1.3.1.1 Professional Information for medicines for human use

SCHEDULING STATUS

S5

1 NAME OF THE MEDICINE

MYLAN VENLAFAXINE XL 75 (capsules)

MYLAN VENLAFAXINE XL 150 (capsules)

2 QUALITIVE AND QUANTITIVE COMPOSITION

MYLAN VENLAFAXINE XL 75

Each capsule contains venlafaxine hydrochloride equivalent to 75 mg venlafaxine.

Sugar free

Excipients with known effect:

This medicine contains less than 1 mmol sodium (23 mg) per capsule, that is to say essentially 'sodium free'.

MYLAN VENLAFAXINE XL 150

Each capsule contains venlafaxine hydrochloride equivalent to 150 mg venlafaxine.

Sugar free

Excipients with known effect:

This medicine contains less than 1 mmol sodium (23 mg) per capsule, that is to say essentially 'sodium free'.

For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

MYLAN VENLAFAXINE XL 75:

A flesh opaque- flesh opaque size 0 hard gelatin capsule containing two (37,5 mg) tablets.

MYLAN VENLAFAXINE XL 150:

A scarlet opaque- scarlet opaque size 00 hard gelatin capsule containing two (75 mg) tablets.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

MYLAN VENLAFAXINE XL is indicated for the treatment of depression, including depression with associated anxiety.

MYLAN VENLAFAXINE XL is indicated for the prevention of relapses of an episode of depression in patients responding to an initial 6 to 8 weeks treatment. In patients responding to 6 months of relapse prevention, MYLAN VENLAFAXINE XL may be used to prevent recurrence. Safety and efficacy beyond one year have not been demonstrated in clinical studies.

4.2 Posology and method of administration

Posology

- The usual recommended dose for MYLAN VENLAFAXINE XL 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.

- It is recommended that MYLAN VENLAFAXINE XL be taken with food.
- Each capsule should be swallowed whole with fluid.
- Do not divide, crush, chew or place capsule in water.
- MYLAN VENLAFAXINE XL should be administered once daily, at approximately the same time either morning or in the evening. The extended-release formulation allows venlafaxine to be released slowly into the digestive tract.

Special populations

Elderly population:

- No specific dosage adjustments of MYLAN VENLAFAXINE XL are recommended based on the patient's age.

Patients with renal impairment:

- Patients with renal impairment should receive lower doses of MYLAN VENLAFAXINE XL.
- The total daily dose of MYLAN VENLAFAXINE XL 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 MYLAN VENLAFAXINE XL should be reduced by 50 % in haemodialysis patients.
- Because of individual variability in clearance in these patients, individualisation of dosage may be desirable.

Patients with hepatic impairment:

- The total daily dose of MYLAN VENLAFAXINE XL 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 MYLAN VENLAFAXINE XL 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.

Paediatric population

- Not for use for children under the age of 18 years *(see section 4.3*).

Maintenance, continuation and extended treatment

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

Discontinuing MYLAN VENLAFAXINE XL

- Dose tapering with an immediate release venlafaxine formulation is recommended when discontinuing MYLAN VENLAFAXINE XL therapy.
- Tapering over at least a two-week period is recommended if MYLAN VENLAFAXINE XL has been used for more than 6 weeks (*see section 4.4 and 4.8*).
- 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 MYLAN VENLAFAXINE XL (*see section 4.4 and 4.8*).

Method of administration

- For oral use.

4.3 Contraindications

- Hypersensitivity to the active substance ~~MYLAN~~ venlafaxine ~~XL~~ or any excipients in the formulation.
- Children under the age of 18 years (*see section 4.4 and 4.8*).
- Pregnancy and lactation (*see section 4.6*).
- Concomitant use in patients taking monoamine oxidase inhibitors (MAOIs) (*see section 4.4*).

4.4 Special warnings and precautions for use

Monoamine oxidase inhibitor (MAOI)

Severe adverse reactions have been reported when MYLAN VENLAFAXINE XL therapy is initiated soon after discontinuation of a monoamine oxidase inhibitor (MAOI) and when an MAOI is initiated soon after discontinuation of MYLAN VENLAFAXINE XL. Reactions have included tremor, myoclonus, diaphoresis, nausea, vomiting, flushing, dizziness, hyperthermia with features resembling neuroleptic malignant syndrome, seizures and death. MYLAN VENLAFAXINE XL must not be initiated for at least 14 days after discontinuing treatment with a monoamine oxidase inhibitor (MAOI). Allow at least 7 days after stopping MYLAN VENLAFAXINE XL before starting a MAOI (*see section 4.5 and 4.3*).

