

**APPROVED PROFESSIONAL INFORMATION**

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

27.	<ul style="list-style-type: none"><li>• The treatment of depression, including depression with associated anxiety.</li></ul>
28.	<ul style="list-style-type: none"><li>• Prevention of relapse of an episode of depression in patients that responded to an initial 6 to 8</li></ul>
29.	weeks period of treatment.
30.	<ul style="list-style-type: none"><li>• In patients responding to six months relapse prevention, <b>ELAVEX XR</b> may be used to prevent</li></ul>
31.	recurrence. Safety and efficacy beyond one year have not been demonstrated in clinical
32.	studies.
33.	<ul style="list-style-type: none"><li>• The treatment of generalised anxiety disorder.</li></ul>
34.	<ul style="list-style-type: none"><li>• Treatment of social anxiety disorder. The effectiveness of <b>ELAVEX XR</b> has not been</li></ul>
35.	demonstrated for longer than 12 weeks for this indication.
36.	
37.	<b>4.2 POSOLOGY AND METHOD OF ADMINISTRATION</b>
38.	<b>POSOLOGY</b>
39.	The usual recommended dose for <b>ELAVEX XR</b> is 75 mg, given once daily. If after several weeks further
40.	clinical improvement is required, the dose may be increase to 150 mg per day.
41.	
42.	If needed the dose can further be increased up to 225 mg given once daily. Dose increments should be
43.	made at intervals of approximately 2 weeks or more, but not less_ than 4 days. The maximum
44.	recommended dose is 375 mg per day. This dose should then be gradually reduced consistent with
45.	patient response and tolerance.
46.	
47.	<b>ELAVEX XR</b> should be administered once daily, at approximately the same time, either in the morning
48.	or in the evening.
49.	
50.	<b>Special populations</b>
51.	<b>Patients with renal impairment:</b>
52.	Patients with renal impairment should receive lower doses of <b>ELAVEX XR</b> .
53.	

54.	The total daily dose of <b>ELAVEX XR</b> must be reduced by 25 - 50 % for patients with renal impairment
55.	with a glomerular filtration rate (GFR) of 10 - 70 ml/min.
56.	The total daily dose of <b>ELAVEX XR</b> must be reduced by 50 % in haemodialysis patients. Administration
57.	must be withheld until dialysis session is completed.
58.	
59.	<b>Patients with Hepatic Impairment</b>
60.	The total daily dose of <b>ELAVEX XR</b> must be reduced by 50 % in patients with moderate hepatic
61.	impairment. Reductions of more than 50 % may be appropriate for some patients.
62.	
63.	<b>Elderly Patients</b>
64.	No specific dosage adjustments of <b>ELAVEX XR</b> are recommended based on patient age.
65.	
66.	<b>Paediatric population</b>
67.	See section 4.3.
68.	
69.	<b>Maintenance, Continuation and Extended Treatment</b>
70.	The need for long-term therapy with <b>ELAVEX XR</b> must be periodically reassessed. Whether the dose of
71.	<b>ELAVEX XR</b> needed to induce remission is identical to the dose needed to maintain and/or sustain
72.	euthymia is unknown.
73.	
74.	<b>Discontinuing ELAVEX XR</b>
75.	Dose tapering is recommended when discontinuing <b>ELAVEX XR</b> therapy (see section 4.8). Tapering
76.	over at least a two-week period is recommended if <b>ELAVEX XR</b> has been used for more than 6 weeks.
77.	In clinical trials with <b>ELAVEX XR</b> extended-release capsules, tapering was achieved by reducing the
78.	daily dose by 75 mg at 1-week intervals. The period required for tapering may depend on the dose,
79.	duration of therapy and the individual patient. Patients should be advised to consult their doctor before
80.	abruptly discontinuing <b>ELAVEX XR</b> (see section 4.8).
81.	

