symptoms of sexual dysfunction (see section 4.8). There have been reports of long-lasting sexual dysfunction where the symptoms have continued despite discontinuation of SNRIs.

Akathisia/psychomotor restlessness

The use of venlafaxine has been associated with the development of akathisia, characterised by a subjectively unpleasant or distressing restlessness and need to move often accompanied by an inability to sit or stand still. This is most likely to occur within the first few weeks of treatment. In patients who develop these symptoms, increasing the dose may be detrimental (see section 4.8).

Dry mouth

Dry mouth is reported in patients treated with venlafaxine. This may increase the risk of caries, and patients should be advised upon the importance of dental hygiene (see section 4.8).

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 venlafaxine therapy. Confirmatory tests, such as gas chromatography/mass spectrometry, will distinguish venlafaxine from PCP and amphetamine.

4.5 Interaction with other medicines and other forms of interaction

Monoamine oxidase inhibitors (MAOIs)

Irreversible non-selective MAOIs

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

Reversible, selective MAO-A inhibitor (moclobemide)

Due to the risk of serotonin syndrome, the combination of VENLAFAXINE XR BIOTECH with a

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

Reversible, non-selective MAOI (linezolid)

The antibiotic linezolid is a weak reversible and non-selective MAOI and should not be given to patients treated with VENLAFAXINE XR BIOTECH (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.

Serotonin syndrome

Serotonin syndrome, a potentially life-threatening condition, may occur with VENLAFAXINE XR BIOTECH treatment, particularly with concomitant use of other medicines that may affect the serotonergic neurotransmitter system (including triptans, SSRIs, SNRIs, amphetamines, lithium, sibutramine, St John's wort [*Hypericum perforatum*], fentanyl and its analogues, tramadol, dextromethorphan, tapentadol, pethidine, methadone and pentazocine), with medicines that impair metabolism of serotonin (such as MAOIs, e.g. methylene blue), with serotonin precursors (such as tryptophan supplements) or with antipsychotics or other dopamine antagonists (see sections 4.3 and 4.4).

If concomitant treatment with VENLAFAXINE XR BIOTECH and an SSRI, an SNRI or a serotonin

receptor agonist (triptan) is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases. The concomitant use of venlafaxine with serotonin precursors (such as tryptophan supplements) is not recommended (see section 4.4).

CNS-active substances

The risk of using venlafaxine, as in VENLAFAXINE XR BIOTECH, in combination with other CNS-active substances has not been systematically evaluated. Consequently, caution is advised when venlafaxine is taken in combination with other CNS-active substances.

Ethanol

Venlafaxine, as in VENLAFAXINE XR BIOTECH, has been shown not to increase the impairment of mental and motor skills caused by ethanol. However, as with all CNS-active substances, patients should be advised to avoid alcohol consumption.

Medicines that prolong the QT interval

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

Relevant classes include:

- class Ia and III antidysrhythmics (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 medicine known to significantly increase QT interval should be avoided.

Effect of other medicines on VENLAFAXINE XR BIOTECH

Ketoconazole (CYP3A4 inhibitor)

A pharmacokinetic study with ketoconazole in CYP2D6 extensive (EM) and poor metabolisers (PM) resulted in higher AUC of venlafaxine (70 % and 21 % in CYP2D6 PM and EM subjects, respectively) and *O*-desmethylvenlafaxine (33 % and 23 % in CYP2D6 PM and EM subjects, respectively) 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 *O*-desmethylvenlafaxine. Therefore, caution is advised if a patient's therapy includes a CYP3A4 inhibitor and VENLAFAXINE XR BIOTECH concomitantly.

Effect of VENLAFAXINE XR BIOTECH on other medicines

Lithium

Serotonin syndrome may occur with the concomitant use of VENLAFAXINE XR BIOTECH and lithium (see ***Serotonin syndrome*** above).

Diazepam

Venlafaxine, as in VENLAFAXINE XR BIOTECH, has no effects on the pharmacokinetics and pharmacodynamics of diazepam and its active metabolite, desmethyldiazepam. Diazepam does not appear to affect the pharmacokinetics of either venlafaxine or *O*-desmethylvenlafaxine. It is unknown whether a pharmacokinetic and/or pharmacodynamic interaction with other benzodiazepines exists.

Imipramine

Venlafaxine did not affect the pharmacokinetics of imipramine and 2-OH-imipramine. There was a dose-dependent increase of 2-OH-desipramine AUC by 2,5 to 4,5-fold when venlafaxine 75 mg to

150 mg daily was administered.