Convulsions

MYLAN VENLAFAXINE XL should be introduced with care in patients with a history of seizures and should be discontinued in any patient developing a seizure.

Overdose

Patients should be advised not to use alcohol, considering its central nervous system (CNS)-

effects and potential of clinical worsening of psychiatric conditions, and the potential for adverse interactions with MYLAN VENLAFAXINE XL including CNS depressant effects *(see section 4.5*). Overdose with MYLAN VENLAFAXINE XL has been reported predominantly in combination with alcohol and/or other medicines, including cases with fatal outcome *(see section 4.9)*.

Prescriptions for MYLAN VENLAFAXINE XL should be written for the smallest quantity consistent with good patient management, in order to reduce the risk of overdose *(see section 4.9).*

Suicide/suicidal thoughts or clinical worsening

The risk of suicide must be considered in all depressed patients. Prescriptions for MYLAN VENLAFAXINE XL should be written for the smallest quantity of capsules consistent with good patient management in order to reduce the possibility of overdose.

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. The 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 MYLAN VENLAFAXINE XL should, nevertheless, be observed closely for clinical worsening of symptoms 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 MYLAN VENLAFAXINE XL, in patients for whom such symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms.

Serotonin syndrome

Serotonin syndrome, a potentially life-threatening condition, may occur with MYLAN VENLAFAXINE XL treatment, particularly with concomitant use of other medicines that may affect the serotonergic neurotransmitter system (including triptans, SSRIs, SNRIs, tricyclic antidepressants, amphetamines, lithium, sibutramine, St. John's Wort (*Hypericum perforatum)*, opioids (e.g. buprenorphine, 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*).

Narrow-angle glaucoma

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

Mania/hypomania

Activation of mania/hypomania has been reported. MYLAN VENLAFAXINE XL should be used with caution in patients with a history of mania or family history of bipolar disorder.

Aggression

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

Hyponatraemia

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

If the decision is made to discontinue treatment, the dosage of MYLAN VENLAFAXINE XL should be tapered (*see section 4.4 and 4.2*).

Allergic reactions

Patients should be advised to notify their doctor if they develop a rash, urticaria, or a related allergic phenomenon (*see section 4.8*).

Co-administration with weight loss medicines

Treatment-associated anorexia has frequently been reported with venlafaxine. Dose-related weight loss has also been noted. Significant weight loss, especially in underweight depressed patients, may be an undesirable effect of venlafaxine treatment. Weight gain has been experienced less frequently. MYLAN VENLAFAXINE XL is not indicated for weight loss, alone or in combination with other medicines.

Serum cholesterol

Measurement of serum cholesterol levels should be considered during long-term treatment.

Abnormal bleeding

Medicines that inhibit serotonin uptake may lead to abnormalities of platelet aggregation. The risk of skin and mucous membrane bleeding including gastrointestinal haemorrhage, may be increased. SSRIs/SNRIs such as MYLAN VENLAFAXINE XL may increase the risk of postpartum haemorrhage *(see sections 4.6 and 4.8*). MYLAN VENLAFAXINE XL should be used cautiously in patients predisposed to bleeding, including patients on anti-coagulants and platelet inhibitors.

Concomitant use of aspirin, nonsteroidal anti-inflammatory drugs (NSAIDs), warfarin, and other anticoagulants or other medicines known to affect platelet function may add to this risk. Case reports and epidemiological studies (case-control and cohort design) have demonstrated an association between use of medicines that interfere with serotonin reuptake and the occurrence of gastrointestinal bleeding.

Inform patients about the risk of bleeding associated with the concomitant use of MYLAN VENLAFAXINE XL and nonsteroidal anti-inflammatory drugs (NSAIDs), aspirin, or other medicines that affect coagulation. For patients taking warfarin, carefully monitor coagulation indices when initiating, titrating, or discontinuing MYLAN VENLAFAXINE XL.

General

Clinical experience with MYLAN VENLAFAXINE XL in patients with concomitant systemic illnesses is limited. Caution is advised in administering MYLAN VENLAFAXINE XL to patients with diseases or conditions that could affect haemodynamic responses or metabolism.

