APPROVED PROFESSIONAL INFORMATION

1.	**SCHEDULING STATUS:**
2.	**S5**
3.	
4.	**1. NAME OF THE MEDICINE**
5.	**ELAVEX 75 mg XR** (Capsules)
6.	**ELAVEX 150 mg XR** (Capsules)
7.	
8.	**2. QUALITATIVE AND QUANTITATIVE COMPOSITION:**
9.	**ELAVEX 75 mg XR**: Each extended release capsule contains venlafaxine hydrochloride equivalent to
10.	75 mg venlafaxine.
11.	**ELAVEX 150 mg XR**: Each extended release capsule contains venlafaxine hydrochloride equivalent to
12.	150 mg venlafaxine.
13.	
14.	For full list of excipients, see section 6.1.
15.	
16.	**3. PHARMACEUTICAL FORM**
17.	Capsules
18.	**ELAVEX 75 mg XR:** Flesh opaque-flesh opaque No. 0, hard gelatin capsules, containing two 37,5 mg
19.	tablets.
20.	**ELAVEX 150 mg XR:** Scarlet opaque-scarlet opaque No. 00, hard gelatin capsules, containing three
21.	50 mg tablets.
22.	
23.	**4. CLINICAL PARTICULARS**
24.	**4.1 THERAPEUTIC INDICATIONS:**
25.	**ELAVEX XR** is indicated for the following:
26.	

- 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.
- In patients responding to six months relapse prevention, **ELAVEX XR** may be used to prevent recurrence. Safety and efficacy beyond one year have not been demonstrated in clinical studies.
- The treatment of generalised anxiety disorder.
- Treatment of social anxiety disorder. The effectiveness of **ELAVEX XR** has not been demonstrated for longer than 12 weeks for this indication.

4.2 POSOLOGY AND METHOD OF ADMINISTRATION

POSOLOGY

The usual recommended dose for **ELAVEX XR** is 75 mg, given once daily. If after several weeks further clinical improvement is required, the dose may be increase to 150 mg per day.

If needed the dose can further be 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 maximum recommended dose is 375 mg per day. This dose should then be gradually reduced consistent with patient response and tolerance.

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

Special populations

Patients with renal impairment:

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

The total daily dose of **ELAVEX XR** must 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 **ELAVEX XR** must be reduced by 50 % in haemodialysis patients. Administration must be withheld until dialysis session is completed.

Patients with Hepatic Impairment

The total daily dose of **ELAVEX XR** must be reduced by 50 % in patients with moderate hepatic impairment. Reductions of more than 50 % may be appropriate for some patients.

Elderly Patients

No specific dosage adjustments of **ELAVEX XR** are recommended based on patient age.

Paediatric population

See section 4.3.

Maintenance, Continuation and Extended Treatment

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

Discontinuing ELAVEX XR

Dose tapering is recommended when discontinuing **ELAVEX XR** therapy (see section 4.8). Tapering over at least a two-week period is recommended if **ELAVEX XR** has been used for more than 6 weeks. In clinical trials with **ELAVEX XR** 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 **ELAVEX XR** (see section 4.8).

METHOD OF ADMINISTRATION

For oral use.

It is recommended that **ELAVEX 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 CONTRA-INDICATIONS:

- Hypersensitivity to venlafaxine or any excipients in the formulation (see section 6.1).
- Concomitant use in patients taking monoamine oxidase inhibitors (MAOIs) (see section 4.4 for details).
- 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:

Severe adverse reactions have been reported when ELAVEX XR therapy is initiated soon after discontinuation of a MAOI and when a MAOI is initiated soon after discontinuation of ELAVEX XR. Reactions have included tremor, myoclonus, diaphoresis, nausea, vomiting, flushing, dizziness, hyperthermia with features resembling neuroleptic malignant syndrome, seizures and death. ELAVEX XR must not be initiated for at least 14 days after discontinuation of treatment with a MAOI. Allow at least 7 days after stopping ELAVEX XR before starting a MAOI (see section 4.5).

<u>Suicide/ suicidal thoughts or clinical worsening</u>

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 **ELAVEX 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.

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.

Patients with a history of suicide-related events, or those exhibiting a significant degree of suicidal ideation prior to commencement of treatment, are known to be at greater risk of suicidal thoughts or suicide attempts, and should receive careful monitoring during treatment.