Imipramine did not affect the pharmacokinetics of venlafaxine and *O*-desmethylvenlafaxine. The clinical significance of this interaction is unknown. Caution should be exercised with co-administration of VENLAFAXINE XR BIOTECH and imipramine.

Haloperidol

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

Risperidone

Venlafaxine increased the risperidone AUC by 50 % but did not significantly alter the pharmacokinetic profile of the total active moiety (risperidone plus 9-hydroxyrisperidone). The clinical significance of this interaction is unknown.

Metoprolol

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

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.

Medicines highly bound to plasma proteins

Venlafaxine is not highly bound to plasma proteins (27 % bound); therefore, administration of VENLAFAXINE XR BIOTECH to a patient taking another medicine that is highly protein bound is not expected to cause increased free concentrations of the other medicine (see section 5.2).

Medicines metabolised by cytochrome P450 isoenzymes

In vivo studies indicate that venlafaxine is a relatively weak inhibitor of CYP2D6. Venlafaxine did not inhibit CYP3A4 (alprazolam and carbamazepine), CYP1A2 (caffeine) and CYP2C9 (tolbutamide) or CYP2C19 (diazepam) *in vivo*.

Oral contraceptives

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

4.6 Fertility, pregnancy and lactation

Pregnancy

VENLAFAXINE XR BIOTECH must not be administered to pregnant women. Safety during pregnancy has not been established (see section 4.3).

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 most cases, these complications are observed immediately or within 24 hours after partus.

Breastfeeding

VENLAFAXINE XR BIOTECH must not be administered to women who are breastfeeding. Safety during breastfeeding has not been established (see section 4.3).

Venlafaxine and its active metabolite, *O*-desmethylvenlafaxine, are excreted in breast milk, therefore, mothers on treatment with VENLAFAXINE XR BIOTECH should not breastfeed.

Patients should be advised to notify their medical practitioner if they become pregnant or intend to become pregnant during therapy.

Fertility

Reduced fertility was observed in a study in which both male and female rats were exposed to *O*-desmethylvenlafaxine.

4.7 Effects on ability to drive and use machines

VENLAFAXINE XR BIOTECH may cause dizzines, sedation and visual impairment (see section 4.8). Any psychoactive medicine may impair judgment, thinking and motor skills. Therefore, any patient taking VENLAFAXINE XR BIOTECH should be cautioned about their ability to drive a vehicle or operate hazardous machinery.

4.8 Undesirable effects

System organ class	**Frequency**	**Side effect**
Blood and lymphatic disorders	*Less frequent*	ecchymosis

Metabolism and nutrition disorders	*Frequent*	increased serum cholesterol (particularly with prolonged administration and possibly with higher doses), weight loss
	Less frequent	weight gain
Psychiatric disorders	*Less frequent*	apathy, hallucinations, myoclonus, convulsions, manic reaction
Nervous system disorders	*Frequent*	abnormal dreams, decreased libido, dizziness, dry mouth, hypertonia, insomnia, nervousness, paraesthesia, sedation, tremor
Eye disorders	*Frequent*	abnormality of accommodation, mydriasis, visual disturbance
Cardiac disorders	*Less frequent*	tachycardia
Vascular disorders	*Frequent*	hypertension, vasodilation (mostly hot flashes/flushes)
	Less frequent	postural hypotension, syncope
Respiratory, thoracic and mediastinal disorders	*Frequent*	yawning
Gastro-intestinal disorders	*Frequent*	abdominal pain, decreased appetite, constipation, nausea, vomiting
	Less frequent	altered taste sensation

Skin and subcutaneous tissue disorders	*Less frequent*	rash
Renal and urinary disorders	*Frequent*	impaired urination (mostly hesitancy)
	Less frequent	urinary retention
Reproductive system and breast disorders	*Frequent*	abnormal ejaculation/orgasm (males), anorgasmia, erectile dysfunction
	Less frequent	abnormal orgasm (females)
General disorders and administration site conditions	*Frequent*	asthenia/fatigue, headache, pain, back pain, chest pain
	Less frequent	photosensitivity reaction

The following have been reported during post-marketing surveillance:

Blood and lymphatic system disorders: Mucous membrane bleeding, prolonged bleeding time, thrombocytopenia, blood dyscrasias (including agranulocytosis, aplastic anaemia, neutropenia and pancytopenia).