Cardiac disease and risk of arrhythmia

MYLAN VENLAFAXINE XL has not been evaluated or used to any appreciable extent in

patients with a recent history of myocardial infarction or unstable heart disease. The mean heart rate may be increased during treatment. As increases in heart rate were observed, caution should be exercised in patients whose underlying medical conditions might be compromised by increases in heart rate (e.g. patients with hyperthyroidism, heart failure, or recent myocardial infarction).

Treatment with MYLAN VENLAFAXINE XL has been associated with an increase in blood pressure in some patients. The presence of treated hypertension or elevated blood pressure at baseline does not seem to predispose patients to further increases during MYLAN VENLAFAXINE XL therapy.

Blood pressure monitoring may be advisable. Either dose reduction or discontinuation should be considered for patients who experience a sustained increase in blood pressure while receiving MYLAN VENLAFAXINE XL.

QTc prolongation, Torsade de Pointes (TdP), ventricular tachycardia and fatal cardiac dysrhythmias have been reported with the use of MYLAN VENLAFAXINE XL, 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 MYLAN VENLAFAXINE XL to patients at high risk of serious cardiac dysrhythmia or QTc prolongation.

Hepatic and renal impaiment

MYLAN VENLAFAXINE XL should not be used in patients with moderate to severe renal impairment or cirrhosis of the liver as this dosage form is not suitable for these patients.

Discontinuing MYLAN VENLAFAXINE XL treatment

Abrupt discontinuation of MYLAN VENLAFAXINE XL can lead to withdrawal effects. Symptoms of withdrawal include dizziness, sensory disturbances (including paraesthesia and electric shock sensations), sleep disturbances (including insomnia and abnormal dreams), agitation, anxiety, nausea, vomiting, tremor, sweating, headache, diarrhoea, palpitations and emotional instability.

Sexual dysfunction

Serotonin-norepinephrine reuptake inhibitors (SNRIs) such as MYLAN VENLAFAXINE XL may cause symptoms of sexual dysfunction (*see section 4.8*).

Diabetes

In patients with diabetes, treatment with a SSRI or MYLAN VENLAFAXINE XL 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 MYLAN VENLAFAXINE XL. This is due to lack of specificity of the screening tests. False-positive test results may be expected for several days following discontinuation of MYLAN VENLAFAXINE XL therapy. Confirmatory tests, such as gas chromatography/mass spectrometry, will distinguish MYLAN VENLAFAXINE XL from PCP and amphetamine.

Paediatric use

Safety and efficacy in children under 18 years of age have not been established (*see section 4.3, 4.4 and 4.8*).

In clinical trials in children with major depressive disorder, there were increased reports of hostility and suicide-related adverse events such as suicidal ideation and self-harm *(see section 4.3*.

Use in elderly patients

MYLAN VENLAFAXINE XL appears to pose no exceptional safety problems for healthy elderly patients.

Abuse and dependence

It is recommended that doctors carefully evaluate patients for a history of medicine abuse and follow such patients closely, observing them for signs of misuse or abuse of MYLAN VENLAFAXINE XL (e.g. development of tolerance, increase in dose, medicine-seeking behaviour).

MYLAN VENLAFAXINE XL contains sodium

This medicine contains less than 1 mmol sodium (23 mg) per capsule, that is to say essentially 'sodium free'.

4.5 Interaction with other medicines and other forms of Interaction

Monoamine oxidase inhibitors - (*see section 4.4 and 4.3*).

Severe adverse reactions have been reported in patients who have recently discontinued taking MAOI's and started on MYLAN VENLAFAXINE XL or have recently had MYLAN VENLAFAXINE XL discontinued prior to initiation of an MAOI (*see section 4.3*).

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

CNS active medicines:

Based on the known mechanism of action of MYLAN VENLAFAXINE XL and the potential for serotonin syndrome, caution is advised when MYLAN VENLAFAXINE XL is co-administered with other medicines that may affect serotogenic neurotransmitter system, such as triptans, selective serotonin re-uptake inhibitors, lithium, sibutramine, tramadol, St John's Wort (*Hypericum perforatum*).

Serotonin syndrome

Serotonin syndrome, a potentially life-threatening condition which may occur with MYLAN VENLAFAXINE XL treatment, particularly with concomitant use of other medicines that may affect the serotonergic neurotransmitter system (including triptans, SSRIs, other SNRIs, tricyclic antidepressants, amphetamines, lithium, sibutramine, tramadol, or St. John's Wort *(Hypericum perforatum)*, opioids (e.g. buprenorphine), with medicines which impair metabolism of serotonin (such as MAOIs, including linezolid (an antibiotic), selegiline (for Parkinson's disease), *(see section 4.3*), or with serotonin precursors (such as tryptophan supplements). Serotonin syndrome symptoms may include mental status changes, autonomic instability, neuromuscular aberrations and/or gastrointestinal symptoms *(see sections 4.3 and 4.4)*.