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 **ELAVEX 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, **ELAVEX XR** should be tapered (see section 4.2)

<u>Serotonin syndrome</u>

Serotonin syndrome, a potentially life-threatening condition, may occur with venlafaxine 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 and other medicines that may affect the serotonergic and/or dopaminergic neurotransmitter systems is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases.

The concomitant use of venlafaxine with serotonin precursors (such as tryptophan supplements) is not recommended.

<u>Narrow angle glaucoma</u>

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.

<u>Blood pressure</u>

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 postmarketing experience. All patients should be carefully screened for high blood pressure and pre-existing hypertension should be controlled before initiation of treatment. Blood pressure should be reviewed periodically, after initiation of treatment and after dose increases.

Caution should be exercised in patients whose underlying conditions might be compromised by increases in blood pressure, e.g., those with impaired cardiac function.

Heart rate

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

Cardiac disease and risk of dysrhythmia

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

Convulsions

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

Hyponatraemia

Cases of hyponatraemia and/or the Syndrome of Inappropriate Antidiuretic Hormone (SIADH) secretion may occur with venlafaxine. This has most frequently been reported in volume-depleted or dehydrated patients. Elderly patients, patients taking diuretics, and patients who are otherwise volume-depleted may be at greater risk for this event.

Abnormal bleeding

Medicines that inhibit serotonin uptake may lead to reduced platelet function. Bleeding events related to SSRI and SNRI use have ranged from ecchymoses, hematomas, epistaxis, and petechiae to gastrointestinal and life-threatening haemorrhages. SSRIs/SNRIs, including venlafaxine, may increase the risk of postpartum haemorrhage (see section 4.6 and 4.8). The risk of haemorrhage may be increased in patients taking venlafaxine. Venlafaxine should be used cautiously in patients predisposed to bleeding, including patients on anticoagulants and platelet inhibitors.

Patients should be advised to notify their doctor if they develop a rash, hives, or a related allergic phenomenon.

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 medicines

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

Mania/hypomania

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

Aggression

Aggression may occur in some patients who have received antidepressants, including venlafaxine. This has been reported under initiation, dose changes and discontinuation of treatment. Venlafaxine should be used cautiously in patients with a history of aggression.

Abuse and dependence

Patients taking venlafaxine 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 **ELAVEX XR** (e.g. drug-seeking behaviour, increases in dose or development of tolerance).

Discontinuation of treatment

Discontinuation effects are well known to occur with antidepressants, and sometimes these effects can be protracted and severe. It is therefore recommended that the dosage of **ELAVEX XR** be tapered gradually and the patient be monitored (see section 4.2). Suicide/suicidal thoughts and aggression have been observed in patients during changes in venlafaxine dosing regimen, including during discontinuation. Therefore, patients should be closely monitored when the dose is reduced or during discontinuation (see above in section 4.4 - Suicide/suicidal thoughts or clinical worsening, and Aggression).

Withdrawal symptoms, when treatment is discontinued, are common, particularly if discontinuation is abrupt.

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, headache, visual_impairment and hypertension are frequently reported reactions. Generally, these symptoms are mild to moderate; however, in some patients they may be severe in intensity. They usually occur within the first few days of discontinuing treatment, but there have been 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 should be gradually tapered

when discontinuing treatment over a period of several weeks or months, according to the patient's needs (see section 4.2). In some patients, discontinuation could take months or longer.

Sexual dysfunction

Serotonin-norepinephrine reuptake inhibitors (SNRIs) may cause symptoms of sexual dysfunction (see section 4.8).

There have been reports of long-lasting sexual dysfunction where the symptoms have continued despite discontinuation of SNRIs.

Akathisia/psychomotor restlessness

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

Dry mouth

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

Diabetes

In patients with diabetes, treatment with an SSRI or venlafaxine may alter glycaemic control. Insulin and/or oral antidiabetic dosage may need to be adjusted.

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 venlafaxine therapy. Confirmatory tests, such as gas

chromatography/mass spectrometry, will distinguish venlafaxine from PCP and amphetamine.

Use in elderly patients

ELAVEX XR appears to pose no exceptional safety problems for healthy elderly patients. Although age-related clinical circumstances, such as renal impairment, may warrant a dose reduction in the elderly.

Paediatric population

Safety and efficacy in children under 18 years of age have not been established (see sections 4.3 and 4.8).

