PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

[Pr]M-VENLAFAXINE XR

Venlafaxine Hydrochloride Extended-Release Capsules

Extended-Release Capsules, 37.5 mg, 75 mg and 150 mg venlafaxine (as venlafaxine hydrochloride), Oral

USP

Antidepressant / Anxiolytic

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RECENT MAJOR LABEL CHANGES

Not applicable.

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Sections or subsections that are not applicable at the time of authorization are not listed.

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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

M-VENLAFAXINE XR (Venlafaxine Hydrochloride Extended-Release Capsules) is indicated for the symptomatic relief of:

- Major depressive disorder
- Anxiety causing clinically significant distress in patients with generalized anxiety disorder (GAD). Anxiety or tension associated with the stress of everyday life usually does not require treatment with an anxiolytic.
- Social anxiety disorder, also known as social phobia.
- Panic disorder, with or without agoraphobia, as defined in DSM-IV

Long-term use of M-VENLAFAXINE XR: The physician who elects to use M-VENLAFAXINE XR for extended periods in the treatment of depression, GAD, social anxiety disorder, or panic disorder should periodically re-evaluate the long-term usefulness of the drug for the individual patient (see 4.1 Dosing Considerations; 4.2 Recommended Dose and Dosage Adjustment).

1.1 Pediatrics

Pediatrics (< 18 years of age): Health Canada has not authorized an indication for pediatric use (see 7 WARNINGS AND PRECAUTIONS, Psychiatric, Potential Association With Behavioural And Emotional Changes, Including Self-Harm).

1.2 Geriatrics

Geriatrics (> 65 years of age): Caution should be exercised in treating geriatric patients. Evidence from clinical studies and experience suggests that use in the geriatric population is associated with no overall differences in effectiveness and safety compared to younger patients. However, greater sensitivity of some older individuals cannot be ruled out.

2 CONTRAINDICATIONS

M-VENLAFAXINE XR is contraindicated in patients:

- Who are hypersensitive to this drug or to any ingredient in the formulation, including any non- medicinal ingredient, or component of the container. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.
- Taking concurrent monoamine oxidase inhibitors (MAOIs) (see 9.4 Drug-Drug Interactions). M-VENLAFAXINE XR should not be used within two weeks of terminating treatment with MAOIs. Treatment with MAOIs should not be started until 2 weeks after discontinuation of M-VENLAFAXINE XR therapy. (see 4.1 Dosing Considerations; 7 WARNINGS AND PRECAUTIONS, Serotonin Syndrome/Neuroleptic Malignant Syndrome; 9.4 Drug-Drug Interactions).

Adverse reactions, some serious, have been reported when Venlafaxine Hydrochloride Extended-Release Capsules therapy is initiated soon after discontinuing an MAOI and when an MAOI is

initiated soon after discontinuation of Venlafaxine Hydrochloride Extended-Release Capsules. These reactions have included tremor, myoclonus, diaphoresis, nausea, vomiting, flushing, dizziness, hyperthermia with features resembling neuroleptic malignant syndrome, seizures and death. In patients receiving antidepressants with pharmacological properties similar to venlafaxine in combination with an MAOI, there have also been reports of serious, sometimes fatal, reactions. For a selective serotonin reuptake inhibitor, these reactions have included hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes that include extreme agitation progressing to delirium and coma. Some cases presented with features resembling neuroleptic malignant syndrome. Severe hypothermia and seizures, sometimes fatal, have been reported in association with the combined use of tricyclic antidepressants and MAOIs. These reactions have also been reported in patients who have recently discontinued these drugs and have been started on an MAOI.

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions
Increased risk of self-harm, harm to others, suicidal thinking and behavior with antidepressants use. Closely monitor all antidepressant-treated patients for clinical worsening and for emergence of agitation-type and/or suicidal thoughts and behaviors (see 7 WARNINGS AND PRECAUTIONS, Psychiatric, Potential Association With Behavioural And Emotional Changes, Including Self-Harm).

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

- **Pregnant Women:** M-VENLAFAXINE XR should not be used during pregnancy unless the benefits markedly outweigh the risks, particularly during the third trimester as there are implications for neonatal health (see 7.1.1 Pregnant Women).
- **Patients with Hepatic or Renal Impairment:** Dosage adjustments are required (see 4.2 Recommended Dose and Dosage Adjustment).
- **Long-term use of M-VENLAFAXINE XR:** The physician who elects to use M-VENLAFAXINE XR for extended periods in the treatment of depression, GAD, social anxiety disorder, or panic disorder should periodically re- evaluate the long-term usefulness of the drug for the individual patient. During long-term therapy for any indication, the M-VENLAFAXINE XR dosage should be maintained at the lowest effective dose and the need for continuing treatment should be periodically reassessed (see 4.2 Recommended Dose and Dosage Adjustment).
- **Switching Patients to or from a Monoamine Oxidase Inhibitor:** M-VENLAFAXINE XR is contraindicated in patients taking concomitant MAOIs. At least 14 days should elapse between discontinuation of an MAOI and initiation of therapy with M-VENLAFAXINE XR. In addition, at least 14 days should be allowed after stopping M-VENLAFAXINE XR before starting an MAOI (see 2 CONTRAINDICATIONS).

4.2 Recommended Dose and Dosage Adjustment

Adults

Major Depressive Disorder

- The recommended dose for M-VENLAFAXINE XR is 75 mg/day, administered once daily with food, either in the morning or in the evening.
- For some patients, it may be desirable to start at 37.5 mg/day for 4-7 days to allow new patients to adjust to the medication before increasing to 75 mg/day.
- Each capsule should be swallowed whole with water. It should not be divided, crushed, chewed, or placed in water.
- While the relationship between dose and antidepressant response for Venlafaxine Hydrochloride Extended-Release Capsules has not been adequately explored patients not responding to the initial 75 mg may benefit from dose increases. Depending on tolerability and the need for further clinical effect, the dose should be increased by up to 75 mg/day up to a maximum of 225 mg/day as a single dose for moderately depressed outpatients.
- Dose increments should be made at intervals of approximately 2 weeks or more, but not less than 4 days.
- There is very limited experience with Venlafaxine Hydrochloride Extended-Release Capsules at doses higher than 225 mg/day, or in severely depressed inpatients.

Generalized Anxiety Disorder (GAD)

- The recommended starting dose of M-VENLAFAXINE XR is 37.5 mg/day administered as a single dose, taken with food, for 4-7 days.
- The usual dose is 75 mg/day administered as a single dose.
- Subsequent dosage increments of up to 75 mg/day may be considered, if clinically warranted.
- Dose increments should be made as needed at intervals of not less than 4 days.
- The maximum recommended daily dose is 225 mg/day as a single dose.

Social Anxiety Disorder (Social Phobia)

- For most patients, the recommended dose for M-VENLAFAXINE XR is 75 mg/day, administered in a single dose.
- For some patients, it may be desirable to start at 37.5 mg/day for 4 to 7 days, to allow new patients to adjust to the medication before increasing to 75 mg/day.
- Depending on tolerability and if clinically warranted, dose increases should be in increments of up to 75 mg/day, as needed, up to a maximum of 225 mg/day.
- Dose increments should be made at intervals of not less than 4 days.

Panic Disorder

- It is recommended that initial single doses of 37.5 mg/day of M-VENLAFAXINE XR be used for 7 days.
- The recommended treatment dose is 75 mg/day, administered in a single dose.

- Although a dose response relationship for effectiveness in patients with panic disorder was not clearly established in fixed-dose studies, certain patients not responding to 75 mg/day may benefit from dose increases to a maximum of 225 mg/day.
- Dose increases should be in increments of up to 75 mg/day, as needed, and should be made at intervals of at least 7 days.

Special Populations

Geriatrics (> 65 years of age): No dose adjustment is required for geriatric patients solely on the basis of their age. As with any antidepressant or anxiolytic, drug for treatment of social anxiety disorder, or panic disorder, however, caution should be exercised in treating the elderly. When individualizing the dosage, extra care should be taken when increasing the dose.

Pediatrics (< 18 years of age): Health Canada has not authorized an indication for pediatric use (see 7 WARNINGS AND PRECAUTIONS, Psychiatric, Potential Association With Behavioural And Emotional Changes, Including Self-Harm).

Pregnant Women: There are no adequate and well controlled studies with venlafaxine in pregnant women. Therefore, venlafaxine should only be used during pregnancy if clearly needed (see 4.9 Discontinuation, 7.1.1 Pregnant Women).

Hepatic Impairment: Given the decrease in clearance and increase in elimination half-life for both venlafaxine and ODV that is observed in patients with hepatic cirrhosis compared with normal subjects (see 10.3 Pharmacokinetics, Special Populations and Conditions), the total daily dose should be reduced by about 50% in patients with mild to moderate hepatic impairment. For such patients, it may be desirable to start at 37.5 mg/day. Because of individual variability in clearance in these patients, individualization of dosage may be desirable. Since there was much individual variability in clearance between patients with cirrhosis, it may be necessary to reduce the dose by even more than 50%, and individualization of dosing may be desirable in some patients.

Renal Impairment: Given the decrease in clearance for venlafaxine and increase in elimination half-life for both venlafaxine and ODV that is observed in patients with renal impairment (GFR = 10-70 mL/min) compared to normal subjects (see 10.3 Pharmacokinetics, Special Populations and Conditions) the total daily dose should be decreased by 25%-50%. In patients undergoing hemodialysis, the total daily dose must be reduced by 50% and the dose be withheld until the dialysis treatment is completed (4 hrs). For such patients, it may be desirable to start at 37.5 mg/day. Since there is so much individual variability in clearance among patients with renal impairment, individualization of dosing may be desirable.

Maintenance/Continuation/Extended Treatment

There is no body of evidence available to answer the question of how long a patient should continue to be treated with M-VENLAFAXINE XR for depression, GAD, social anxiety disorder or panic disorder.

During long-term therapy for any indication, the M-VENLAFAXINE XR dosage should be maintained at the lowest effective dose and the need for continuing treatment should be periodically reassessed (see 4.1 Dosing Considerations).

Major Depressive Disorder: It is generally agreed that acute episodes of major depression require several months or longer of sustained pharmacotherapy beyond response to the acute episode. Whether the dose needed to induce remission is identical to the dose needed for maintenance is unknown.

Maintenance of efficacy of Venlafaxine Hydrochloride Extended-Release Capsules has been shown in a placebo controlled study in which patients responding during 8 weeks of acute treatment with Venlafaxine Hydrochloride Extended-Release Capsules were assigned randomly to placebo or to the same dose of Venlafaxine Hydrochloride Extended-Release Capsules [75, 150, or 225 mg/day, in the morning (i.e. qAM)] during 26 weeks of maintenance treatment (see 14.1 Clinical Trials by Indication, Major Depressive Disorder).

It is not known whether or not the dose of Venlafaxine Hydrochloride Extended-Release Capsules needed for maintenance treatment is identical to the dose needed to achieve an initial response. Patients should be periodically reassessed to determine the need for maintenance treatment and the appropriate dose for such treatment.

Social Anxiety Disorder: In patients with social anxiety disorder, there are no efficacy data beyond 6 months of treatment with Venlafaxine Hydrochloride Extended-Release Capsules. The need for continuing medication in patients with social anxiety disorder who improve with M-VENLAFAXINE XR treatment should be periodically reassessed.