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

Indinavir:

Pharmacokinetic studies showed a 28 % decrease in AUC and a 36 % decrease in Cmax for indinavir. lndinavir does not affect the pharmacokinetics of MYLAN VENLAFAXINE XL and O- desmethylvenlafaxine. The clinical significance of this interaction is unknown.

Warfarin:

Potentiation of anticoagulant effects may occur in patients taking warfarin following addition of MYLAN VENLAFAXINE XL.

Alcohol:

Patients should be advised not to use alcohol, considering its CNS-effects and potential of clinical worsening of psychiatric conditions, and the potential for adverse interactions with

venlafaxine including CNS depressant effects.

Haloperidol:

Haloperidol may have a 42 % decrease in total clearance after oral administration, with a 70 % increase in AUC, an 88 % increase in Cmax but without any change in half-life. This should be taken into account in patients treated with haloperidol and MYLAN VENLAFAXINE XL concomitantly.

Cimetidine:

Cimetidine inhibits the first-pass metabolism of MYLAN VENLAFAXINE XL but has no apparent effect on the formation or elimination of O-desmethylvenlafaxine, which is present in a much greater quantity in the systemic circulation. Consequently, the overall pharmacological activity of MYLAN VENLAFAXINE XL plus O-desmethylvenlafaxine is expected to increase only slightly.

No dosage adjustments seem necessary when MYLAN VENLAFAXINE XL is co-administered with cimetidine. However, for elderly patients or patients with hepatic dysfunction concomitantly taking MYLAN VENLAFAXINE XL and cimetidine, the extent of interaction is not known and potentially could be more pronounced. For such patients, clinical monitoring is indicated.

Metoprolol

MYLAN VENLAFAXINE XL appeared to reduce the blood pressure lowering effect of metoprolol. Caution should be exercised with co-administration of MYLAN VENLAFAXINE XL and metoprolol.

Risperidone:

MYLAN VENLAFAXINE XL may increase the risperidone AUC by 32 % but does not

significantly alter the pharmacokinetics profile of the total active moiety (risperidone plus 9- hydroxyrisperidone).

Diazepam:

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

Lithium:

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

Medicines highly bound to plasma proteins:

MYLAN VENLAFAXINE XL is not highly bound to plasma proteins (27 % bound); therefore, administration of MYLAN VENLAFAXINE XL to a patient taking another medicine that is highly protein bound is not expected to cause increased free concentration of the other medicine.

Medicines metabolised by cytochrome P450 iso-enzymes:

MYLAN VENLAFAXINE XL is a relatively weak inhibitor of CYP2D6. MYLAN VENLAFAXINE XL does not inhibit CYP3A4, CYP1A2 and CYP2C9 *in vitro.*

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/ Contraception in males and females

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

Pregnancy

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

Some neonates exposed to MYLAN VENLAFAXINE XL late in the third trimester have developed complications requiring tube-feeding, respiratory support or prolonged hospitalisation. Such complications can arise immediately upon delivery.

Observational data indicate an increased risk (less than 2-fold) of postpartum haemorrhage following SSRI/SNRI such as MYLAN VENLAFAXINE XL exposure within the month prior to birth (*see sections 4.4 and 4.8*).

Breastfeeding

MYLAN VENLAFAXINE XL and O-desmethylvenlafaxine are excreted in human milk; therefore, women on treatment with MYLAN VENLAFAXINE XL should not breastfeed their infants.

4.7 Effects on ability to drive and use machines

MYLAN VENLAFAXINE XL may impair judgement, thinking or motor skills and patients should be cautioned about operating hazardous machinery, including driving, until they are reasonably certain that MYLAN VENLAFAXINE XL does not affect them adversely.

4.8 Undesirable effects

Summary of the safety profile

In children reports of hostility, suicidal ideation and self-harm.

The most commonly observed adverse events associated with the use of MYLAN VENLAFAXINE XL are nervous system complaints, including headache, dizziness, dry mouth, insomnia, nervousness and somnolence; gastro-intestinal complaints, including anorexia, constipation and nausea; abnormal ejaculation/orgasm, sweating and asthenia.

The occurrence of many frequently observed adverse events is dose related. Adverse events generally decrease in intensity and frequency with continued therapy, and generally do not lead to cessation of treatment.