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTION:

Monoamine oxidase inhibitors (see sections 4.3 and 4.4)

Recent discontinuation from a MAOI followed by initiation of **ELAVEX XR**, or recent discontinuation from **ELAVEX XR**, prior to initiation of MAOI may result in emergence of severe adverse reactions (see section 4.3).

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

CNS Active medicines

Based on the known mechanism of action of **ELAVEX XR** and the potential for serotonin syndrome, caution is advised when **ELAVEX XR** is co-administered with other medicines that may affect the serotonergic neurotransmitter system (such as triptans, selective serotonin re-uptake inhibitors or lithium).

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 **ELAVEX XR** and O-desmethyl venlafaxine.

The clinical significance of this interaction is unknown.

Warfarin

Potentiation of anticoagulant effects may occur in patients taking warfarin following the addition of **ELAVEX XR**.

Ethanol

ELAVEX XR may increase the impairment of mental and motor skills caused by ethanol. Patients should be advised to avoid alcohol consumption while taking **ELAVEX XR**.

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 medicines known to significantly increase QT interval should be avoided.

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 concomitantly.

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 **ELAVEX XR** concomitantly.

Cimetidine

At steady state, cimetidine has been shown to inhibit first-pass metabolism of **ELAVEX XR**; however cimetidine had no apparent effect on the formation or elimination of O-desmethyl venlafaxine which is present in a much greater quantity in the systemic circulation. The overall pharmacological activity of **ELAVEX XR** plus O-desmethyl venlafaxine is expected to increase only slightly in most patients. No adjustments seem necessary when **ELAVEX XR** is co-administered with cimetidine. However, for elderly or patients with hepatic dysfunction concomitantly taking **ELAVEX XR** and cimetidine the extent of interaction is not known and potentially may be more pronounced. For such patients, clinical monitoring is indicated.

Imipramine

ELAVEX XR 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 **ELAVEX XR** and O-desmethyl venlafaxine. This should be taken into account in patients treated with imipramine and venlafaxine concomitantly.

Risperidone

ELAVEX XR may increase the risperidone AUC by 32 % but does 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 and metoprolol.

Diazepam

Diazepam does not appear to affect the pharmacokinetics of either **ELAVEX XR** or O-desmethylvenlafaxine.

ELAVEX XR has no effect on the pharmacokinetic and pharmacodynamics of diazepam and its active metabolite, desmethyldiazepam.

Lithium

The steady-state pharmacokinetics of **ELAVEX XR** and O-desmethyl venlafaxine are not affected when lithium is co-administered. The pharmacokinetics of lithium is also not affected by **ELAVEX XR**.

Medicines highly bound to plasma proteins

ELAVEX XR is not highly bound to plasma proteins (27 % bound); therefore, administration of **ELAVEX 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

ELAVEX XR is a relatively weak inhibitor of CYP2D6. **ELAVEX XR** does not inhibit CYP3A4, CYP1A2 and CYP2C9 *in vitro*.

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 drug interaction with venlafaxine. No interaction study with hormonal contraceptives has been performed.

4.6 FERTILITY, PREGNANCY AND LACTATION:

Safety during human pregnancy and lactation has not been established (see section 4.3).

Neonates exposed to **ELAVEX XR** late in the third trimester have developed complications requiring respiratory support or prolonged hospitalisation. Discontinuation/withdrawal effects have been seen in newborns.

ELAVEX XR and O-desmethyl venlafaxine are excreted in breast milk; therefore, a decision should be made whether to stop breastfeeding or to discontinue **ELAVEX XR**. Patients should be advised to notify their doctor if they become pregnant or intend to fall pregnant during therapy.

4.7 EFFECTS ON THE ABILITY TO DRIVE AND USE MACHINES

ELAVEX XR may impair judgment, thinking and motor skills. Therefore, patients should be cautioned about their ability to drive or operate hazardous machinery.

4.8 UNDESIRABLE EFFECTS

a. Summary of the safety profile

The most commonly observed events associated with the use of **ELAVEX XR** 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.

Incidence terminology:

The occurrence of many frequently observed adverse events is dose related. Adverse events generally decrease in intensity and frequency with continued therapy.

417.

418. b. Tabulated list of adverse reactions

419. The following side-effects have been reported with the use of **ELAVEX XR:**

420.