Panic Disorder: In one study in panic disorder, in which patients who were responders in the final 2 weeks of a 12-week acute treatment with Venlafaxine Hydrochloride Extended-Release Capsules were assigned randomly to placebo or to the same dose of Venlafaxine Hydrochloride Extended-Release Capsules (75, 150, or 225 mg/day) during 6 months of maintenance treatment, patients continuing Venlafaxine Hydrochloride Extended-Release Capsules treatment showed a significantly longer time to relapse than patients switched to placebo (see 14.1 Clinical Trials by Indication, Panic Disorder).

4.4 Administration

Administer once daily with food, either in the morning or in the evening.

4.5 Missed Dose

If a dose is missed, it should not be made up for it by doubling up on the dose next time. The patient should skip the missed dose and take the next dose as scheduled.

4.9 Discontinuation

When discontinuing M-VENLAFAXINE XR after more than 1 week of therapy, it is generally recommended that the dose be tapered gradually to minimize the risk of discontinuation symptoms. Discontinuation symptoms have been assessed both in patients with depression and in those with GAD. Abrupt discontinuation, dose reduction, or tapering of venlafaxine at various doses has been found to be associated with the appearance of new symptoms, the frequency of which increased with higher dose levels and with longer duration of treatment. It is therefore recommended that the dosage of M-VENLAFAXINE XR be tapered gradually whenever possible and the patient monitored. The period required for tapering and the amount of dose reduction

may depend on the dose, duration of therapy and the individual patient. If venlafaxine has been used for more than 6 weeks, tapering over at least a two week period is recommended. In some patients, discontinuation may need to occur very gradually over periods of months or longer (see 7 WARNINGS AND PRECAUTIONS, Psychiatric, Potential Association With Behavioural And Emotional Changes, Including Self-Harm; 7 WARNINGS AND PRECAUTIONS, Discontinuation).

- **Pregnant Women:** Due to the potential for discontinuation symptoms, if a decision is taken to discontinue M-VENLAFAXINE XR treatment, a gradual reduction in the dose rather than an abrupt cessation is recommended (see 7 WARNINGS AND PRECAUTIONS, Discontinuation).

5 OVERDOSAGE

Pre-market Overdose Report

Venlafaxine Immediate Release Tablets: There were 14 reports of acute overdose with immediate release tablets, either alone or in combination with other drugs and/or alcohol, among the patients included in the pre-marketing evaluation. The majority of the reports involved ingestions in which the total dose of venlafaxine taken was estimated to be no more than several-fold higher than the usual therapeutic dose. The 3 patients who took the highest doses were estimated to have ingested approximately 6.75 g, 2.75 g and 2.5 g. The resultant peak plasma levels of venlafaxine for the latter 2 patients were 6.24 and 2.35 mcg/mL, respectively, and the peak plasma levels of O- desmethylvenlafaxine were 3.37 and 1.30 mcg/mL, respectively. Plasma venlafaxine levels were not obtained for the patient who ingested 6.75 g of venlafaxine. All 14 patients recovered without sequelae. Most patients reported no symptoms. Among the remaining patients, somnolence was the most commonly reported symptom. The patient who ingested 2.75 g of venlafaxine was observed to have 2 generalized convulsions and a prolongation of QTc to 500 msec, compared with 405 msec at baseline. Mild sinus tachycardia was reported in 2 of the other patients.

Venlafaxine Hydrochloride Extended-Release Capsules: Among the patients included in the pre-marketing evaluation of Venlafaxine Hydrochloride Extended-Release Capsules, there were 2 reports of acute overdosage with Venlafaxine Hydrochloride Extended-Release Capsules in depression trials, either alone or in combination with other drugs. One patient took a combination of 6 g of Venlafaxine Hydrochloride Extended-Release Capsules and 2.5 mg of lorazepam. This patient was hospitalized, treated symptomatically, and recovered without any untoward effects. The other patient took 2.85 g of Venlafaxine Hydrochloride Extended-Release Capsules. This patient reported paresthesia of all four limbs but recovered without sequelae. There were 2 reports of acute overdose with Venlafaxine Hydrochloride Extended-Release Capsules in anxiety trials. One patient took a combination of 0.75 g Venlafaxine Hydrochloride Extended-Release Capsules and 200 mg of paroxetine and 50 mg of zolpidem. This patient was described as being alert, able to communicate, and a little sleepy. This patient was hospitalized, treated with activated charcoal, and recovered without any untoward effects. The other patient took 1.2 g of Venlafaxine Hydrochloride Extended-Release Capsules. This patient recovered and no other specific problems were found. The patient had moderate dizziness, nausea, numb hands and feet, and hot-cold spells 5 days after the overdose. There were no reports of acute overdose with Venlafaxine Hydrochloride Extended-Release Capsules in social anxiety disorder

trials. There were 2 reports of acute overdose with Venlafaxine Hydrochloride Extended-Release Capsules in panic disorder trials. One patient took 0.675 g of Venlafaxine Hydrochloride Extended-Release Capsules once and the other patient took 0.45 g of Venlafaxine Hydrochloride Extended-Release Capsules for 2 days. No signs or symptoms were associated with either overdose and no actions were taken to treat them.

Post-market Overdose Report with Venlafaxine (Dosage Form Unknown)

In post-marketing experience, overdose with venlafaxine was reported in combination with alcohol and/or other drugs such as methylphenidate, opioids, and benzodiazepines, including cases with fatal outcomes (see 9.3 Drug-Behavioural Interactions). Patients should be advised not to use alcohol, considering its central nervous system (CNS)-effects and potential of clinical worsening of psychiatric conditions, as well as the potential for adverse interactions with venlafaxine including CNS-depressant effects.

Fatal overdose has been reported with venlafaxine alone and at doses as low as approximately 1 gram.

The most commonly reported events in overdose include tachycardia, changes in level of consciousness (ranging from somnolence to coma), mydriasis, convulsion, and vomiting. Other events reported include electrocardiographic changes (e.g., prolongation of QT interval, bundle branch block, QRS prolongation), ventricular tachycardia, bradycardia, hypotension, delayed rise in plasma creatine kinase levels, rhabdomyolysis, liver necrosis, serotonin syndrome, vertigo, and death. Muscle enzymes should be monitored in patients with venlafaxine overdose to detect development of rhabdomyolysis at an early stage and to initiate appropriate treatment.

Published retrospective studies report that venlafaxine overdosage may be associated with an increased risk of fatal outcomes compared to that observed with SSRI antidepressant products, but lower than that for tricyclic antidepressants. Epidemiological studies have shown that venlafaxine- treated patients have a higher burden of suicide risk factors than SSRI patients. The extent to which the finding of an increased risk of fatal outcomes can be attributed to the toxicity of venlafaxine in overdosage as opposed to some characteristics of venlafaxine-treated patients is not clear.

Prescriptions for venlafaxine should be written for the smallest quantity consistent with good patient management, in order to reduce the risk of overdose.

Management of Overdose

Treatment should consist of those general measures employed in the management of overdosage with any antidepressant. Ensure an adequate airway, oxygenation, and ventilation. Monitor cardiac rhythm and vital signs. General supportive and symptomatic measures are also recommended. Induction of emesis is not recommended. Activated charcoal should be administered. Due to the large volume of distribution of this drug, forced diuresis, dialysis, hemoperfusion and exchange transfusion are unlikely to be of benefit. No specific antidotes for venlafaxine are known.

In managing overdosage, consider the possibility of multiple drug involvement.

For the most recent information in the management of a suspected drug overdose, contact

your regional poison control centre or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669).

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 1 – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength / Composition	Non-medicinal Ingredients
Oral	Capsule (extended-release) / 37.5 mg, 75 mg, 150 mg	Microcrystalline cellulose, hypromellose, ethylcellulose, purified talc, capsule shell (gelatin, purified water, titanium dioxide, iron oxide black and iron oxide red) and printing ink (shellac, dehydrated alcohol, isopropyl alcohol, butyl alcohol, propylene glycol, strong ammonia solution, black iron oxide, potassium hydroxide and purified water).

M-VENLAFAXINE XR 37.5 mg: Each hard gelatin capsule with opaque gray cap and opaque peach body, imprinted in black ink with "V" on cap and "37.5" on body and filled with white to off-white pellets. Available in bottles of 100, 500 and 1000 capsules and blister of 3 x 10 capsules.

M-VENLAFAXINE XR 75 mg: Each hard gelatin capsule with opaque peach cap and body, imprinted in black ink with "V" on cap and "75" on body and filled with white to off-white pellets. Available in bottles of 100 and 500 capsules and blister of 3 x 10 capsules.

M-VENLAFAXINE XR 150 mg: Each hard gelatin capsule with opaque dark orange cap and body, imprinted in black ink with "V" on cap and "150" on body and filled with white to off-white pellets. Available in bottles of 100 and 500 capsules and blister of 3 x 10 capsules.

7 WARNINGS AND PRECAUTIONS

Carcinogenesis and Mutagenesis

For animal data see 16 NON-CLINICAL TOXICOLOGY, Carcinogenicity; Genotoxicity.

Cardiovascular

Hypertension: Dose-related increases in blood pressure have been reported in some patients treated with venlafaxine. Also, rare cases of hypertensive crisis and malignant hypertension have been reported in normotensive and treated-hypertensive patients in post-marketing experience.

Caution should be exercised in patients whose underlying conditions might be compromised by increases in blood pressure. All patients should have their blood pressure evaluated before starting venlafaxine and monitored regularly during treatment. Pre-existing hypertension should be controlled before treatment with venlafaxine.

- **Acute Severe Hypertension:** Cases of severe elevated blood pressure requiring immediate treatment have been reported in post-marketing experience, including reports of

hypertensive crisis and malignant hypertension. The reports included normotensives and treated-hypertensive patients as well. Patients should be told to consult their doctors if they have symptoms associated with acute severe hypertension, such as headache (particularly in the back of head/neck when waking up), stronger heart beat and possibly more rapid, palpitations, dizziness, easy fatigability, blurred vision, chest pain.

- **Sustained Hypertension:** Venlafaxine treatment has been associated with sustained hypertension (see Table 2). Sustained increases in blood pressure could have adverse consequences. For patients who experience a sustained increase in blood pressure while receiving venlafaxine, either dose reduction or discontinuation should be considered after a benefit-risk assessment is made.
- **Venlafaxine Immediate Release Tablets:** Treatment with immediate release venlafaxine HCl tablets was associated with modest but sustained increases in blood pressure during pre-marketing studies. Sustained hypertension, defined as treatment-emergent supine diastolic blood pressure (SDBP) > 90 mmHg and > 10 mmHg above baseline for 3 consecutive visits, showed the following incidence and dose-relationship:

Table 2 – Probability of Sustained Elevation in SDBP (Pool of Pre-marketing Depression Studies with Venlafaxine HCl)

Treatment Group	(%) Incidence of Sustained Elevation in SDBP	
Venlafaxine	Immediate Release Tablets	Venlafaxine Hydrochloride Extended-Release Capsules
< 100 mg/day	2	3
101-200 mg/day	5	2
201-300 mg/day	6	4
> 300 mg/day	13	NE*
Placebo	2	0

* Not evaluable

An analysis of the blood pressure increases in patients with sustained hypertension and in the 19 patients who were discontinued from treatment because of hypertension (< 1% of total venlafaxine- treated group) showed that most of the blood pressure increases were in the range of 10 to 15 mmHg, SDBP.