82.	<b>METHOD OF ADMINISTRATION</b>
83.	For oral use.
84.	It is recommended that <b>ELAVEX XR</b> be taken with food. Each capsule should be swallowed whole with
85.	fluid. Do not divide, crush, chew or place capsule in water.
86.	
87.	<b>4.3 CONTRA-INDICATIONS:</b>
88.	• Hypersensitivity to venlafaxine or any excipients in the formulation (see section 6.1).
89.	• Concomitant use in patients taking monoamine oxidase inhibitors (MAOIs) (see section 4.4 for
90.	details).
91.	• Children under 18 years (see sections 4.4 and 4.8).
92.	• Pregnancy and lactation (see section 4.6).
93.	
94.	<b>4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE:</b>
95.	<b>Severe adverse reactions have been reported when ELAVEX XR therapy is initiated soon after</b>
96.	<b>discontinuation of a MAOI and when a MAOI is initiated soon after discontinuation of ELAVEX</b>
97.	<b>XR. Reactions have included tremor, myoclonus, diaphoresis, nausea, vomiting, flushing,</b>
98.	<b>dizziness, hyperthermia with features resembling neuroleptic malignant syndrome, seizures and</b>
99.	<b>death. ELAVEX XR must not be initiated for at least 14 days after discontinuation of treatment</b>
100.	<b>with a MAOI. Allow at least 7 days after stopping ELAVEX XR before starting a MAOI (see section</b>
101.	<b>4.5).</b>
102.	
103.	<u>Suicide/ suicidal thoughts or clinical worsening</u>
104.	Patients with major depressive disorder, both adults and children, may experience worsening of their
105.	depression and or the emergence of suicidal ideation and behaviour, whether or not they are taking
106.	antidepressant medicines. This risk may persist until significant remission occurs. A causal role, however,
107.	for antidepressant medicine in inducing such behaviour has not been established. Patients being treated
108.	with <b>ELAVEX XR</b> should, nevertheless, be observed closely for clinical worsening and suicidality,

109.	especially at the beginning of a course of therapy or at any time of dose changes, either increases or
110.	decreases.
111.	
112.	The smallest quantity of medicine, consistent with good patient management, should be provided to
113.	reduce the risk of overdose. Risk assessment for suicide should be performed regularly.
114.	
115.	Patients with a history of suicide-related events, or those exhibiting a significant degree of suicidal
116.	ideation prior to commencement of treatment, are known to be at greater risk of suicidal thoughts or
117.	suicide attempts, and should receive careful monitoring during treatment.
118.	
119.	Because of the possibility of co-morbidity between major depressive disorder and other psychiatric and
120.	non-psychiatric disorders, the same precautions observed when treating patients with major depressive
121.	disorders should be observed when treating patients with other psychiatric and non-psychiatric disorders.
122.	
123.	The following symptoms have been reported in patients being treated with antidepressants for major
124.	depressive disorder as well as for other indications, both psychiatric and non-psychiatric: anxiety,
125.	agitation, panic attacks, insomnia, irritability, hostility (aggressiveness, impulsivity, akathisia, hypomania,
126.	and mania). Although a causal link between the emergence of suicidal impulses has not been
127.	established, consideration should be given to changing the therapeutic regimen, including possibly
128.	discontinuing <b>ELAVEX XR</b> in patients for whom such symptoms are severe, abrupt in onset, or were not
129.	part of the patient's presenting symptoms.
130.	If the decision is made to discontinue treatment, <b>ELAVEX XR</b> should be tapered (see section 4.2)
131.	
132.	<u>Serotonin syndrome</u>
133.	Serotonin syndrome, a potentially life-threatening condition, may occur with venlafaxine treatment,
134.	particularly with concomitant use of other medicines that may affect the serotonergic neurotransmitter
135.	system (including triptans, SSRIs, SNRIs, amphetamines, lithium, sibutramine, St. John's Wort
136.	( <i>Hypericum perforatum</i> ), fentanyl and its analogues, tramadol, dextromethorphan, tapentadol, pethidine,

137.	methadone and pentazocine), with medicines that impair metabolism of serotonin (such as MAOIs e.g.
138.	methylene blue), with serotonin precursors (such as tryptophan supplements) or with antipsychotics or
139.	other dopamine antagonists (see sections 4.3 and 4.5).
140.	
141.	Serotonin syndrome symptoms may include mental status changes (e.g., agitation, hallucinations,
142.	coma), autonomic instability (e.g., tachycardia, labile blood pressure, hyperthermia), neuromuscular
143.	aberrations (e.g., hyperreflexia, incoordination) and/or gastrointestinal symptoms (e.g., nausea, vomiting,
144.	diarrhoea). Serotonin syndrome in its most severe form, can resemble neuroleptic malignant syndrome
145.	(NMS), which includes hyperthermia, muscle rigidity, autonomic instability with possible rapid fluctuation
146.	of vital signs and mental status changes.
147.	
148.	If concomitant treatment with venlafaxine and other medicines that may affect the serotonergic and/or
149.	dopaminergic neurotransmitter systems is clinically warranted, careful observation of the patient is
150.	advised, particularly during treatment initiation and dose increases.
151.	The concomitant use of venlafaxine with serotonin precursors (such as tryptophan supplements) is not
152.	recommended.
153.	
154.	<u>Narrow angle glaucoma</u>
155.	Mydriasis may occur in association with venlafaxine. It is recommended that patients with raised
156.	intraocular pressure or patients at risk for acute narrow-angle glaucoma (angle-closure glaucoma) be
157.	closely monitored.
158.	
159.	<u>Blood pressure</u>
160.	Dose-related increases in blood pressure have been commonly reported with venlafaxine. In some
161.	cases, severely elevated blood pressure requiring immediate treatment has been reported in
162.	postmarketing experience. All patients should be carefully screened for high blood pressure and pre-
163.	existing hypertension should be controlled before initiation of treatment. Blood pressure should be
164.	reviewed periodically, after initiation of treatment and after dose increases.