Tabulated list of adverse reactions

MedDRA system organ class	**Frequency**	**Adverse reactions**
Blood and lymphatic system disorders	Less frequent	Ecchymosis, mucous membrane bleeding, prolonged bleeding time, thrombocytopenia, blood dyscrasias including agranulocytosis, aplastic anaemia, neutropenia and pancytopenia
Immune system disorders	Less frequent	Anaphylaxis
Metabolism and nutrition disorders	Frequent	Weight loss, changes in serum cholesterol
	Less frequent	Weight gain, abnormal liver function tests, hyponatraemia, increased prolactin, Syndrome of Inappropriate Antidiuretic Hormone Secretion (SAIDH)
Psychiatric disorders	Frequent	Insomnia, abnormal dreams, nervousness
	Less frequent	Apathy, hallucinations, mania, hypomania, derealisation
	Frequency not known	Suicidal ideation and suicidal behaviour, aggression (*see*

MedDRA system organ class	Frequency	Adverse reactions
		section 4.4)
Nervous system disorders	Frequent	Dizziness, hypertonia, paraesthesia, tremor, sedation, headache
	Less frequent	Agitation, myoclonus, akathisia, convulsions, manic reaction, neuroleptic malignant syndrome (NMS), serotonergic syndrome, delirium, extrapyramidal reactions, tardive dyskinesia
	Frequency unknown	Amnesia, anxiety, confusion, depersonalisation, depression, emotional lability, hyperaesthesia, somnolence, abnormal thinking, trismus, twitching, aggression, migraine
Eye disorders	Frequent	Abnormal vision, abnormality of accommodation, mydriasis, visual impairment
	Less frequent	Angle closure glaucoma
Ear and labyrinth disorders	Less frequent	Tinnitus
	Frequency not known	Vertigo
Cardiac disorders	Frequent	Chest pain
	Less frequent	Tachycardia, oedema, QT prolongation, ventricular fibrillation, ventricular tachycardia (including Torsades de Pointes)
	Frequency unknown	Palpitations
Vascular disorders	Frequent	Hypertension, vasodilation
	Less frequent	Postural hypotension
Respiratory, thoracic and	Frequent	Yawning

MedDRA system organ class	Frequency	Adverse reactions
mediastinal disorders	Less frequent	Pulmonary eosinophilia
	Frequency unknown	Pharyngitis, rhinitis, dyspnoea, bronchitis
Gastrointestinal disorders	Frequent	Nausea, vomiting, constipation, decreased appetite, dry mouth, abdominal pain
	Less frequent	Diarrhoea, hepatitis, pancreatitis, bruxism, taste perversion
	Frequency unknown	Dyspepsia, eructation, flatulence, anorexia and increased appetite (weight)
Skin and subcutaneous tissue disorders	Frequent	Sweating, photosensitivity reaction
	Less frequent	Rash, alopecia, erythema multiforme, Stevens-Johnson syndrome, urticaria, pruritus
Musculoskeletal and connective tissue disorders	Frequent	Arthralgia, neck pain, back pain
	Less frequent	Rhabdomyolysis
	Frequency unknown	Myalgia
Renal and urinary disorders	Frequent	Impaired urination
	Less frequent	Urinary retention, urinary frequency
Reproductive system and breast disorders	Frequent	Decreased libido, impotence, abnormal ejaculation/orgasm (*see section 4.4)*, anorgasmia
	Less frequent	Menorrhagia
General disorders and administration site conditions	Frequent	Asthenia, chills, fatigue

Description of selected adverse reactions

Paediatric population *(see section 4.3)*

As with adults, decreased appetite, weight loss, increased blood pressure, and increased serum cholesterol were observed. Particularly, the following adverse reactions were observed: abdominal pain, agitation, dyspepsia, ecchymosis, epistaxis, and myalgia.

Reporting of suspected adverse reactions

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

4.9 Overdose

In overdose, side effects can be precipitated and/or be of increased severity (*see section 4.8)*.