- **Venlafaxine Hydrochloride Extended-Release Capsules**
    - **Major Depressive Disorder:** In placebo-controlled pre-marketing depression studies with Venlafaxine Hydrochloride Extended-Release Capsules, a final on-therapy mean increase in supine diastolic pressure (SDBP) of < 1.2 mmHg was observed for Venlafaxine Hydrochloride Extended-Release Capsules-treated patients compared with a mean decrease of 0.2 mmHg for placebo-treated patients. Less than 3% of Venlafaxine Hydrochloride Extended-Release Capsules patients treated with doses of 75 to 300

mg/day had sustained elevations in blood pressure (defined as treatment- emergent SDBP > 90 mmHg and > 10 mmHg above baseline for 3 consecutive on-therapy visits). An insufficient number of patients received doses of Venlafaxine Hydrochloride Extended-Release Capsules > 300 mg/day to evaluate systematically sustained blood pressure increases. Less than 1% of Venlafaxine Hydrochloride Extended-Release Capsules-treated patients in double-blind, placebo-controlled pre-marketing depression studies discontinued treatment because of elevated blood pressure compared with 0.4% of placebo- treated patients.

- **Generalized Anxiety Disorder (GAD):** In placebo-controlled pre-marketing anxiety studies with Venlafaxine Hydrochloride Extended-Release Capsules 37.5-225 mg/day, a final on-drug mean increase in SDBP of 0.4 mmHg was observed for Venlafaxine Hydrochloride Extended-Release Capsules treated patients compared with a mean decrease of 0.8 mmHg for placebo treated patients.
- **Social Anxiety Disorder (Social Phobia):** In 4 placebo-controlled pre-marketing social anxiety disorder studies with Venlafaxine Hydrochloride Extended-Release Capsules 75-225 mg/day up to 12 weeks, a final on-drug mean increase in SDBP of 0.9 mmHg was observed for Venlafaxine Hydrochloride Extended-Release Capsules-treated patients compared with a mean decrease of 1.6 mmHg for placebo-treated patients. In one placebo-controlled pre-marketing social anxiety disorder study with Venlafaxine Hydrochloride Extended-Release Capsules up to 6 months, a final on-drug mean decrease in SDBP of 0.2 mmHg was observed for Venlafaxine Hydrochloride Extended-Release Capsules-treated patients who received fixed doses of 75 mg/day and a mean increase of 1.5 mmHg was observed for Venlafaxine Hydrochloride Extended-Release Capsules-treated patients who received flexible doses of 150 to 225 mg/day, compared with a mean decrease of 0.6 mmHg for placebo-treated patients.

  Among patients treated with 75-225 mg per day of Venlafaxine Hydrochloride Extended-Release Capsules in all pre-marketing social anxiety disorder studies, 0.6% (5/771) experienced sustained hypertension.

  In all pre-marketing social anxiety disorder studies with patients treated with 75-225 mg per day, 0.6% (5/771) of the Venlafaxine Hydrochloride Extended-Release Capsules-treated patients discontinued treatment because of elevated blood pressure.
- **Panic Disorder:** In placebo-controlled pre-marketing panic disorder studies with Venlafaxine Hydrochloride Extended-Release Capsules 75-225 mg/day up to 12 weeks, a final on-drug mean increase in SDBP of 0.3 mmHg was observed for Venlafaxine Hydrochloride Extended-Release Capsules-treated patients compared with a mean decrease of 1.1 mmHg for placebo-treated patients.

  Among patients treated with 75 to 225 mg/day of Venlafaxine Hydrochloride Extended-Release Capsules in pre-marketing panic disorder studies up to 12 weeks, 0.9% (9/973) experienced sustained hypertension.

  In pre-marketing panic disorder studies up to 12 weeks, 0.5% (5/1001) of the Venlafaxine Hydrochloride Extended-Release Capsules-treated patients discontinued treatment because of elevated blood pressure.

Cardiac Disease: Venlafaxine has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were systematically excluded from many clinical studies during the product's clinical trials. Therefore, it should be used with caution in these patients.

ECG Changes in Clinical Trials: Evaluation of the electrocardiograms for 769 patients who received venlafaxine immediate release tablets in 4- to 6-week double-blind trials showed that the incidence of trial-emergent conduction abnormalities did not differ from that with placebo.

The electrocardiograms for 357 patients who received Venlafaxine Hydrochloride Extended-Release Capsules and 285 patients who received placebo in 8 to 12 week double-blind, placebo-controlled trials in depression were analyzed. The mean change from baseline in corrected QT interval (QTc) for Venlafaxine Hydrochloride Extended-Release Capsules-treated patients in depression studies was increased relative to that for placebo-treated patients (increase of 4.7 msec for Venlafaxine Hydrochloride Extended-Release Capsules and decrease of 1.9 msec for placebo). The clinical significance of this change is unknown. Three of 705 Venlafaxine Hydrochloride Extended-Release Capsules-treated patients in phase III studies experienced QTc prolongation to 500 msec during treatment. Baseline QTc was > 450 msec for all 3 patients.

Electrocardiograms are available for 815 patients who received Venlafaxine Hydrochloride Extended-Release Capsules and 379 patients who received placebo in up to 6-month, double-blind, placebo-controlled trials in generalized anxiety disorder. The mean change from baseline in the corrected QT interval (QTc) for Venlafaxine Hydrochloride Extended-Release Capsules-treated patients in the GAD studies did not differ significantly from that with placebo. One of the 815 Venlafaxine Hydrochloride Extended-Release Capsules-treated patients experienced QTc prolongation to 593 msec. Baseline QTc was 460 msec for this one patient.

Electrocardiograms were evaluated for 401 patients who received Venlafaxine Hydrochloride Extended-Release Capsules and 444 patients who received placebo in four 12-week double-blind, placebo-controlled trials in social anxiety disorder. The mean change from baseline in QTc for Venlafaxine Hydrochloride Extended-Release Capsules-treated patients in the 12-week social anxiety disorder studies was increased relative to that for placebo-treated patients (increase of 4.1 msec for Venlafaxine Hydrochloride Extended-Release Capsules and decrease of 1.4 msec for placebo). Electrocardiograms were evaluated for 101 patients who received Venlafaxine Hydrochloride Extended-Release Capsules 75 mg/day, 96 patients who received 150-225 mg/day, and 90 patients who received placebo in one 6-month double-blind, placebo-controlled trial in social anxiety disorder. A mean decrease from baseline in QTc of 0.05 ms was observed for patients treated with Venlafaxine Hydrochloride Extended-Release Capsules 75 mg/day, a mean increase from baseline in QTc of 3.4 ms was observed for patients treated with Venlafaxine Hydrochloride Extended-Release Capsules 150-225 mg/day, and a mean increase from baseline in QTc of 0.5 ms was observed for patients treated with placebo in the 6-month social anxiety disorder study.

Electrocardiograms were evaluated for 661 patients who received Venlafaxine Hydrochloride Extended-Release Capsules and 395 patients who received placebo in three 10- to 12-week double-blind, placebo-controlled trials in panic disorder. The mean change from baseline in QTc for Venlafaxine Hydrochloride Extended-Release Capsules-treated patients in the panic disorder

studies was increased relative to that for placebo-treated patients (increase of 1.5 msec for Venlafaxine Hydrochloride Extended-Release Capsules and decrease of 0.7 msec for placebo).

No case of sudden unexplained death or serious ventricular arrhythmia, which are possible clinical sequelae of QTc prolongation, was reported in Venlafaxine Hydrochloride Extended-Release Capsules pre-marketing studies.

The mean heart rate was increased by about 3-4 beats per minute during treatment with venlafaxine in clinical trials of depression and GAD. The mean change from baseline in heart rate for Venlafaxine Hydrochloride Extended-Release Capsules-treated patients in the social anxiety disorder studies was significantly higher than that for placebo (a mean increase of 5 beats per minute for Venlafaxine Hydrochloride Extended-Release Capsules and no change for placebo).

The mean change from baseline in heart rate for Venlafaxine Hydrochloride Extended-Release Capsules-treated patients in the panic disorder studies was significantly higher than that for placebo (a mean increase of 3 beats per minute for Venlafaxine Hydrochloride Extended-Release Capsules and a mean decrease of less than 1 beat per minute for placebo).

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.

QTc Prolongation and Torsade de Pointes: The QT effect of venlafaxine was evaluated in a thorough QTc study. In healthy subjects, venlafaxine did not prolong the QTc interval at a dose of 450 mg/day (given as 225 mg twice a day). Cases of QTc prolongation, Torsade de Pointes (TdP), ventricular tachycardia and sudden death have been reported during the post-marketing use of venlafaxine, including at therapeutic doses. Caution should be exercised when venlafaxine is prescribed in patients with cardiovascular disease or family history of QT prolongation, or in patients taking medicines known to increase QT interval, especially for patients with increased risk of QT prolongation, i.e., the elderly, patients with congenital long QT syndrome, congestive heart failure, heart hypertrophy, hypokalemia, or hypomagnesemia (see 5 OVERDOSAGE; 8.2 Clinical Trial Adverse Reactions; 9.4 Drug-Drug Interactions).

Dependence/Tolerance

In vitro studies revealed that venlafaxine has virtually no affinity for opiate, benzodiazepine, phencyclidine (PCP), or N-methyl-D-aspartic acid (NMDA) receptors. It has no significant CNS stimulant activity in rodents. In primate drug discrimination studies, venlafaxine showed no significant stimulant or depressant abuse liability.

While venlafaxine has not been systematically studied in clinical trials for its potential for abuse, there was no indication of drug-seeking behaviour in the clinical trials. However, it is not possible to predict on the basis of pre-marketing experience the extent to which a CNS active drug will be misused, diverted, and/or abused once marketed. Consequently, physicians should carefully evaluate patients for history of drug abuse and follow such patients closely, observing them for signs of misuse or abuse of venlafaxine (e.g., development of tolerance, incrementation of dose, drug-seeking behaviour).

Driving and Operating Machinery

In healthy volunteers receiving an immediate release venlafaxine formulation at a stable regimen

of 150 mg/day, some impairment of psychomotor performance was observed. Patients should be cautioned about operating hazardous machinery, including automobiles, or engaging in tasks requiring alertness until they have been able to assess the drug's effect on their own psychomotor performance.

Endocrine and Metabolism

Serum Cholesterol Elevation: Clinically relevant increases in total serum cholesterol were recorded in 5.3% of venlafaxine-treated patients and 0% of placebo-treated patients treated for at least 3 months in placebo-controlled trials in major depressive disorders. (see 7 WARNINGS AND PRECAUTIONS, Monitoring Laboratory Changes, Serum Cholesterol Elevation).

Consistent with the above findings, elevations of High Density Lipoprotein Cholesterol (HDL), Low Density Lipoprotein Cholesterol (LDL) and the overall ratio of Total Cholesterol/HDL have been observed in placebo controlled clinical trials for social anxiety disorder and panic disorder.