165.	Caution should be exercised in patients whose underlying conditions might be compromised by increases
166.	in blood pressure, e.g., those with impaired cardiac function.
167.	
168.	<u>Heart rate</u>
169.	Increases in heart rate can occur, particularly with higher doses. Caution should be exercised in patients
170.	whose underlying conditions might be compromised by increases in heart rate.
171.	
172.	<u>Cardiac disease and risk of dysrhythmia</u>
173.	Venlafaxine has not been evaluated in patients with a recent history of myocardial infarction or unstable
174.	heart disease. Therefore, it should be used with caution in these patients.
175.	In postmarketing experience, cases of QTc prolongation, Torsade de Pointes (TdP), ventricular
176.	tachycardia, and fatal cardiac dysrhythmias have been reported with the use of venlafaxine, especially
177.	in overdose or in patients with other risk factors for QTc prolongation/TdP. The balance of risks and
178.	benefits should be considered before prescribing venlafaxine to patients at high risk of serious cardiac
179.	dysrhythmia or QTc prolongation.
180.	
181.	<u>Convulsions</u>
182.	Convulsions may occur with venlafaxine therapy. Venlafaxine should be introduced with
183.	caution in patients with a history of convulsions, and concerned patients should be closely monitored.
184.	Treatment should be discontinued in any patient who develops seizures.
185.	
186.	<u>Hyponatraemia</u>
187.	Cases of hyponatraemia and/or the Syndrome of Inappropriate Antidiuretic Hormone (SIADH) secretion
188.	may occur with venlafaxine. This has most frequently been reported in volume-depleted or dehydrated
189.	patients. Elderly patients, patients taking diuretics, and patients who are otherwise volume-depleted may
190.	be at greater risk for this event.
191.	
192.	<u>Abnormal bleeding</u>

193.	Medicines that inhibit serotonin uptake may lead to reduced platelet function. Bleeding events related to
194.	SSRI and SNRI use have ranged from ecchymoses, hematomas, epistaxis, and petechiae to
195.	gastrointestinal and life-threatening haemorrhages. SSRIs/SNRIs, including venlafaxine, may increase
196.	the risk of postpartum haemorrhage (see section 4.6 and 4.8). The risk of haemorrhage may be increased
197.	in patients taking venlafaxine. Venlafaxine should be used cautiously in patients predisposed to bleeding,
198.	including patients on anticoagulants and platelet inhibitors.
199.	Patients should be advised to notify their doctor if they develop a rash, hives, or a related allergic
200.	phenomenon.
201.	
202.	<u>Serum cholesterol</u>
203.	Serum cholesterol increases have been reported in patients treated for at least 3 months. During long-
204.	term treatment, serum cholesterol measurement should be considered.
205.	
206.	<u>Co-administration with weight loss medicines</u>
207.	The safety and efficacy of venlafaxine therapy in combination with weight loss medicines, including
208.	phentermine, have not been established. Co-administration of venlafaxine and weight loss medicines is
209.	not recommended. Venlafaxine is not indicated for weight loss alone or in combination with other
210.	products.
211.	
212.	<u>Mania/hypomania</u>
213.	Mania/hypomania may occur in a small proportion of patients with mood disorders who have received
214.	antidepressants, including venlafaxine. Venlafaxine should be used cautiously in patients with a history
215.	or family history of bipolar disorder.
216.	
217.	<u>Aggression</u>
218.	Aggression may occur in some patients who have received antidepressants, including venlafaxine. This
219.	has been reported under initiation, dose changes and discontinuation of treatment. Venlafaxine should
220.	be used cautiously in patients with a history of aggression.