Immune system disorders: Angioedema and anaphylaxis.

Psychiatric disorders: Depersonalisation, agitation, tardive dyskinesia, aggression, amnesia, anxiety, depression, emotional lability and trismus.

Nervous system disorders: Headache, confusion, impaired coordination and balance, akathisia/psychomotor restlessness, neuroleptic malignant syndrome (NMS), serotonergic syndrome, delirium, extrapyramidal reactions (including dystonia and dyskinesia), hypaesthesia, somnolence and abnormal thinking.

Eye disorders: Angle-closure glaucoma.

Ear and labyrinth disorders: Tinnitus.

Cardiac disorders: Palpitations, hypotension, QT prolongation, ventricular fibrillation and ventricular tachycardia (including torsades de pointes).

Respiratory, thoracic and mediastinal disorders: Pulmonary eosinophilia, pharyngitis and rhinitis.

Gastrointestinal disorders: Bruxism, diarrhoea, gastrointestinal haemorrhage, pancreatitis, anorexia, increased appetite, dyspepsia, eructation and flatulence.

Hepato-biliary disorders: Abnormal liver function tests, hyponatraemia, hepatitis, syndrome of inappropriate antidiuretic hormone (SIADH) secretion and increased prolactin.

Skin and subcutaneous tissue disorders: Sweating, including night sweats, alopecia, erythema multiforme, Stevens-Johnson syndrome,

pruritus, urticaria and toxic epidermal necrolysis.

Musculoskeletal and connective tissue disorders: Rhabdomyolysis and myalgia.

Reproductive system and breast disorders: Menstrual disorders associated with increased bleeding or increased irregular bleeding (e.g. menorrhagia, metrorrhagia), increased urinary frequency and urinary incontinence.

General disorders and administration site conditions: Chills.

Discontinuation of treatment

Discontinuation of VENLAFAXINE XR BIOTECH (particularly when abrupt) may lead 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 with venlafaxine.

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 XR BIOTECH treatment is no longer required, gradual discontinuation by dose tapering should be carried out (see sections 4.2 and 4.4).

Paediatric population

In general, the adverse reaction profile of venlafaxine (in placebo-controlled clinical trials) in children and adolescents (ages 6 to 17 years) was similar to that seen for adults. As with adults, decreased appetite, weight loss, increased blood pressure and increased serum cholesterol were observed (see section 4.4).

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

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

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of VENLAFAXINE XR BIOTECH is important. It allows continued monitoring of the benefit/risk balance of VENLAFAXINE XR BIOTECH. Health care providers are requested to report any suspected adverse drug reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

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, convulsions and vomiting. Other reported events include electrocardiographic changes (e.g. prolongation of QT interval, bundle branch block, QRS prolongation [see section 5.1]), ventricular tachycardia, bradycardia, hypotension, hypoglycaemia, vertigo and deaths.

Published retrospective studies report that venlafaxine overdosage may be associated with an increased risk of fatal outcomes compared to that observed with SSRI antidepressants, but lower than that for tricyclic antidepressants. Epidemiological studies have shown that venlafaxine-

treated patients have a higher burden of suicide risk factors than SSRI patients. The extent to which the finding of an increased risk of fatal outcomes can be attributed to the toxicity of venlafaxine in overdosage, as opposed to some characteristics of venlafaxine-treated patients, is not clear.

Prescriptions for VENLAFAXINE XR BIOTECH should be written for the smallest quantity of the medicine consistent with good patient management in order to reduce the risk of overdose.

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 venlafaxine are known.

5. PHARMACOLOGICAL PROPERTIES

Category and class: A 1.2 Psychoanaleptics (antidepressants)

5.1 Pharmacodynamic properties

Pharmacotherapeutic group:

Other antidepressants - ATC code: NO6A X16.

Mechanism of action

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

acute (single dose) and chronic administration. Venlafaxine and ODV are very similar with respect to their overall action on neurotransmitter reuptake and receptor binding.

Venlafaxine has virtually no affinity for rat brain muscarinic, cholinergic, H_1-histaminergic or α_1-adrenergic receptors *in vitro*. Pharmacological activity at these receptors may be related to various side effects seen with other antidepressant medicines, such as anticholinergic, sedative and cardiovascular side effects. Reports of QTc prolongation/TdP and ventricular dysrhythmia have been reported, especially in overdose or in patients with other risk factors for QTc prolongation/TdP (see sections 4.4, 4.8 and 4.9).