- Somnolence was the most commonly reported symptom.
- Generalised convulsions may occur.
- In post-marketing experience, overdose with MYLAN VENLAFAXINE XL was reported predominantly in combination with alcohol and/or other medicines, including cases with fatal outcome. The most commonly reported events in overdose include tachycardia, changes in level of consciousness (ranging from somnolence to coma), mydriasis, convulsion, and vomiting. Other reported events include electrocardiographic changes (e.g., prolongation of QT interval, bundle branch block, QRS prolongation, ventricular tachycardia, bradycardia, hypotension, vertigo, and deaths. Severe poisoning symptoms may occur in adults after intake of approximately 3 grams of venlafaxine as contained in MYLAN VENLAFAXINE XL.
- Published retrospective studies report that MYLAN VENLAFAXINE XL overdosage may be associated with an increased risk of fatal outcomes compared to that

observed with SSRI antidepressant medicines, but lower than that for tricyclic antidepressants. Epidemiological studies have shown that MYLAN VENLAFAXINE XL -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 MYLAN VENLAFAXINE XL in overdosage, as opposed to some characteristics of MYLAN VENLAFAXINE XL -treated patients, is not clear.

Treatment should be symptomatic and supportive.

- Severe poisoning may require complex emergency treatment and monitoring. Therefore, in event of suspected overdose involving MYLAN VENLAFAXINE XL, prompt contact with (e.g. national poison information center or hospital emergency) is recommended.
- 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, hemoperfusion and exchange transfusion are unlikely to be of benefit.
- No specific antidotes for MYLAN VENLAFAXINE XL are known.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

PHARMACOLOGICAL CLASSIFICATION:

A 1.2 Psychoanaleptics (antidepressants)

Pharmacotherapeutic group: Other antidepressants - ATC code: NO6A X16

Venlafaxine and its major metabolite, O-desmethylvenlafaxine, are inhibitors of serotonin and norepinephrine (noradrenaline) re-uptake and also weakly inhibit dopamine re-uptake. Venlafaxine and O-desmethylvenlafaxine reduce beta-adrenergic responsiveness after both

acute (single dose) and chronic administration. Venlafaxine and its major metabolite appear to be equipotent with respect to their overall action on neurotransmitter re-uptake and receptor binding.

Mechanism of action:

5.2 Pharmacokinetic properties

Absorption:

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

After administration of MYLAN VENLAFAXINE XL, peak plasma concentrations of venlafaxine and O-desmethylvenlafaxine are attained within 6,0 ± 1,5 and 8,8 ± 2,2 hours, respectively.

The absorption (AUC) is the same as the venlafaxine immediate release tablet.

Metabolism:

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

Distribution:

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

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

Elimination:

Venlafaxine and its metabolites are excreted primarily through the kidneys. Approximately 87 % of a venlafaxine dose is recovered in the urine within 48 hours as either unchanged

venlafaxine, unconjugated O-desmethylvenlafaxine, conjugated O-desmethylvenlafaxine, or other minor metabolites.

Elderly:

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

Effects on Food:

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

Patients with renal impairment:

In patients with moderate to severe impairment of renal function, the total clearance of both venlafaxine and O-desmethylvenlafaxine was reduced, and t½ was prolonged. The reduction in total clearance was most pronounced in subjects with creatinine clearance less than 30 ml/min.

Dosage adjustment is recommended for these patients (*see section 4.2*)**.**

Patients with hepatic impairment:

In patients with compensated hepatic cirrhosis (mild to moderate hepatic impairment), the pharmacokinetic disposition of both venlafaxine and O-desmethylvenlafaxine were significantly altered. The reduction in both the metabolism of venlafaxine and the elimination of O- desmethylvenlafaxine resulted in significantly higher plasma concentrations of both.

Dosage adjustment is recommended in these patients *(see section 4.2)*.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Hypromellose (Methocel K100M), Eudragit RS 100, sodium lauryl sulphate, magnesium stearate, Eudragit E12,5, hard gelatin capsule

6.2 Incompatibilities

Not applicable

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store at or below 25 °C and protect from light.

Do not remove blisters from carton until required for use.

6.5 Nature and contents of container

Blister strips comprising of white opaque PVC/PE/PVDC/Aluminium foil.

Blister strips will be placed into an outer carton of printed cardboard along with a printed package insert.

Each unit carton will contain a total of 30 capsules.

Not all pack sizes may be marketed.

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

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

7 HOLDER OF THE CERTIFICATE OF REGISTRATION

Viatris South Africa (Pty) Ltd

4 Brewery Street

Isando

Johannesburg, 1600

Republic of South Africa

8 REGISTRATION NUMBER(S)

MYLAN VENLAFAXINE XL 75: 43/1.2/0097

MYLAN VENLAFAXINE XL 150: 43/1.2/0098

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

20 April 2012

10 DATE OF REVISION OF TEXT

18 December 2023