221.	
222.	<u>Abuse and dependence</u>
223.	Patients taking venlafaxine over long periods of time show no signs of drug-seeking behaviour,
224.	development of tolerance, or dose escalation. Doctors are nevertheless advised to carefully evaluate
225.	patients for a history of drug abuse, to monitor such patients closely and screen them for signs of misuse
226.	or abuse of <b>ELAVEX XR</b> (e.g. drug-seeking behaviour, increases in dose or development of tolerance).
227.	
228.	<u>Discontinuation of treatment</u>
229.	Discontinuation effects are well known to occur with antidepressants, and sometimes these effects can
230.	be protracted and severe. It is therefore recommended that the dosage of <b>ELAVEX XR</b> be tapered
231.	gradually and the patient be monitored (see section 4.2). Suicide/suicidal thoughts and aggression have
232.	been observed in patients during changes in venlafaxine dosing regimen, including during
233.	discontinuation. Therefore, patients should be closely monitored when the dose is reduced or during
234.	discontinuation (see above in section 4.4 - Suicide/suicidal thoughts or clinical worsening, and
235.	Aggression).
236.	Withdrawal symptoms, when treatment is discontinued, are common, particularly if discontinuation is
237.	abrupt.
238.	
239.	The risk of withdrawal symptoms may be dependent on several factors, including the duration and dose
240.	of therapy and the rate of dose reduction. Dizziness, sensory disturbances (including paraesthesia),
241.	sleep disturbances (including insomnia and intense dreams), agitation or anxiety, nausea and/or
242.	vomiting, tremor, headache, visual_impairment and hypertension are frequently reported reactions.
243.	Generally, these symptoms are mild to moderate; however, in some patients they may be severe in
244.	intensity. They usually occur within the first few days of discontinuing treatment, but there have been
245.	very rare reports of such symptoms in patients who have inadvertently missed a dose. Generally, these
246.	symptoms are self-limiting and usually resolve within 2 weeks, though in some individuals they may be
247.	prolonged (2-3 months or more). It is therefore advised that venlafaxine should be gradually tapered
248.	

249.	when discontinuing treatment over a period of several weeks or months, according to the patient's needs
250.	(see section 4.2). In some patients, discontinuation could take months or longer.
251.	
252.	<u>Sexual dysfunction</u>
253.	Serotonin-norepinephrine reuptake inhibitors (SNRIs) may cause symptoms of sexual dysfunction (see
254.	section 4.8).
255.	There have been reports of long-lasting sexual dysfunction where the symptoms have continued despite
256.	discontinuation of SNRIs.
257.	
258.	<u>Akathisia/psychomotor restlessness</u>
259.	The use of venlafaxine has been associated with the development of akathisia, characterised by a
260.	subjectively unpleasant or distressing restlessness and need to move often accompanied by an inability
261.	to sit or stand still. This is most likely to occur within the first few weeks of treatment. In patients who
262.	develop these symptoms, increasing the dose may be detrimental.
263.	
264.	<u>Dry mouth</u>
265.	Dry mouth has been reported in patients treated with venlafaxine. This may increase the risk of caries,
266.	and patients should be advised upon the importance of dental hygiene.
267.	
268.	<u>Diabetes</u>
269.	In patients with diabetes, treatment with an SSRI or venlafaxine may alter glycaemic control. Insulin
270.	and/or oral antidiabetic dosage may need to be adjusted.
271.	
272.	<u>Drug-Laboratory Test Interactions</u>
273.	False-positive urine immunoassay screening tests for phencyclidine (PCP) and amphetamine have been
274.	reported in patients taking venlafaxine. This is due to lack of specificity of the screening tests. False
275.	positive test results may be expected for several days following discontinuation of venlafaxine therapy.
276.	Confirmatory tests, such as gas

277.	chromatography/mass spectrometry, will distinguish venlafaxine from PCP and amphetamine.
278.	
279.	<u>Use in elderly patients</u>
280.	<b>ELAVEX XR</b> appears to pose no exceptional safety problems for healthy elderly patients. Although age-
281.	related clinical circumstances, such as renal impairment, may warrant a dose reduction in the elderly.
282.	
283.	<u>Paediatric population</u>
284.	<b>Safety and efficacy in children under 18 years of age have not been established (see sections 4.3</b>
285.	<b>and 4.8).</b>
286.	
287.	<b>4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTION:</b>
288.	<i>Monoamine oxidase inhibitors</i> (see sections 4.3 and 4.4)
289.	Recent discontinuation from a MAOI followed by initiation of <b>ELAVEX XR</b> , or recent discontinuation from
290.	<b>ELAVEX XR</b> , prior to initiation of MAOI may result in emergence of severe adverse reactions (see section
291.	4.3).
292.	
293.	These reactions have included tremor, myoclonus, diaphoresis, nausea, vomiting, flushing, dizziness,
294.	hyperthermia with features resembling narcoleptic malignant syndrome, seizures and death.
295.	
296.	<i>CNS Active medicines</i>
297.	Based on the known mechanism of action of <b>ELAVEX XR</b> and the potential for serotonin syndrome,
298.	caution is advised when <b>ELAVEX XR</b> is co-administered with other medicines that may affect the
299.	serotonergic neurotransmitter system (such as triptans, selective serotonin re-uptake inhibitors or
300.	lithium).
301.	
302.	<i>Indinavir</i>
303.	A pharmacokinetic study with indinavir has shown a 28 % decrease in AUC and a 36 % decrease in C <sub>max</sub>
304.	for indinavir. Indinavir did not affect the pharmacokinetics of <b>ELAVEX XR</b> and O-desmethyl venlafaxine.