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

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

5.2 Pharmacokinetic properties

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

Absorption

At least 92 % of venlafaxine is absorbed following single oral doses of immediate-release venlafaxine. Absolute bioavailability is 40 % to 45 % due to presystemic metabolism. After immediate-release venlafaxine administration, the peak plasma concentrations of venlafaxine and ODV occur in 2 and 3 hours, respectively. Following the administration of venlafaxine prolonged-release capsules, peak plasma concentrations of venlafaxine and ODV are attained within 5,5 hours and 9 hours, respectively. When equal daily doses of venlafaxine are administered as either an immediate-release tablet or prolonged-release capsule, the prolonged-release capsule

provides a slower rate of absorption, but the same extent of absorption compared with the immediate-release tablet. Food does not affect the bioavailability of venlafaxine and ODV.

Distribution

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

Biotransformation

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

Elimination

Venlafaxine and its metabolites are excreted primarily through the kidneys. Approximately 87 % of a venlafaxine dose is recovered in the urine within 48 hours as either unchanged venlafaxine (5 %), unconjugated ODV (29 %), conjugated ODV (26 %) or other minor inactive metabolites (27 %). Mean ± SD plasma steady-state clearances of venlafaxine and ODV are 1,3 ± 0,6 L/h/kg and 0,4 ± 0,2 L/h/kg, respectively.

Special populations

Age and gender

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

CYP2D6 extensive/poor metabolisers

Plasma concentrations of venlafaxine are higher in CYP2D6 poor metabolisers than extensive metabolisers. Because the total exposure (AUC) of venlafaxine and ODV is similar in poor and extensive metabolisers, there is no need for different venlafaxine dosing regimens for these two groups.

Hepatic impairment

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

Renal impairment

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

5.3 Preclinical safety data

No further information of relevance available.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Extended-release mini film coated tablets

Microcrystalline cellulose

Povidone

Talc

Colloidal silicon dioxide

Magnesium stearate

Ethyl cellulose

Copovidone

Capsule shell (VENLAFAXINE XR 37,5 BIOTECH)

Gelatine

Iron oxide black (E172)

Iron oxide red (E172)

Iron oxide yellow (E172)

Titanium dioxide (E171)

Red ink (butyl alcohol, dehydrated alcohol, isopropyl alcohol, propylene glycol, shellac, strong ammonia solution, iron oxide red (E172)).

Capsule shell (VENLAFAXINE XR 75 BIOTECH)

Gelatine

Iron oxide black (E172)

Iron oxide red (E172)

Titanium dioxide (E171)

Red ink (butyl alcohol, dehydrated alcohol, isopropyl alcohol, propylene glycol, shellac, strong ammonia solution, iron oxide red (E172)).

Capsule shell (VENLAFAXINE XR 150 BIOTECH)

Gelatine

FD&C Blue 1 (E133)

FD&C Red 40 (E129)

FD&C Yellow 6 (E110)

Titanium dioxide (E171)

White ink (butyl alcohol, dehydrated alcohol, isopropyl alcohol, povidone, propylene glycol, shellac, sodium hydroxide, titanium dioxide (E171).

6.2 Incompatibilities

None known.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

- Store at or below 25 °C. Protect from moisture.
- Keep blister strips in outer carton until required for use.

6.5 Nature and contents of container

PVC/PVdC//aluminium (white opaque//silver) blister strips containing 10 capsules per blister strip, packed in an outer carton.

PVC/Aclar//aluminium (white opaque//silver) blister strips containing 10 capsules per blister strip, packed in an outer carton.

Pack sizes: 30 (3 blister strips x 10 capsules) and 100 (10 blister strips x 10 capsules).

6.6 Special precautions for disposal and other handling

None.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Biotech Laboratories (Pty) Ltd

Ground Floor Block K West Central Park

Signed: _____ Date of submission: 23 April 2024

400 16th Road, Randjespark

Halfway House

Midrand 1685

8. REGISTRATION NUMBERS

VENLAFAXINE XR 37,5 BIOTECH: 51/1.2/0638

VENLAFAXINE XR 75 BIOTECH: 51/1.2/0639

VENLAFAXINE XR 150 BIOTECH: 51/1.2/0640

9. DATE OF FIRST AUTHORISATION

16 February 2021

10. DATE OF REVISION OF THE TEXT

30 September 2024