Measurement of serum cholesterol levels (including a complete lipid profile/fractionation and an assessment of the patient's individual risk factors) should be considered especially during long-term treatment.

Changes in Appetite and Weight: Treatment-emergent anorexia and weight loss were more commonly reported for venlafaxine-treated patients than for placebo-treated patients in depression and GAD, social anxiety disorder and panic disorder trials. Significant weight loss, especially in underweight depressed/GAD patients, may be an undesirable result of treatment. Venlafaxine is not recommended for weight loss alone or in combination with other products such as phentermine or sibutramine.

Based on the known mechanisms of action, the potential harm of co-administration includes the possibility of serotonin syndrome. (see 9.4 Drug-Drug Interactions).

Gastrointestinal

Results of testing in healthy volunteers demonstrated differences in the gastrointestinal tolerability of different formulations of venlafaxine. Data from healthy volunteers showed reduced incidence and severity of nausea with Venlafaxine Hydrochloride Extended-Release Capsules, compared with immediate release tablets.

In a 12-week study comparing immediate release tablets with Venlafaxine Hydrochloride Extended-Release Capsules, once daily Venlafaxine Hydrochloride Extended-Release Capsules was significantly more effective at weeks 8 and 12, compared with immediate release tablets given twice daily for treating major depression. Analysis of safety data from this trial showed that the incidence of treatment-emergent nausea and nausea severity over time were lower with Venlafaxine Hydrochloride Extended-Release Capsules than with immediate release tablets. Additionally, the incidence of vomiting was lower with Venlafaxine Hydrochloride Extended-Release Capsules than with immediate release tablets.

Hematologic

Abnormal Bleeding: SSRIs and SNRIs, including M-VENLAFAXINE XR, may increase the risk of bleeding events by causing abnormal platelet aggregation. Concomitant use of acetylsalicylic acid

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

Bleeding events related to SSRIs and SNRIs use have ranged from ecchymoses, hematomas, epistaxis, and petechiae to life threatening hemorrhages. SSRIs/SNRIs, including M-VENLAFAXINE XR, may increase the risk of postpartum hemorrhage (see 7.1.1 Pregnant Women).

Patients should be cautioned about the risk of bleeding associated with the concomitant use of M-VENLAFAXINE XR and NSAIDs, ASA, or other drugs that affect coagulation (see 9.4 Drug-Drug Interactions). Caution is advised in patients with a history of bleeding disorder or predisposing conditions (e.g. thrombocytopenia).

Hepatic/Biliary/Pancreatic

In patients with hepatic impairment, the pharmacokinetic disposition of both venlafaxine and O-desmethylvenlafaxine (ODV) are significantly altered. Dosage adjustment is necessary in these patients (see 4.2 Recommended Dose and Dosage Adjustment).

Immune

Venlafaxine and ODV produced only limited effects in immunological studies which were generally at doses greater than those required to produce antidepressant effects in animals.

Allergic Reactions: Patients should be advised to notify their physician if they develop a rash, hives or a related allergic phenomenon (see 2 CONTRAINDICATIONS).

Monitoring and Laboratory Tests

Suicidal Ideation: Rigorous clinical monitoring for suicidal ideation or other indicators of potential for suicidal behaviour is advised in patients of all ages. This includes monitoring for agitation-type emotional and behavioural changes (see 7 WARNINGS AND PRECAUTIONS, Psychiatric, Potential Association With Behavioural And Emotional Changes, Including Self-Harm).

Blood Pressure: It is recommended that patients receiving venlafaxine have their blood pressure evaluated before starting venlafaxine and monitored regularly during treatment.

Serum Cholesterol Elevation: Measurement of serum cholesterol levels (including a complete lipid profile/fractionation and an assessment of the patient's individual risk factors) should be considered especially during long-term treatment. (see 8.2 Clinical Trial Adverse Reactions, Laboratory Changes – Cholesterol)

Musculoskeletal

Bone Fracture Risk: Epidemiological studies show an increased risk of bone fractures following exposure to some antidepressants, including SSRIs/SNRIs. The risks appear to be greater at the initial stages of treatment, but significant increased risks were also observed at later stages of treatment. The possibility of fracture should be considered in the care of patients treated with M-VENLAFAXINE XR Elderly patients and patients with important risk factors for bone fractures should be advised of possible adverse events which increase the risk of falls, such as dizziness and orthostatic hypotension, especially at the early stages of treatment but also soon after

withdrawal. Preliminary data from observational studies show association of SSRIs/SNRIs and low bone mineral density in older men and women. Until further information becomes available, a possible effect on bone mineral density with long term treatment with SSRIs/SNRIs, including M-VENLAFAXINE XR, cannot be excluded, and may be a potential concern for patients with osteoporosis or major risk factors for bone fractures.

Neurologic

Seizures: M-VENLAFAXINE XR should be used cautiously in patients with a history of seizures, and should be promptly discontinued in any patient who develops seizures. Seizures have also been reported as a discontinuation symptom (see 4.2 Recommended Dose and Dosage Adjustment; 7 WARNINGS AND PRECAUTIONS, Discontinuation).

During pre-marketing testing, seizures were reported in 8 out of 3082 immediate release tablet-treated patients (0.3%). In 5 of the 8 cases with immediate release tablets, patients were receiving doses of 150 mg/day or less. During pre-marketing depression studies no seizures were seen in 705 Venlafaxine Hydrochloride Extended-Release Capsules-treated patients. Pre-marketing, no seizures occurred among 1381 Venlafaxine Hydrochloride Extended-Release Capsules-treated patients in generalized anxiety disorder studies or among 277 Venlafaxine Hydrochloride Extended-Release Capsules-treated patients in social anxiety disorder studies. In panic disorder studies, 1 seizure occurred among 1001 Venlafaxine Hydrochloride Extended-Release Capsules-treated patients (0.1%). However, patients with a history of convulsive disorders were excluded from most of these studies. M-VENLAFAXINE XR should be used cautiously in patients with a history of seizures, and should be promptly discontinued in any patient who develops seizures.

Serotonin Syndrome/Neuroleptic Malignant Syndrome: Serotonin toxicity also known as serotonin syndrome is a potentially life-threatening condition and has been reported with SSRIs and SNRIs, including M-VENLAFAXINE XR, particularly during combined use with other serotonergic drugs (see 9.4 Drug- Drug Interactions).

Serotonin toxicity is characterised by neuromuscular excitation, autonomic stimulation (e.g. tachycardia, flushing) and altered mental state (e.g. anxiety, agitation, hypomania). In accordance with the Hunter Criteria, serotonin toxicity diagnosis is likely when, in the presence of at least one serotonergic agent, one of the following is observed:

- Spontaneous clonus
- Inducible clonus or ocular clonus with agitation or diaphoresis
- Tremor and hyperreflexia
- Hypertonia and body temperature > 38°C and ocular clonus or inducible clonus.

Neuroleptic malignant syndrome has also been rarely reported with Venlafaxine Hydrochloride Extended-Release Capsules, particularly during combined use with neuroleptic/antipsychotic drugs. The clinical manifestations of neuroleptic malignant syndrome often overlap with those of serotonin toxicity, including hyperthermia, hypertonia, altered mental status, and autonomic instability. In contrast to serotonin toxicity, patients with neuroleptic malignant syndrome may present with “lead pipe” muscle rigidity as well as hyporeflexia.

The concomitant use of M-VENLAFAXINE XR with MAOIs, including linezolid and methylthioninium chloride (methylene blue) is contraindicated (see 2 CONTRAINDICATIONS). M-VENLAFAXINE XR should be used with caution in patients receiving other serotonergic drugs, neuroleptics/antipsychotics or dopamine antagonist drugs (see 9.4 Drug-Drug Interactions). If concomitant treatment with M-VENLAFAXINE XR and other serotonergic agents is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases. If serotonin toxicity is suspected, discontinuation of the serotonergic agents should be considered.

Ophthalmologic

Angle-Closure Glaucoma: As with other antidepressants, M-VENLAFAXINE XR can cause mydriasis, which may trigger an angle-closure attack in a patient with anatomically narrow ocular angles. Healthcare providers should inform patients to seek immediate medical assistance if they experience eye pain, changes in vision or swelling or redness in or around the eye.

Psychiatric

Potential Association With Behavioural And Emotional Changes, Including Self-Harm

- Pediatrics: Placebo-Controlled Clinical Trial Data

  Recent analyses of placebo-controlled clinical trial safety databases from SSRIs and other newer anti-depressants suggest that use of these drugs in patients under the age of 18 may be associated with behavioural and emotional changes, including an increased risk of suicidal ideation and behaviour over that of placebo.

  The small denominators in the clinical trial database, as well as the variability in placebo rates, preclude reliable conclusions on the relative safety profiles among the drugs in the class.

- Adults and Pediatrics: Additional data

  There are clinical trial and post-marketing reports with SSRIs and other newer anti-depressants, in both pediatrics and adults, of severe agitation-type adverse events coupled with self-harm or harm to others. The agitation-type events include: akathisia/psychomotor restlessness, agitation, disinhibition, emotional lability, hostility, aggression, depersonalization. In some cases, the events occurred within several weeks of starting treatment.

Rigorous clinical monitoring for suicidal ideation or other indicators of potential for suicidal behaviour is advised in patients of all ages. This includes monitoring for agitation-type emotional and behavioural changes.

An FDA meta-analysis of placebo-controlled clinical trials of antidepressant drugs in adult patients ages 18 to 24 years with psychiatric disorders showed an increased risk of suicidal behaviour with antidepressants compared to placebo.

Patients, their families, and their caregivers should be encouraged to be alert to the emergence of anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, mania, other unusual changes in behaviour, worsening of depression, and suicidal ideation, especially when initiating therapy or during any

change in dose or dosage regimen.

Discontinuation: Discontinuation symptoms have been assessed both in patients with depression and those with anxiety. Abrupt discontinuation, dose reduction, or tapering of venlafaxine at various doses has been found to be associated with the appearance of new symptoms, the frequency of which increased with increased dose level and with longer duration of treatment. If venlafaxine is used until or shortly before birth, discontinuation effects in the newborn should be considered.

Reported symptoms include aggression, agitation, anorexia, anxiety, asthenia, confusion, convulsions, coordination impaired, diarrhoea, dizziness, dry mouth, dysphoric mood, fasciculation, fatigue, flu-like symptoms, headache, hypomania, impaired coordination and balance, insomnia, nausea, nightmares, nervousness, paresthesia, electric shock sensations, sensory disturbances (including shock like electrical sensations), sleep disturbances, somnolence, sweating, tinnitus, tremor, vertigo, and vomiting. Where such symptoms occurred they were usually self-limiting but in a few patients continued for several weeks. In pre-marketing studies, the majority of discontinuation reactions were mild and resolved without treatment.

Discontinuation effects are well known to occur with antidepressants, and sometimes these effects can be protracted and severe (see 4.9 Discontinuation, 8.5 Post-Market Adverse Reactions). Suicide/suicidal thoughts and aggression have been observed in patients during changes in venlafaxine dosing regimen, including during discontinuation (see 7 WARNINGS AND PRECAUTIONS, Psychiatric, Potential Association With Behavioural And Emotional Changes, Including Self-Harm).