305.	The clinical significance of this interaction is unknown.
306.	
307.	<i>Warfarin</i>
308.	Potential of anticoagulant effects may occur in patients taking warfarin following the addition of
309.	<b>ELAVEX XR.</b>
310.	
311.	<i>Ethanol</i>
312.	<b>ELAVEX XR</b> may increase the impairment of mental and motor skills caused by ethanol. Patients should
313.	be advised to avoid alcohol consumption while taking <b>ELAVEX XR.</b>
314.	
315.	<i>Medicines that prolong the QT interval</i>
316.	The risk of QTc prolongation and/or ventricular dysrhythmias (e.g., TdP) is increased with concomitant
317.	use of other medicines which prolong the QTc interval. Co-administration of such medicines should be
318.	avoided (see section 4.4).
319.	Relevant classes include:
320.	• class Ia and III antidysrhythmics (e.g. quinidine, amiodarone, sotalol, dofetilide)
321.	• some antipsychotics (e.g. thioridazine)
322.	• some macrolides (e.g. erythromycin)
323.	• some antihistamines
324.	• some quinolone antibiotics (e.g. moxifloxacin)
325.	The above list is not exhaustive and other individual medicines known to significantly increase QT interval
326.	should be avoided.
327.	
328.	<i>Ketoconazole</i>
329.	Concomitant use of CYP3A4 inhibitors (e.g., atazanavir, clarithromycin, indinavir, itraconazole,
330.	voriconazole, posaconazole, ketoconazole, nelfinavir, ritonavir, saquinavir, telithromycin) and
331.	venlafaxine may increase levels of venlafaxine and O-desmethylvenlafaxine. Therefore, caution is
332.	advised if a patient's therapy includes a CYP3A4 inhibitor and venlafaxine concomitantly.

333.	
334.	<i>Haloperidol</i>
335.	A pharmacokinetic study with haloperidol has shown for haloperidol a 42 % decrease in total oral
336.	clearance, a 70 % increase in AUC, an 88 % increase in C <sub>max</sub> , but no change in half- life. This should be
337.	taken into account in patients treated with haloperidol and <b>ELAVEX XR</b> concomitantly.
338.	
339.	<i>Cimetidine</i>
340.	At steady state, cimetidine has been shown to inhibit first-pass metabolism of <b>ELAVEX XR</b> ; however
341.	cimetidine had no apparent effect on the formation or elimination of O-desmethyl venlafaxine which is
342.	present in a much greater quantity in the systemic circulation. The overall pharmacological activity of
343.	<b>ELAVEX XR</b> plus O-desmethyl venlafaxine is expected to increase only slightly in most patients. No
344.	adjustments seem necessary when <b>ELAVEX XR</b> is co-administered with cimetidine. However, for elderly
345.	or patients with hepatic dysfunction concomitantly taking <b>ELAVEX XR</b> and cimetidine the extent of
346.	interaction is not known and potentially may be more pronounced. For such patients, clinical monitoring
347.	is indicated.
348.	
349.	<i>Imipramine</i>
350.	<b>ELAVEX XR</b> did not affect the pharmacokinetics of imipramine and 2-OH-imipramine. However,
351.	desipramine AUC, C <sub>max</sub> and C <sub>min</sub> , increased by about 35 % in the presence of venlafaxine. There was an
352.	increase of 2-OH-desipramine AUC by 2,5 to 4,5-fold. Imipramine did not affect the pharmacokinetics of
353.	<b>ELAVEX XR</b> and O-desmethyl venlafaxine. This should be taken into account in patients treated with
354.	imipramine and venlafaxine concomitantly.
355.	
356.	<i>Risperidone</i>
357.	<b>ELAVEX XR</b> may increase the risperidone AUC by 32 % but does not significantly alter the
358.	pharmacokinetic profile of the total active moiety (risperidone plus 9 hydroxyrisperidone). The clinical
359.	significance of this interaction is unknown.
360.	