SYSTEM ORGAN CLASS	FREQUENCY	ADVERSE REACTION
Blood and the lymphatic system disorders	Less frequent	Thrombocytopenia, blood dyscrasias (including agranulocytosis, aplastic anaemia, neutropenia and pancytopenia)
Immune system disorders	Less frequent	Anaphylactic reaction
Endocrine disorders	Less frequent	Syndrome of inappropriate antidiuretic hormone secretion (SIADH), increased prolactin.
Metabolism and nutrition disorders	Frequent	Decreased appetite
	Less frequent	Hyponatraemia
	Frequency unknown	Increased appetite
Psychiatric disorders	Frequent	Insomnia, confusional state, depersonalization, abnormal dreams, nervousness, libido decreased, agitation
	Less frequent	Mania, hypomania, hallucination, derealization, bruxism, apathy, delirium
	Frequency unknown	Suicidal ideation and suicidal behaviours, aggression, anxiety, depression, emotional lability, somnolence
Nervous system disorders	Frequent	Headache, migraine, dizziness, sedation, akathisia, tremor, paraesthesia, dysgeusia
	Less frequent	Syncope, myoclonus, balance disorder, co-ordination abnormal, dyskinesia, Neuroleptic

444.

			Malignant Syndrome (NMS), serotonin syndrome, convulsion, dystonia, tardive dyskinesia
		Frequency unknown	Amnesia, hypoaesthesia, trismus
	Eye disorders	Frequent	Abnormality accommodation, mydriasis, visual disturbance
		Less frequent	Angle closure glaucoma
	Ear and labyrinth disorders	Less frequent	Tinnitus
		Frequency unknown	Vertigo
	Cardiac disorders	Frequent	Tachycardia, palpitations
		Less frequent	Torsade de pointes, QT prolongation, ventricular fibrillation, ventricular tachycardia
		Frequency unknown	Stress cardiomyopathy (takotsubo cardiomyopathy)
	Vascular disorders	Frequent	Hypertension, vasodilatation (mostly hot flushes)
		Less frequent	Hypotension, postural hypotension
	Respiratory, thoracic and mediastinal disorders	Frequent	Yawning, dyspnoea
		Less frequent	Pulmonary eosinophilia, interstitial lung disease
		Frequency unknown	Pharyngitis, rhinitis
	Gastrointestinal disorders	Frequent	Dry mouth, anorexia, constipation, dyspepsia, nausea, vomiting, abdominal pain
		Less frequent	Altered taste sensation, diarrhoea, pancreatitis, gastrointestinal haemorrhage
		Frequency unknown	Eructation, flatulence
	Hepato-biliary disorders	Less frequent	Abnormal liver function test, hepatitis

Skin and subcutaneous tissue disorders	Frequent	Hyperhidrosis (including night sweats)
	Less frequent	Rash, alopecia, erythema multiforme, Stevens-Johnson syndrome, pruritus, urticaria, ecchymosis, angioedema, photosensitivity reaction
	Frequency unknown	Toxic epidermal necrolysis
Musculoskeletal, connective tissue and bone disorders	Frequent	Hypertonia, neck pain, back pain
	Less frequent	Rhabdomyolysis, arthralgia
	Frequency unknown	Myalgia
Renal and urinary disorders	Frequent	Impaired urination (mostly hesitancy), pollakiuria
	Less frequent	Urinary retention, urinary incontinence
	Frequency unknown	Urinary frequency
Reproductive system and breast disorders	Frequent	Metrorrhagia, erectile dysfunction, ejaculation disorder, anorgasmia
	Less frequent	Abnormal orgasm, menorrhagia
	Frequency unknown	Postpartum haemorrhage
General disorders and administration site conditions	Frequent	Asthenia, fatigue, chills, pain
	Less frequent	Mucosal haemorrhage
Investigations	Frequent	Increased serum cholesterol (particularly with prolonged administration and possibly with higher doses), weight loss
	Less frequent	Weight gain, prolonged bleeding time

<u>Reporting of suspected adverse reactions</u>

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals 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

The most commonly reported symptom is somnolence. Generalized seizures may occur. There is a risk of hypoglycaemia. Electrocardiographic changes (e.g. prolongation of QT interval, bundle branch block, QRS prolongation) sinus and ventricular tachycardia, bradycardia, hypotension, vertigo and death have been reported.