Therefore, it is recommended that the dosage be tapered gradually and individually and the patient be closely monitored during discontinuation. Time to event onset after dose reduction or discontinuation can vary in individual patients and range from the same day to several weeks. In some patients, discontinuation could take months or longer. (see 4.2 Recommended Dose and Dosage Adjustment).

Concomitant Illness: Clinical experience with venlafaxine in patients with concomitant systemic illness is limited. Caution is advised in administering venlafaxine to patients with diseases or conditions that could affect hemodynamic responses or metabolism (see 7 WARNINGS AND PRECAUTIONS, Cardiovascular). Patients should be questioned about any prescription or over the counter drugs, herbal or natural products or dietary supplements that they are taking, or planning to take, since there is a potential for interactions. (see 9.4 Drug-Drug Interactions; 9.6 Drug-Herb Interactions).

Aggression: Aggression may occur in some patients who have received antidepressants, including venlafaxine treatment, dose reduction, or discontinuation. As with other antidepressants, venlafaxine should be used cautiously in patients with a history of aggression.

The risk of suicide attempt must be considered, especially in depressed patients; the smallest quantity of drug, consistent with good patient management, should be provided to reduce the risk of overdose with this drug.

The same precautions observed when treating patients with depression should be observed when treating patients with GAD or social anxiety disorder (see 7 WARNINGS AND

PRECAUTIONS, Psychiatric, Potential Association With Behavioural And Emotional Changes, Including Self-Harm).

Insomnia and Nervousness: Treatment-emergent insomnia and nervousness were more commonly reported for patients treated with venlafaxine than with placebo (see 8.2 Clinical Trial Adverse Reactions) in depression, GAD, social anxiety disorder and panic disorder studies, as shown in Table 3.

Table 3 - Incidence of Insomnia and Nervousness in Placebo-Controlled Depression, GAD, Social Anxiety Disorder, and Panic Disorder Trials

Symptom	Depression		GAD		Social Anxiety Disorder		Panic Disorder	
	Venlafaxine Hydrochloride Extended-Release Capsules n = 357	Placebo n = 285	Venlafaxine Hydrochloride Extended-Release Capsules n = 1381	Placebo n = 555	Venlafaxine Hydrochloride Extended-Release Capsules n = 819	Placebo n = 695	Venlafaxine Hydrochloride Extended-Release Capsules n = 1001	Placebo n = 662
Insomnia	17%	11%	15%	10%	24%	8%	17%	9%
Nervousness	10%	5%	6%	4%	10%	5%	4%	6%

Insomnia and nervousness each led to drug discontinuation in 0.9% of the patients treated with Venlafaxine Hydrochloride Extended-Release Capsules in depression studies.

In GAD trials, insomnia and nervousness led to drug discontinuation in 3% and 2%, respectively, of the patients treated with Venlafaxine Hydrochloride Extended-Release Capsules up to 8 weeks and 2% and 0.7%, respectively, of the patients treated with Venlafaxine Hydrochloride Extended-Release Capsules up to 6 months. In social anxiety disorder trials, insomnia and nervousness led to drug discontinuation in 2% and 1%, respectively, of the patients treated with Venlafaxine Hydrochloride Extended-Release Capsules up to 12 weeks and 2% and 3%, respectively, of the patients treated with Venlafaxine Hydrochloride Extended-Release Capsules up to 6 months. In panic disorder trials, insomnia and nervousness led to drug discontinuation in 1% and 0.1%, respectively, of the patients treated with Venlafaxine Hydrochloride Extended-Release Capsules up to 12 weeks.

Activation of Mania/Hypomania: During Phase II and III trials, mania or hypomania occurred in 0.5% of venlafaxine immediate release tablet-treated patients and in 0.3% and 0% of Venlafaxine Hydrochloride Extended-Release Capsules-treated patients in depression and anxiety studies respectively. In pre-marketing social anxiety disorder studies, 0.2% of Venlafaxine Hydrochloride Extended-Release Capsules-treated patients and no placebo-treated patients experienced mania or hypomania. In pre-marketing panic disorder studies, 0.1% of Venlafaxine Hydrochloride Extended-Release Capsules-treated patients and 0% placebo-treated patients experienced mania or hypomania. Mania or hypomania occurred in 0.4% of all venlafaxine-treated patients. Mania/hypomania has also been reported in a small proportion of patients with major affective disorder who were treated with other marketed antidepressants. As with all antidepressants, M-VENLAFAXINE XR should be used cautiously in patients with a history or family history of bipolar disorder.

A major depressive episode may be the initial presentation of bipolar disorder. Patients with bipolar disorder may be at an increased risk of experiencing manic episodes when treated with antidepressants alone. Therefore, the decision to initiate symptomatic treatment of depression should only be made after patients have been adequately assessed to determine if they are at risk for bipolar disorder.

Renal

Hyponatremia: Cases of hyponatremia may occur with venlafaxine, 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.

The hyponatremia appeared to be reversible when venlafaxine was discontinued.

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

Renal Impairment: In patients with renal impairment (GFR=10-70 mL/min), the pharmacokinetic disposition of both venlafaxine and ODV are significantly altered. Dosage adjustment is necessary in these patients (see 4.2 Recommended Dose and Dosage Adjustment).

Reproductive Health: Female and Male Potential

- **Fertility**

  The effect of venlafaxine on fertility in humans is unknown. Animal studies suggest a decrease in fertility when exposed to the major metabolite of venlafaxine (ODV). See 16 NON-CLINICAL TOXICOLOGY.

- **Function**

  Sexual Dysfunction: SNRIs, including M-VENLAFAXINE XR, may cause symptoms of sexual dysfunction. Patients should be informed that there have been reports of long-lasting sexual dysfunction where the symptoms have continued despite discontinuation of SNRIs (see 8.2 Clinical Trial Adverse Reactions).

- **Teratogenic Risk**

  See 16 NON-CLINICAL TOXICOLOGY, Reproductive and Developmental Toxicology.

7.1 Special Populations

7.1.1 Pregnant Women

There are no adequate and well controlled studies with venlafaxine in pregnant women. Therefore, venlafaxine should only be used during pregnancy if clearly needed. Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy.

Complications following late third trimester exposure

Post-marketing reports indicate that some neonates exposed to venlafaxine, SSRIs, or other newer antidepressants late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding. Such complications can arise immediately upon delivery. Reported clinical findings have included respiratory distress, cyanosis, apnea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycemia, hypotonia, hypertonia, hyperreflexia, tremor, jitteriness, irritability, and constant crying. These features are consistent with either a direct toxic effect of SSRIs and other newer antidepressants, or, possibly a drug discontinuation syndrome. It should be noted that, in some cases, the clinical picture is consistent with serotonin syndrome (see 7 WARNINGS AND PRECAUTIONS, Neurologic, Serotonin Syndrome/Neuroleptic Malignant Syndrome). When treating a pregnant woman with M-VENLAFAXINE XR during the third trimester, the physician should carefully consider the potential risks and benefits of treatment (see 4.2 Recommended Dose and Dosage Adjustment).

Any change in antidepressant medication (including dosage) during pregnancy should be discussed with the attending physician beforehand to discuss the benefits/risks with the patient.

Exposure to SNRIs in mid to late pregnancy may increase the risk for preeclampsia, and exposure to SNRIs near delivery may increase the risk for postpartum hemorrhage (see 7 WARNINGS AND PRECAUTIONS, Hematologic, Abnormal Bleeding).

7.1.2 Breast-feeding

Because venlafaxine and its active metabolite, O-desmethylvenlafaxine, have been reported to be excreted in human milk, lactating women should not breast-feed their infants while receiving venlafaxine. If the mother is taking M-VENLAFAXINE XR while breast-feeding, the potential for discontinuation effects in the infant upon cessation of breast-feeding should be considered.

7.1.3 Pediatrics

Pediatrics (< 18 years of age): Health Canada has not authorized an indication for pediatric use (see 7 WARNINGS AND PRECAUTIONS, Psychiatric, Potential Association With Behavioural And Emotional Changes, Including Self-Harm).

7.1.4 Geriatrics

Geriatrics (> 65 years of age): Of the 2,897 patients in Phase II and III trials with venlafaxine immediate release tablets, 357 (12%) were 65 years of age or older. Forty-three (4%) of the patients in pre-marketing depression and 77 (6%) in GAD trials respectively, with Venlafaxine Hydrochloride Extended-Release Capsules, were 65 years of age or older. Ten (1%) patients in placebo-controlled social anxiety disorder studies were 65 years or older.

Sixteen (2%) patients in placebo-controlled panic disorder studies were 65 years or older. Caution should be exercised in treating geriatric patients. Evidence from clinical studies suggests that no overall differences in effectiveness and safety were observed between these geriatric patients and younger patients, and other reported clinical experience has not identified

differences in response between the elderly and younger patients. However, greater sensitivity of some older individuals cannot be ruled out.

8 ADVERSE REACTIONS

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

Major Depressive Disorder

During depression trials, the most commonly observed adverse events associated with the use of venlafaxine immediate release tablets and Venlafaxine Hydrochloride Extended-Release Capsules (incidence of 5% or greater) and not seen at an equivalent incidence among placebo-treated patients (i.e., incidence for immediate release formulation/Venlafaxine Hydrochloride Extended-Release Capsules at least twice that for placebo), derived from the 2% incidence Table 4, were:

Venlafaxine Immediate Release: asthenia, sweating, nausea, constipation, anorexia, vomiting, somnolence, dry mouth, dizziness, nervousness, anxiety, tremor, blurred vision, and abnormal ejaculation/orgasm and impotence in men.

Venlafaxine Hydrochloride Extended-Release Capsules: abnormal dreams, anorexia, dizziness, dry mouth, nausea, nervousness, somnolence, sweating, and tremor as well as abnormal ejaculation/orgasm in men.

Incidence in Controlled Trials: The table that follows (Table 4) enumerates adverse events that occurred at an incidence of 2% or more, and were more frequent than in the placebo group, among venlafaxine-treated depressed patients.

Venlafaxine Immediate Release: patients participated in 4- to 8- week placebo-controlled trials in which doses in the range of 75 to 375 mg/day were administered.

Venlafaxine Hydrochloride Extended-Release Capsules: patients participated in 8- to 12-week placebo-controlled trials in which doses in the range of 75 to 225 mg/day were administered.

Reported adverse events were classified using a standard COSTART-based Dictionary terminology.

The prescriber should be aware that the cited frequencies for Venlafaxine Hydrochloride Extended-Release Capsules cannot be compared with figures obtained from other clinical investigations of venlafaxine tablets which involved different treatments, uses and investigators. The cited figures for Venlafaxine Hydrochloride Extended-Release Capsules, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and non-drug factors to the side effect incidence rate in the population studied.