361.	<i>Metoprolol</i>
362.	Concomitant administration of venlafaxine and metoprolol to healthy volunteers in a pharmacokinetic
363.	interaction study for both medicines resulted in an increase of plasma concentrations of metoprolol by
364.	approximately 30-40 % without altering the plasma concentrations of its active metabolite, $\alpha$ -
365.	hydroxymetoprolol. The clinical relevance of this finding in hypertensive patients is unknown. Metoprolol
366.	did not alter the pharmacokinetic profile of venlafaxine or its active metabolite, O-desmethylvenlafaxine.
367.	Caution should be exercised with co-administration of venlafaxine and metoprolol.
368.	
369.	<i>Diazepam</i>
370.	Diazepam does not appear to affect the pharmacokinetics of either <b>ELAVEX XR</b> or O-
371.	desmethylvenlafaxine.
372.	<b>ELAVEX XR</b> has no effect on the pharmacokinetic and pharmacodynamics of diazepam and its active
373.	metabolite, desmethyldiazepam.
374.	
375.	<i>Lithium</i>
376.	The steady-state pharmacokinetics of <b>ELAVEX XR</b> and O-desmethyl venlafaxine are not affected when
377.	lithium is co-administered. The pharmacokinetics of lithium is also not affected by <b>ELAVEX XR</b> .
378.	
379.	<i>Medicines highly bound to plasma proteins</i>
380.	<b>ELAVEX XR</b> is not highly bound to plasma proteins (27 % bound); therefore, administration of <b>ELAVEX</b>
381.	<b>XR</b> to a patient taking another medicine that is highly protein bound is not expected to cause increased
382.	free concentrations of the other medicine.
383.	
384.	<i>Medicines metabolised by cytochrome P450 isoenzymes</i>
385.	<b>ELAVEX XR</b> is a relatively weak inhibitor of CYP2D6. <b>ELAVEX XR</b> does not inhibit CYP3A4, CYP1A2
386.	and CYP2C9 <i>in vitro</i> .
387.	
388.	<i>Oral contraceptives</i>

389.	<p>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.</p>
390.	
391.	
392.	
393.	<p><b>4.6 FERTILITY, PREGNANCY AND LACTATION:</b></p>
394.	<p>Safety during human pregnancy and lactation has not been established (see section 4.3).</p>
395.	<p>Neonates exposed to <b>ELAVEX XR</b> late in the third trimester have developed complications requiring respiratory support or prolonged hospitalisation. Discontinuation/withdrawal effects have been seen in newborns.</p>
396.	
397.	
398.	
399.	<p><b>ELAVEX XR</b> and O-desmethyl venlafaxine are excreted in breast milk; therefore, a decision should be made whether to stop breastfeeding or to discontinue <b>ELAVEX XR</b>. Patients should be advised to notify their doctor if they become pregnant or intend to fall pregnant during therapy.</p>
400.	
401.	
402.	
403.	<p><b>4.7 EFFECTS ON THE ABILITY TO DRIVE AND USE MACHINES</b></p>
404.	<p><b>ELAVEX XR</b> may impair judgment, thinking and motor skills. Therefore, patients should be cautioned about their ability to drive or operate hazardous machinery.</p>
405.	
406.	
407.	<p><b>4.8 UNDESIRABLE EFFECTS</b></p>
408.	<p><u>a. Summary of the safety profile</u></p>
409.	<p>The most commonly observed events associated with the use of <b>ELAVEX XR</b> are nervous system complaints, such as headache, dizziness, insomnia, somnolence, nervousness and dry mouth;</p>
410.	
411.	<p>gastrointestinal complaints, including anorexia, nausea and constipation; and abnormal ejaculation/orgasm, sweating and asthenia.</p>
412.	
413.	
414.	<p>Incidence terminology:</p>
415.	<p>The occurrence of many frequently observed adverse events is dose related. Adverse events generally decrease in intensity and frequency with continued therapy.</p>
416.	