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 **ELAVEX XR** are known.

5. PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacological classification: A 1.2 Psychoanaleptics (antidepressants)

Mechanism of action

Venlafaxine and its major metabolite, O-desmethyl venlafaxine are serotonin and norepinephrine re-uptake inhibitors and also weakly inhibit dopamine re-uptake.

Venlafaxine and O-desmethyl venlafaxine reduce ß-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.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

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

Peak plasma concentrations of venlafaxine and O-desmethylvenlafaxine are attained within 6,0± 1,5 and 8,8 ± 2,2 hours respectively.

Food delays the absorption of venlafaxine but has no effect on the extent of absorption of venlafaxine or on the extent of formation of O-desmethyl venlafaxine.

Distribution/ Metabolism

Venlafaxine is extensively metabolised in the liver. O-desmethyl venlafaxine is the major active metabolite of venlafaxine. The mean disposition half-life of venlafaxine and O-desmethyl venlafaxine is approximately 5 and 11 hours, respectively.

Plasma concentrations of venlafaxine and O-desmethyl venlafaxine generally correlated well with dose levels. Venlafaxine and O-desmethyl venlafaxine are less than 35 % bound to plasma proteins (venlafaxine and O-desmethyl venlafaxine 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-desmethyl venlafaxine, conjugated O-desmethyl venlafaxine, or other minor metabolites.

Special populations

Elderly: A 20 % reduction in clearance was noted for O-desmethyl venlafaxine in subjects over 60 years old.

Renal impairment: In patients with moderate to severe impairment of renal function, the total clearance of both venlafaxine and O-desmethyl venlafaxine was reduced, and $t_{1/2}$, was prolonged. The reduction in total clearance was most pronounced in subjects with creatinine clearance < 30 ml/min. Dosage adjustment is recommended for these patients (see section 4.2).

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

6. PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Ammonio methacrylate copolymer type B

Sodium lauryl sulphate

Hypromellose

Magnesium stearate

Eudragit E 100

<u>Capsule content:</u>

ELAVEX 75 mg XR:

Titanium dioxide (E171)

Red iron oxide (E172)

Gelatin

ELAVEX 150 mg XR:

Titanium dioxide (E171)

585.	Erythrosine (E127)
586.	Indigo carmine (E132)
587.	Gelatin
588.	
589.	**6.2 INCOMPATIBILITES**
590.	Not applicable
591.	
592.	**6.3 SHELF LIFE**
593.	24 months
594.	
595.	**6.4 SPECIAL PRECAUTIONS FOR STORAGE**
596.	Store in a cool, dry place at or below 25 °C.
597.	Keep the blister strips in the outer carton until required for use.
598.	Store in unit carton until before use.
599.	KEEP OUT OF REACH OF CHILDREN
600.	
601.	**6.5 NATURE AND CONTENTS OF CONTAINER**
602.	**ELAVEX 75 mg XR:** is packaged in an opaque white PVC/PE/PVDC/ Aluminium blister foil. There are 3
603.	blister strips of 10 capsules each, packed in an outer cardboard box as a pack size of 30 capsules.
604.	**ELAVEX 150 mg XR:** is packaged in an opaque white PVC/PE/PVDC/ Aluminium lister foil. There are 3
605.	blister strips of 10 capsules each, packed in an outer cardboard box as a pack size of 30 capsules.
606.	
607.	**6.6 SPECIAL PRECAUTIONS FOR DISPOSAL AND OTHER HANDLING**
608.	No special requirements.
609.	
610.	**7. HOLDER OF CERTIFICATE OF REGISTRATION**
611.	Accord Healthcare (Pty) Ltd
612.	Building 31, Ground Floor,

613.	Woodlands Office Park,
614.	20 Woodlands Drive, Woodmead,
615.	Johannesburg, 2191
616.	Tel: +27 11 234 5701/2
617.	Email: medinfo@accordhealth.co.za
618.	
619.	**8. REGISTRATION NUMBERS**
620.	**ELAVEX 75 mg XR**: 43/1.2/0138
621.	**ELAVEX 150 mg XR**: 43/1.2/0139
622.	
623.	**9. DATE OF FIRST AUTHORISATION/ RENEWAL OF THE AUTHORISATION**
624.	11 June 2018
625.	
626.	**10. DATE OF REVISION OF THE TEXT**
627.	30 September 2024
628.	