Table 4 – Treatment-Emergent Adverse Experience Incidence in Placebo-Controlled Clinical Trials (Percentage)[1] in Depressed Patients

Body System / Preferred Term	Venlafaxine Immediate Release (n = 1033)	Placebo (n = 609)	Venlafaxine Hydrochloride Extended-Release Capsules (n = 357)	Placebo (n = 285)
Body as a whole				
Headache	25	24	26 #	33
Asthenia	12	6	8	7
Infection	6	5	6 #	9
Chills	3	< 1	< 1	1
Cardiovascular				
Vasodilatation	4	3	4	2
Increased blood pressure/ hypertension	2	< 1	4	1
Tachycardia	2	< 1	< 1	< 1
Dermatological				
Sweating	12	3	14	3
Rash	3	2	1	1
Gastrointestinal				
Nausea	37	11	31	12
Constipation	15	7	8	5
Anorexia	11	2	8	4
Diarrhoea	8	7	8 #	9
Vomiting	6	2	4	2
Dyspepsia	5	4	7 #	9
Flatulence	3	2	4	3
Metabolic				
Weight loss	1	< 1	3	0
Nervous				
Somnolence	23	9	17	8
Dry mouth	22	11	12	6
Dizziness	19	7	20	9
Insomnia	18	10	17	11
Nervousness	13	6	10	5

Body System / Preferred Term	Venlafaxine Immediate Release (n = 1033)	Placebo (n = 609)	Venlafaxine Hydrochloride Extended-Release Capsules (n = 357)	Placebo (n = 285)
Anxiety	6	3	2 #	5
Tremor	5	1	5	2
Abnormal Dreams	4	3	7	2
Hypertonia	3	2	1	0
Paraesthesia	3	2	3	1
Libido decreased	2	< 1	3	< 1
Agitation	2	< 1	3	1
Depression	1	1	3	< 1
Thinking abnormal	2	< 1	< 1	1
Respiration				
Pharyngitis	4	4	7	6
Yawn	3	0	3	0
Special Senses				
Abnormal vision	6	2	4	< 1
Taste perversion	2	< 1	1	< 1
Urogenital system				
Abnormal ejaculation/ orgasm	12[2]	< 1[2]	16[2]	< 1[2]
Impotence	6[2]	< 1 [2]	4[2]	< 1 [2]
Anorgasmia	< 1[3]	< 1 [3]	3[3]	< 1 [3]
Urinary frequency	3	2	1	1
Urination impaired	2	< 1	< 1	0

[1] Events reported by at least 2% of patients treated with venlafaxine immediate release/ Venlafaxine Hydrochloride Extended-Release Capsules are included, and are rounded to the nearest %. Events for which the venlafaxine immediate release/ Venlafaxine Hydrochloride Extended-Release Capsules incidence was equal to or less than placebo included the following: abdominal pain, accidental injury, anxiety, back pain, bronchitis, diarrhea, dysmenorrhoea, dyspepsia, flu syndrome, headache, infection, pain, palpitation, rhinitis and sinusitis.

Incidence greater than 2%, but active drug incidence less than incidence for placebo.

[2] Incidence based on number of male patients (For venlafaxine immediate release: n = 439, Placebo: n = 245; For Venlafaxine Hydrochloride Extended-Release Capsules: n = 126, Placebo: n = 108)

[3] Incidence based on number of female patients (For venlafaxine immediate release: n = 594, Placebo: n = 364; For Venlafaxine Hydrochloride Extended-Release Capsules: n = 231, Placebo: n = 177)

Dose Dependency of Adverse Events: A comparison of adverse event rates in a fixed-dose study comparing venlafaxine immediate release tablets 75, 225, and 375 mg/day with placebo in

depressed patients revealed a dose dependency for some of the more common adverse events associated with venlafaxine use, as shown in the table that follows (Table 5). The rule for including events was to enumerate those that occurred at an incidence of 5% or more for at least one of the venlafaxine groups and for which the incidence was at least twice the placebo incidence for at least one venlafaxine group. Tests for potential dose relationships for these events (Cochran-Armitage Test, with a criterion of exact 2-sided p-value < 0.05) suggested a dose-dependency for several adverse events in this list, including chills, hypertension, anorexia, nausea, agitation, dizziness, somnolence, tremor, yawning, sweating, and abnormal ejaculation.

Table 5 – Treatment-Emergent Adverse Experience Incidence (Percentage) in a Dose Comparison Trial in Depressed Patients

Body System / Preferred Term	Placebo (n = 92)	Venlafaxine Immediate Release Tablets (mg/day)		
		75 (n = 89)	225 (n = 89)	375 (n = 88)
Body as a whole				
Abdominal pain	3.3	3.4	2.2	8
Asthenia	3.3	16.9	14.6	14.8
Chills	1.1	2.2	5.6	6.8
Infection	2.2	2.2	5.6	2.3
Cardiovascular				
Hypertension	1.1	1.1	2.2	4.5
Vasodilatation	0	4.5	5.6	2.3
Digestive System				
Anorexia	2.2	14.6	13.5	17
Dyspepsia	2.2	6.7	6.7	4.5
Nausea	14.1	32.6	38.2	58
Vomiting	1.1	7.9	3.4	6.8
Nervous				
Agitation	0	1.1	2.2	4.5
Anxiety	4.3	11.2	4.5	2.3
Dizziness	4.3	19.1	22.5	23.9
Insomnia	9.8	22.5	20.2	13.6
Libido decreased	1.1	2.2	1.1	5.7
Nervousness	4.3	21.3	13.5	12.5
Somnolence	4.3	16.9	18	26.1
Tremor	0	1.1	2.2	10.2
Respiratory				
Yawn	0	4.5	5.6	8

Body System / Preferred Term	Placebo (n = 92)	Venlafaxine Immediate Release Tablets (mg/day)		
		75 (n = 89)	225 (n = 89)	375 (n = 88)
Skin and Appendages				
Sweating	5.4	6.7	12.4	19.3
Special senses				
Abnormality of accommodation	0	9.1	7.9	5.6
Urogenital System				
Abnormal ejaculation / orgasm	0	4.5	2.2	12.5
Impotence (Number of men)	0 (n = 63)	5.8 (n = 52)	2.1 (n = 48)	3.6 (n = 56)

Generalized Anxiety Disorder

During GAD trials, the most commonly observed adverse events associated with the use of Venlafaxine Hydrochloride Extended-Release Capsules, derived from the 2% incidence Table 6 were: nausea, dry mouth, anorexia, abnormal ejaculation, constipation, sweating, abnormal vision, impotence in men, vasodilatation, dizziness, somnolence, libido decreased, abnormal dreams, yawn and tremor.

The tables that follow (Table 6 and 7) enumerate adverse events that occurred at an incidence of 2% or more, and at a higher rate than the placebo group, among Venlafaxine Hydrochloride Extended-Release Capsules-treated anxious patients.

Table 6 – Treatment-Emergent Adverse Event Incidence (%) in Placebo-Controlled Venlafaxine Hydrochloride Extended-Release Capsules North American Clinical Trials (210 US, 214 US and 218 US) in GAD Patients[1,2] (8-28 Weeks, Dosage Range 75-225 mg)

Body System / Preferred term	Venlafaxine Hydrochloride Extended-Release Capsules (n = 600)	Placebo (n = 328)
Body as a whole		
Asthenia	16	10
Accidental injury	5	4
Fever	3	2
Chills	3	< 1
Cardiovascular system		
Vasodilatation	8	3
Hypertension	4	3
Tachycardia	3	2
Digestive system		

Body System / Preferred term	Venlafaxine Hydrochloride Extended-Release Capsules (n = 600)	Placebo (n = 328)
Nausea	46	18
Dry mouth	24	9
Diarrhea	16	13
Anorexia	13	3
Constipation	12	6
Vomiting	7	4
Flatulence	3	2
Nervous system		
Dizziness	27	13
Somnolence	24	11
Insomnia	24	15
Nervousness	13	8
Libido decreased	6	3
Abnormal dreams	6	3
Tremor	5	2
Hypertonia	4	3
Paresthesia	3	2
Thinking abnormal	3	2
Twitching	3	< 1
Trismus	2	< 1
Confusion	2	< 1
Respiratory system		
Yawn	5	< 1
Cough increased	4	3
Skin and appendages		
Sweating	12	2
Special senses		
Abnormal vision	8	1
Urogenital system		
Abnormal ejaculation/orgasm (male)[3]	15	0
Anorgasmia	4	< 1
(male)[3]	5	< 1
(female)[4]	3	0

Body System / Preferred term	Venlafaxine Hydrochloride Extended-Release Capsules (n = 600)	Placebo (n = 328)
Urinary frequency	4	2
Impotence (male)[3]	6	< 1
Urination impaired	2	0
Menstrual disorder (female)[4]	3	2

1 Incidence rounded to the nearest %, for events reported by at least 2% of patients treated with Venlafaxine Hydrochloride Extended-Release Capsules, except the following events which had an incidence equal to or less than placebo: abdominal pain, agitation, anxiety, arthralgia, back pain, chest pain, depression, dyspepsia, flu syndrome, headache, infection, migraine, myalgia, neck pain, pain, palpitation, pharyngitis, rash, rhinitis, sinusitis, and tinnitus

2 < 1% indicates an incidence greater than zero but less than 1%.

3 Incidence is based on number of male patients (For Venlafaxine Hydrochloride Extended-Release Capsules: n = 242, Placebo: n = 131)

4 Incidence is based on number of female patients (For Venlafaxine Hydrochloride Extended-Release Capsules: n = 358, Placebo: n = 197)

Table 7 – Treatment-Emergent Adverse Event Incidence (%) in a Dose Comparison Trial (378 EU, 24 Weeks) with GAD Patients[1,2]

Body System / Preferred term	Placebo (n = 130)	Venlafaxine Hydrochloride Extended-Release Capsules		
		37.5 mg (n = 140)	75 mg (n = 134)	150 mg (n = 137)
Body as a whole				
Accidental injury	4	5	5	7
Asthenia	9	11	13	12
Back pain	5	7	5	5
Chest pain	2	5	2	2#
Cyst	0	1	2	0
Flu syndrome	6	6	5	7
Headache	26	28	24	25
Infection	4	9	5	12
Withdrawal syndrome	0	0	0	2
Cardiovascular System				
Hypertension	2	1	2	5
Migraine	< 1	4	2#	2#
Tachycardia	0	0	2#	2
Vasodilation	2#	4	2#	4
Digestive System				
Anorexia	2#	4	2#	3

Body System / Preferred term	Placebo (n = 130)	Venlafaxine Hydrochloride Extended-Release Capsules		
		37.5 mg (n = 140)	75 mg (n = 134)	150 mg (n = 137)
Constipation	5	8	13	15
Diarrhoea	8	8	7	10
Dry mouth	4	6	13	17
Dyspepsia	5	4	6	3
Nausea	14	22	34	42
Vomiting	6	5	8	7
Musculoskeletal System				
Arthralgia	4	4	5	2#
Myalgia	2#	1	< 1	3
Tenosynovitis	< 1	2	0	0
Nervous System				
Abnormal dreams	2#	4	6	3
Anxiety	6	5	2#	7
Depersonalization	< 1	< 1	< 1	2
Depression	2#	4	2	< 1
Dizziness	14	15	22	31
Hypertonia	< 1	3	2#	3
Insomnia	10	7	12	15
Libido decreased	< 1	3	2#	4
Nervousness	2#	4	3	3
Paresthesia	2	1	2	10
Somnolence	4	1	6	7
Thinking abnormal	0	2	0	0
Tremor	0	2	4	4
Vertigo	< 1	2	2	0
Respiratory System				
Bronchitis	< 1	3	2#	4
Cough increased	2#	3	3	2
Dyspnea	2#	1	2	0
Rhinitis	2#	4	4	3
Sinusitis	< 1	4	5	4
Yawn	0	0	2	5
Skin and Appendages				

Body System / Preferred term	Placebo (n = 130)	Venlafaxine Hydrochloride Extended-Release Capsules		
		37.5 mg (n = 140)	75 mg (n = 134)	150 mg (n = 137)
Eczema	< 1	2	2#	2#
Rash	2#	< 1	3	2
Sweating	5	9	11	18
Special Senses				
Abnormal vision	2#	< 1	8	4
Conjunctivitis	0	4	2#	2#
Mydriasis	0	< 1	< 1	2
Tinnitus	< 1	4	4	3
Urogenital System				
Abnormal ejaculation/orgasm (male)[3]	0	1	0	2
Anorgasmia (male)[3]	0	2	0	8
(female)[4]	0	0	0	2
Dysmenorrhoea (female)[4]	3	4	1	1
Dysuria	0	< 1	2	2#
Impotence (male)[3]	0	2	2	3
Menorrhagia (female)[4]	0	3	1	2
Urinary frequency	2#	2	< 1	2#

[1] Incidence rounded to the nearest %, for events reported by at least 2% of patients in any Venlafaxine Hydrochloride Extended-Release Capsules treatment group and at an incidence greater than the respective placebo incidence. # indicates that the incidence is less than 2% but rounds to 2%.