417.																																					
418.	<u>b. Tabulated list of adverse reactions</u>																																				
419.	The following side-effects have been reported with the use of <b>ELAVEX XR</b> :																																				
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445.			Malignant Syndrome (NMS), serotonin
446.			syndrome, convulsion, dystonia, tardive
447.			dyskinesia
448.		Frequency unknown	Amnesia, hypoaesthesia, trismus
449.	<b>Eye disorders</b>	Frequent	Abnormality accommodation, mydriasis,
450.			visual disturbance
451.		Less frequent	Angle closure glaucoma
452.	<b>Ear and labyrinth disorders</b>	Less frequent	Tinnitus
453.		Frequency unknown	Vertigo
454.	<b>Cardiac disorders</b>	Frequent	Tachycardia, palpitations
455.		Less frequent	Torsade de pointes, QT prolongation,
456.			ventricular fibrillation, ventricular tachycardia
457.		Frequency unknown	Stress cardiomyopathy (takotsubo
458.			cardiomyopathy)
459.	<b>Vascular disorders</b>	Frequent	Hypertension, vasodilatation (mostly hot
460.			flushes)
461.		Less frequent	Hypotension, postural hypotension
462.	<b>Respiratory, thoracic and mediastinal disorders</b>	Frequent	Yawning, dyspnoea
463.		Less frequent	Pulmonary eosinophilia, interstitial lung
464.			disease
465.		Frequency unknown	Pharyngitis, rhinitis
466.	<b>Gastrointestinal disorders</b>	Frequent	Dry mouth, anorexia, constipation,
467.			dyspepsia, nausea, vomiting, abdominal pain
468.		Less frequent	Altered taste sensation, diarrhoea,
469.			pancreatitis, gastrointestinal haemorrhage
470.		Frequency unknown	Eructation, flatulence
471.	<b>Hepato-biliary disorders</b>	Less frequent	Abnormal liver function test, hepatitis
472.			

473.	<b>Skin and subcutaneous tissue disorders</b>	Frequent	Hyperhidrosis (including night sweats)
474.		Less frequent	Rash, alopecia, erythema multiforme, Stevens-Johnson syndrome, pruritus, urticaria, ecchymosis, angioedema, photosensitivity reaction
475.			
476.		Frequency unknown	Toxic epidermal necrolysis
477.			
478.			
479.	<b>Musculoskeletal, connective tissue and bone disorders</b>	Frequent	Hypertonia, neck pain, back pain
480.		Less frequent	Rhabdomyolysis, arthralgia
481.		Frequency unknown	Myalgia
482.	<b>Renal and urinary disorders</b>	Frequent	Impaired urination (mostly hesitancy), pollakiuria
483.		Less frequent	Urinary retention, urinary incontinence
484.			
485.	Frequency unknown	Urinary frequency	
486.			
487.			
488.	<b>Reproductive system and breast disorders</b>	Frequent	Metrorrhagia, erectile dysfunction, ejaculation disorder, anorgasmia
489.		Less frequent	Abnormal orgasm, menorrhagia
490.		Frequency unknown	Postpartum haemorrhage
491.	<b>General disorders and administration site conditions</b>	Frequent	Asthenia, fatigue, chills, pain
492.		Less frequent	Mucosal haemorrhage
493.	<b>Investigations</b>	Frequent	Increased serum cholesterol (particularly with prolonged administration and possibly with higher doses), weight loss
494.			
495.		Less frequent	Weight gain, prolonged bleeding time
496.			
497.			
498.	<u>Reporting of suspected adverse reactions</u>		
499.			
500.			

501.	Reporting suspected adverse reactions after authorisation of the medicine is important. It allows
502.	continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to
503.	report any suspected adverse reactions to SAHPRA via the “ <b>6.04 Adverse Drug Reactions Reporting</b>
504.	<b>Form</b> ”, found online under SAHPRA’s publications: <a href="https://www.sahpra.org.za/Publications/Index/8">https://www.sahpra.org.za/Publications/Index/8</a>
505.	
506.	<b>4.9 OVERDOSE</b>
507.	The most commonly reported symptom is somnolence. Generalized seizures may occur. There is a risk
508.	of hypoglycaemia. Electrocardiographic changes (e.g. prolongation of QT interval, bundle branch block,
509.	QRS prolongation) sinus and ventricular tachycardia, bradycardia, hypotension, vertigo and death have
510.	been reported.
511.	
512.	<b>Recommended Treatment</b>
513.	General supportive and symptomatic measures are recommended; cardiac rhythm and vital signs must
514.	be monitored.
515.	When there is a risk of aspiration, induction of emesis is not recommended.
516.	Administration of activated charcoal may also limit medicine absorption.
517.	Forced diuresis, dialysis, haemoperfusion and exchange transfusion are unlikely to be of benefit.
518.	No specific antidotes for <b>ELAVEX XR</b> are known.
519.	
520.	<b>5. PHARMACOLOGICAL PROPERTIES</b>
521.	<b>5.1 PHARMACODYNAMIC PROPERTIES</b>
522.	Pharmacological classification: A 1.2 Psychoanaleptics (antidepressants)
523.	
524.	<u>Mechanism of action</u>
525.	Venlafaxine and its major metabolite, O-desmethyl venlafaxine are serotonin and norepinephrine re-
526.	uptake inhibitors and also weakly inhibit dopamine re-uptake.
527.	
528.	