[2] < 1% indicates an incidence greater than zero but less than 1%.

[3] Incidence is based on number of male patients (For Venlafaxine Hydrochloride Extended-Release Capsules: n = 60 (37.5 mg), 51 (75 mg), 48 (150 mg); Placebo: n = 54)

[4] Incidence is based on number of female patients (For Venlafaxine Hydrochloride Extended-Release Capsules: n = 80 (37.5 mg), 83 (75 mg), 89 (150 mg); Placebo: n = 76)

Social Anxiety Disorder

During social anxiety disorder trials, the following adverse events occurred in at least 5% of the Venlafaxine Hydrochloride Extended-Release Capsules patients and at a rate at least twice that of the placebo group for the four 12-week placebo-controlled trials for the social anxiety disorder indication (Table 8): asthenia, nausea, anorexia, constipation, insomnia, dry mouth, somnolence, nervousness, libido decreased, tremor, yawn, sweating, abnormal vision, as well as abnormal ejaculation, impotence, and anorgasmia in men. In a 6- month social anxiety disorder trial, the following adverse events occurred in at least 5% of the patients who received either dose of Venlafaxine Hydrochloride Extended-Release Capsules and at a rate at least twice that of the placebo group (Table 9): asthenia, vasodilatation, anorexia, constipation, nausea, dizziness, dry mouth, libido decreased, nervousness, paresthesia, somnolence, tremor, twitching, pharyngitis,

yawn, sweating, abnormal vision, as well as abnormal ejaculation and impotence in men, and dysmenorrhea in women.

The tables that follow (Tables 8 and 9) enumerate adverse events that occurred at an incidence of 2% or more, and were more frequent than in the placebo group, among venlafaxine-treated patients with social anxiety disorder in 12-week and 6-month studies, respectively.

Table 8 – Treatment-Emergent Adverse Event Incidence (%) in Short-Term, Placebo-Controlled Venlafaxine Hydrochloride Extended-Release Capsules Clinical Trials (387 EU/CA, 388 EU, 392-US, and 393 US) in Social Anxiety Disorder Patients[1,2] (12 Weeks, Dosage Range 75-225 mg)

Body System / Preferred term	Venlafaxine Hydrochloride Extended-Release Capsules (n = 562)	Placebo (n = 566)
Body as a Whole		
Asthenia	19	8
Abdominal pain	6	4
Accidental injury	4	3
Cardiovascular System		
Hypertension	5	3
Palpitation	3	2#
Vasodilatation	2	1
Digestive System		
Nausea	30	9
Anorexia	15	2
Constipation	9	3
Diarrhea	7	5
Dyspepsia	6	5
Vomiting	4	2
Metabolic and Nutritional		
Weight loss	3	< 1
Nervous System		
Insomnia	23	8
Somnolence	18	7
Dry mouth	15	4
Dizziness	15	8
Libido decreased	9	2
Nervousness	9	4
Tremor	6	2#
Anxiety	6	4
Agitation	3	1
Abnormal dreams	3	1

Body System / Preferred term	Venlafaxine Hydrochloride Extended-Release Capsules (n = 562)	Placebo (n = 566)
Thinking abnormal	2	< 1
Twitching	2	0
Sleep disorder	2#	< 1
Trismus	2#	0
Respiratory System		
Yawn	7	< 1
Sinusitis	2#	1
Skin		
Sweating	15	4
Special Senses		
Abnormal vision	5	1
Tinnitus	2#	< 1
Urogenital System		
Abnormal ejaculation/orgasm (men)[3]	12	< 1
(women)[4]	2#	< 1
Impotence[3]	7	2#
Anorgasmia (men)[3]	7	< 1
(women)[4]	4	0
Menstrual disorder[4]	2#	1
Urinary frequency	2#	< 1

[1] Incidence rounded to the nearest %, for events reported by at least 2% of patients in any Venlafaxine Hydrochloride Extended-Release Capsules treatment group, and at an incidence greater than the respective placebo incidence. # indicates that the incidence is less than 2% but rounds to 2%.

[2] < 1% means greater than zero but less than 1%.

[3] Percentage based on the number of males (Venlafaxine Hydrochloride Extended-Release Capsules = 308, placebo = 284).

[4] Percentage based on the number of females (Venlafaxine Hydrochloride Extended-Release Capsules = 254, placebo = 282).

Table 9 – Treatment-Emergent Adverse Event Incidence (%) in a Long-Term, Placebo-Controlled Venlafaxine Hydrochloride Extended-Release Capsules Clinical Trial (390 US) in Social Anxiety Disorder Patients[1,2] (6 Months, Dosage Range 75- 225 mg)

Body System / Preferred term	Venlafaxine Hydrochloride Extended-Release Capsules		Placebo (n = 129)
	75 mg (n = 128)	150-225 mg (n = 129)	
Body as a Whole			
Allergic reaction	< 1	2#	< 1
Asthenia	25	19	11

Body System / Preferred term	Venlafaxine Hydrochloride Extended-Release Capsules		Placebo (n = 129)
	75 mg (n = 128)	150-225 mg (n = 129)	
Back pain	9	5	8
Chest pain	3	2	0
Fever	3	0	2
Flu syndrome	9	4	6
Headache	57	45	43
Pain	9	5	7
Cardiovascular system			
Hypertension	3	7	4
Palpitation	3	4	< 1
Postural hypotension	2#	< 1	0
Vasodilatation	2	5	2
Digestive system			
Anorexia	19	22	3
Constipation	8	9	2
Diarrhea	13	9	10
Dyspepsia	11	12	11
Dysphagia	0	2	0
Flatulence	3	4	2#
Nausea	37	34	10
Vomiting	5	4	3
Hemic and lymphatic			
Ecchymosis	< 1	2	0
Metabolic and nutritional			
Hyperlipemia	2#	0	0
Weight gain	2	< 1	< 1
Musculoskeletal system			
Leg cramps	2#	< 1	0
Nervous system			
Abnormal dreams	3	4	< 1
Agitation	3	2#	2#
Amnesia	2#	< 1	0
Apathy	< 1	2#	0
Depersonalization	2	< 1	0
Dizziness	24	19	12
Dry mouth	23	19	6
Insomnia	26	30	16

Body System / Preferred term	Venlafaxine Hydrochloride Extended-Release Capsules		Placebo (n = 129)
	75 mg (n = 128)	150-225 mg (n = 129)	
Libido decreased	5	10	2
Libido increased	2#	0	< 1
Nervousness	10	14	6
Paresthesia	4	6	2#
Sleep disorder	0	2#	< 1
Somnolence	24	29	14
Tremor	2	7	2#
Twitching	2	5	< 1
Vertigo	< 1	2#	0
Respiratory system			
Asthma	2#	2	0
Dyspnea	2#	< 1	0
Pharyngitis	11	9	5
Rhinitis	13	6	7
Upper respiratory infection	8	5	7
Yawn	5	12	0
Skin			
Contact dermatitis	0	2	0
Rash	5	< 1	3
Sweating	10	12	2
Urticaria	< 1	2	0
Special senses			
Abnormal vision	3	7	3
Conjunctivitis	< 1	2	0
Mydriasis	2#	4	0
Taste perversion	0	2#	< 1
Tinnitus	0	2	< 1
Urogenital system			
Urinary frequency	0	2#	< 1
Urination impaired	2#	2#	0
Urine abnormality	0	2#	0
Abnormal ejaculation/orgasm (men)[3]	12	18	1
(women)[4]	0	2	0
Amenorrhea [4]	0	4	0
Anorgasmia (men)[3]	0	3	0

Body System / Preferred term	Venlafaxine Hydrochloride Extended-Release Capsules		Placebo (n = 129)
	75 mg (n = 128)	150-225 mg (n = 129)	
(women)	0	4	0
Dysmenorrhea [4]	13	12	5
Impotence [3]	3	8	0
Menstrual disorder [4]	0	2	0
Metrorrhagia [4]	3	0	0
Unintended pregnancy [4]	2#	0	0
Uterine spasm [4]	2#	0	0

[1] Incidence rounded to the nearest %, for events reported by at least 2% of patients in any Venlafaxine Hydrochloride Extended-Release Capsules treatment group, and at an incidence greater than the respective placebo incidence. # indicates that the incidence is less than 2% but rounds to 2%

[2] < 1% means greater than zero but less than 1%.

[3] Percentage based on the number of males (Venlafaxine Hydrochloride Extended-Release Capsules 75 mg = 67, Venlafaxine Hydrochloride Extended-Release Capsules 150-225 mg = 79, placebo = 73).

[4] Percentage based on the number of females (Venlafaxine Hydrochloride Extended-Release Capsules 75 mg = 61, Venlafaxine Hydrochloride Extended-Release Capsules 150-225 mg = 50, placebo = 56).

Panic Disorder

During panic disorder trials, the following adverse events occurred in at least 5% of the Venlafaxine Hydrochloride Extended-Release Capsules patients and at a rate at least twice that of the placebo group for the placebo-controlled trials for the panic disorder indication (Table 10): anorexia, constipation, dry mouth, somnolence, tremor, abnormal ejaculation in men, and sweating.

The table that follows (Table 10) enumerates adverse events that occurred at an incidence of 2% or more, and were more frequent than in the placebo group, among venlafaxine-treated patients with panic disorder.