529.	Venlafaxine and O-desmethyl venlafaxine 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.
530.	
531.	
532.	
533.	<b>5.2 PHARMACOKINETIC PROPERTIES</b>
534.	<u>Absorption</u>
535.	Venlafaxine is well absorbed and undergoes extensive first-pass metabolism.
536.	Peak plasma concentrations of venlafaxine and O-desmethylvenlafaxine are attained within $6,0 \pm 1,5$ and
537.	$8,8 \pm 2,2$ hours respectively.
538.	Food delays the absorption of venlafaxine but has no effect on the extent of absorption of venlafaxine or
539.	on the extent of formation of O-desmethyl venlafaxine.
540.	
541.	<u>Distribution/ Metabolism</u>
542.	Venlafaxine is extensively metabolised in the liver. O-desmethyl venlafaxine is the major active
543.	metabolite of venlafaxine. The mean disposition half-life of venlafaxine and O-desmethyl venlafaxine is
544.	approximately 5 and 11 hours, respectively.
545.	Plasma concentrations of venlafaxine and O-desmethyl venlafaxine generally correlated well with dose
546.	levels. Venlafaxine and O-desmethyl venlafaxine are less than 35 % bound to plasma proteins
547.	(venlafaxine and O-desmethyl venlafaxine are 27 % and 30 % bound to plasma proteins respectively).
548.	
549.	<u>Elimination</u>
550.	Venlafaxine and its metabolites are excreted primarily through the kidneys.
551.	Approximately 87 % of a venlafaxine dose is recovered in the urine within 48 hours as either unchanged
552.	venlafaxine, unconjugated O-desmethyl venlafaxine, conjugated O-desmethyl venlafaxine, or other
553.	minor metabolites.
554.	
555.	<u>Special populations</u>
556.	

557.	<i>Elderly:</i> A 20 % reduction in clearance was noted for O-desmethyl venlafaxine in subjects over 60 years
558.	old.
559.	
560.	<i>Renal impairment:</i> In patients with moderate to severe impairment of renal function, the total clearance
561.	of both venlafaxine and O-desmethyl venlafaxine was reduced, and $t_{1/2}$ , was prolonged. The reduction in
562.	total clearance was most pronounced in subjects with creatinine clearance < 30 ml/min. Dosage
563.	adjustment is recommended for these patients (see section 4.2).
564.	
565.	<i>Hepatic impairment:</i> In patients with compensated hepatic cirrhosis, the pharmacokinetics disposition of
566.	both, venlafaxine and O-desmethyl venlafaxine was significantly altered. The reduction in both the
567.	metabolism of venlafaxine and elimination of O-desmethyl venlafaxine resulted in higher plasma
568.	concentrations of both. Dosage adjustment is recommended in these patients (see section 4.2).
569.	
570.	<b>6. PHARMACEUTICAL PARTICULARS</b>
571.	<b>6.1 LIST OF EXCIPIENTS</b>
572.	Ammonio methacrylate copolymer type B
573.	Sodium lauryl sulphate
574.	Hypromellose
575.	Magnesium stearate
576.	Eudragit E 100
577.	
578.	<u>Capsule content:</u>
579.	<b>ELAVEX 75 mg XR:</b>
580.	Titanium dioxide (E171)
581.	Red iron oxide (E172)
582.	Gelatin
583.	<b>ELAVEX 150 mg XR:</b>
584.	Titanium dioxide (E171)

Applicant/HCR: *Accord Healthcare (Pty) Ltd*  
 Product Name: *Elavex 75 mg XR and Elavex 150 mg XR*  
 Strength: *75 mg/150 mg venlafaxine hydrochloride per extended release capsule*

585.	Erythrosine (E127)
586.	Indigo carmine (E132)
587.	Gelatin
588.	
589.	<b>6.2 INCOMPATIBILITES</b>
590.	Not applicable
591.	
592.	<b>6.3 SHELF LIFE</b>
593.	24 months
594.	
595.	<b>6.4 SPECIAL PRECAUTIONS FOR STORAGE</b>
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.	<b>6.5 NATURE AND CONTENTS OF CONTAINER</b>
602.	<b>ELAVEX 75 mg XR:</b> 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.	<b>ELAVEX 150 mg XR:</b> 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.	<b>6.6 SPECIAL PRECAUTIONS FOR DISPOSAL AND OTHER HANDLING</b>
608.	No special requirements.
609.	
610.	<b>7. HOLDER OF CERTIFICATE OF REGISTRATION</b>
611.	Accord Healthcare (Pty) Ltd
612.	Building 31, Ground Floor,

**Applicant/HCR: Accord Healthcare (Pty) Ltd**  
**Product Name: Elavex 75 mg XR and Elavex 150 mg XR**  
**Strength: 75 mg/150 mg venlafaxine hydrochloride per extended release capsule**

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