Table 10 – Treatment-Emergent Adverse Event Incidence (%) in Short-Term Placebo-Controlled Venlafaxine Hydrochloride Extended-Release Capsules Clinical Trials (391-CA/EU, 353-US/CA, 398-EU and 399-AC) in Panic Disorder Patients[1,2] (10-12 Weeks, Dosage Range 37.5-225 mg)

Body System / Preferred Term	Venlafaxine Hydrochloride Extended-Release Capsules (n = 1001)	PLACEBO (n = 662)
Body as a Whole		
Asthenia	10	8
Cardiovascular System		
Hypertension	4	3
Vasodilatation	3	2
Tachycardia*	2	< 1
Digestive System		
Nausea	21	14

Body System / Preferred Term	Venlafaxine Hydrochloride Extended-Release Capsules (n = 1001)	PLACEBO (n = 662)
Dry mouth	12	6
Constipation	9	3
Anorexia	8	3
Nervous System		
Insomnia	17	9
Somnolence	12	6
Dizziness	11	10
Tremor	5	2
Libido decreased	4	2
Vertigo*	2	1
Skin		
Sweating	10	2
Urogenital System		
Abnormal ejaculation (men) [3]	7	< 1
Impotence (men)[3]	4	< 1
Anorgasmia (men)[3]	2	0

[1] Adverse events for which the Venlafaxine Hydrochloride Extended-Release Capsules reporting rate was less than or equal to the placebo rate are not included. These events are: abdominal pain, abnormal vision, accidental injury, anxiety, back pain, diarrhea, dysmenorrhea, dyspepsia, flu syndrome, headache, infection, nervousness, pain, paresthesia, pharyngitis, rash, rhinitis, and vomiting.

[2] < 1% means greater than zero but less than 1%.

[3] Percentage based on the number of males (Venlafaxine Hydrochloride Extended-Release Capsules R = 335, placebo = 238).

* Occurred at less than 2% but frequency rounded up to 2%

Adverse Events that Led to Discontinuation of Treatment in Clinical Trials

Nineteen percent (537/2897) of venlafaxine immediate release and 12% (88/705) of Venlafaxine Hydrochloride Extended-Release Capsules-treated patients in Phase II and III depression studies discontinued treatment due to an adverse reaction. Approximately 18% of the 1381 patients who received Venlafaxine Hydrochloride Extended-Release Capsules for up to 8 weeks in placebo-controlled clinical trials for GAD discontinued treatment due to an adverse experience, compared with 12% of the 555 placebo-treated patients in those studies. Approximately 14% of the 562 patients who received Venlafaxine Hydrochloride Extended-Release Capsules for up to 12 weeks in 4 placebo-controlled clinical trials for social anxiety disorder discontinued treatment due to an adverse experience, compared with 5% of the 566 placebo-treated patients in those studies. Approximately 20% of the 257 patients who received Venlafaxine Hydrochloride Extended-Release Capsules in a 6-month placebo-controlled clinical trial for social anxiety disorder discontinued treatment due to an adverse experience, compared with 7% of the 129 placebo-treated patients in that study. The more common events (>1%) associated with discontinuation of treatment in all 5 trials and considered to be drug-related (i.e., those events associated with dropout at a rate approximately twice or greater for venlafaxine compared to placebo) are shown in Table 11.

Table 11 – Adverse Reactions (Percentage) Leading to Discontinuation of Treatment

	Depression Indication				GAD Indication		Social Anxiety Indication	
	Immediate Release Venlafaxine (n = 2897)	Placebo (n = 609)	Venlafaxine Hydrochloride Extended-Release Capsules (n = 705)	Placebo (n = 285)	Venlafaxine Hydrochloride Extended-Release Capsules (n = 1381)	Placebo (n = 555)	Venlafaxine Hydrochloride Extended-Release Capsules (n = 819)	Placebo (n = 695)
CNS								
Somnolence	3	1	2	< 1	3	< 1	2	< 1
Insomnia	3	1	< 1	< 1	3	< 1	2	< 1
Dizziness	3	< 1	2	1	4	2	2	< 1
Nervousness	2	< 1	< 1	1	2	< 1	< 1	0
Anxiety	2	1	< 1	< 1	1 #	1	< 1	< 1
Tremor	< 1	< 1	< 1	< 1	1	0	< 1	< 1
Gastrointestinal								
Dry Mouth	2	< 1	< 1	0	2	< 1	< 1	< 1
Anorexia	1	< 1	< 1	< 1	< 1	< 1	< 1	< 1
Nausea	6	1	4	< 1	8	< 1	3	< 1
Vomiting	< 1	< 1	1	0	1	< 1	< 1	0
Urogenital								
Abnormal Ejaculation*	3	0	< 1	< 1	< 1	0	< 1	0
Impotence*	< 1	< 1	0	0	< 1	0	2	0
Other								
Headache	3	1	2 #	1	3	< 1	1	< 1
Asthenia	2	< 1	< 1	1	3	< 1	2	< 1
Sweating	2	< 1	< 1	0	2	< 1	< 1	< 1

* : percentages based on the number of males

\# : greater than 1% but active drug rate not twice rate for placebo

Adaptation to Certain Adverse Events

In pre-marketing experience with venlafaxine immediate release tablets over a 6-week period, and Venlafaxine Hydrochloride Extended-Release Capsules over a 12 week period, there was evidence of adaptation to some adverse events with continued therapy (e.g., dizziness and

nausea), but less to other effects (e.g., abnormal ejaculation and dry mouth). The incidence of nausea in the GAD studies, during weeks 1 and 2 were 28% and 14% for Venlafaxine Hydrochloride Extended-Release Capsules-treated patients and 6% and 4% for placebo-treated patients, respectively. The incidence of dizziness during weeks 1 and 2 were 12% and 6% for Venlafaxine Hydrochloride Extended-Release Capsules-treated patients and 4% and 4% for placebo-treated patients, respectively.

Vital Sign Changes

Treatment with venlafaxine immediate release tablets (averaged over all dose groups) in clinical trials was associated with a mean increase in pulse rate of approximately 3 beats per minute, compared to no change for placebo. It was associated with mean increases in diastolic blood pressure ranging from 0.7 to 2.5 mmHg averaged over all dose groups, compared to mean decreases ranging from 0.9 to 3.8 mmHg for placebo. However, there is a dose dependency for blood pressure increase (see 7 WARNINGS AND PRECAUTIONS, Cardiovascular, Sustained Hypertension for effects on blood pressure).

Treatment with Venlafaxine Hydrochloride Extended-Release Capsules for up to 12 weeks in pre-marketing depression trials was associated with a mean increase in pulse rate of approximately 2 beats per minute, compared with 1 beat per minute for placebo. It was associated with mean increases in diastolic blood pressure ranging from 0.7 to 0.9 mmHg, compared with mean decreases ranging from 0.5 to 1.4 mmHg for placebo. Venlafaxine Hydrochloride Extended-Release Capsules treatment for up to 6 months in pre-marketing placebo-controlled generalized anxiety disorder trials was associated with a mean final on-therapy increase in pulse rate of approximately 2 beats per minute, compared with less than 1 beat per minute for placebo.

Venlafaxine Hydrochloride Extended-Release Capsules treatment for up to 12 weeks in 4 pre-marketing placebo-controlled social anxiety disorder trials was associated with mean final on-therapy increase in pulse rate of approximately 3 beats per minute, compared with an increase of approximately 1 beat per minute for placebo. Venlafaxine Hydrochloride Extended-Release Capsules treatment for up to 6 months in a pre-marketing placebo-controlled social anxiety disorder trial was associated with mean final on-therapy increase of approximately 2 beats per minute in the 75 mg/day group and an increase of approximately 4 beats per minute in the 150 to 225 mg/day group, compared with an increase of approximately 2 beats per minute for placebo.

Mean changes in supine diastolic blood pressure were also associated with venlafaxine treatment in the social anxiety disorder trials (see 7 WARNINGS AND PRECAUTIONS, Cardiovascular, Sustained Hypertension).

Venlafaxine Hydrochloride Extended-Release Capsules treatment for up to 12 weeks in pre-marketing placebo-controlled panic disorder trials was associated with mean final on-therapy increase in pulse rate of approximately 1 beat per minute, compared with a decrease of less than 1 beat per minute for placebo. A dose-dependence effect was noted in the 2 fixed-dose studies. In one study, no change in mean pulse rate was observed in the placebo and Venlafaxine Hydrochloride Extended-Release Capsules 75 mg dosage groups, and a mean increase of 1 beat/min was observed in the Venlafaxine Hydrochloride Extended-Release Capsules 150 group.

In another study, there was a mean increase of less than 1 beat/min in both placebo and Venlafaxine Hydrochloride Extended-Release Capsules 75 mg groups, and a mean increase of 3 beats/min in the Venlafaxine Hydrochloride Extended-Release Capsules 225 mg group.

Mean changes in supine diastolic blood pressure and sustained hypertension were also associated with Venlafaxine Hydrochloride Extended-Release Capsules treatment in the panic disorder trials (see 7 WARNINGS AND PRECAUTIONS, Cardiovascular, Sustained Hypertension).

Laboratory Changes - Cholesterol

Clinically and statistically relevant increases in cholesterol levels have been noted in studies using venlafaxine immediate release tablets and Venlafaxine Hydrochloride Extended-Release Capsules (see 7 WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests, Serum Cholesterol Elevation).

Venlafaxine Immediate Release Tablets: Patients treated with venlafaxine immediate release tablets for at least 3 months in placebo-controlled 12-month extension trials for major depressive disorder had a mean final on-therapy increase in total cholesterol of 9.1 mg/dL (0.2364 mmol/L) compared with a decrease of 7.1 mg/dL (0.1835 mmol/L) among placebo-treated patients. This increase was duration dependent over the study period and tended to be greater with higher doses. Clinically relevant increases in serum cholesterol, defined as 1) a final on-therapy increase in serum cholesterol > 50 mg/dL (1.2930 mmol/L) from baseline and to a value > 261 mg/dL (6.7495 mmol/L) or 2) an average on- therapy increase in serum cholesterol >50 mg/dL (1.2930 mmol/L) from baseline and to a value > 261 mg/dL (6.7495 mmol/L), were recorded in 5.3% of venlafaxine-treated patients and 0% of placebo- treated patients.

Venlafaxine Hydrochloride Extended-Release Capsules: Venlafaxine Hydrochloride Extended-Release Capsules treatment for up to 12 weeks in pre-marketing placebo-controlled trials for major depressive disorder was associated with a mean final on-therapy increase in serum cholesterol concentration of approximately 1.5 mg/dL (0.0381 mmol/L) compared with a mean final decrease of 7.4 mg/dL (0.1919 mmol/L) for placebo.

Venlafaxine Hydrochloride Extended-Release Capsules treatment for up to 8 weeks and up to 6 months in pre-marketing placebo-controlled GAD trials was associated with mean final on-therapy increases in serum cholesterol concentration of approximately 1 mg/dL (0.0247 mmol/L) and 2.3 mg/dL (0.0606 mmol/L), respectively while placebo subjects experienced mean final decreases of 4.9 mg/dL (0.1278 mmol/L) and 7.7 (0.1990 mmol/L) mg/dL, respectively.

Elevations of total serum cholesterol, High Density Lipoprotein Cholesterol (HDL), Low Density Lipoprotein Cholesterol (LDL) and the overall ratio of Total Cholesterol/HDL have been observed in placebo controlled clinical trials for social anxiety disorder and panic disorder.

Measurement of serum cholesterol levels (including a complete lipid profile/fractionation and an assessment of the patient's individual risk factors) should be considered especially during long-term treatment.

Patients treated with Venlafaxine Hydrochloride Extended-Release Capsules for up to 12 weeks in 4 pre-marketing placebo-controlled social anxiety disorder trials had a mean final on-therapy increases in total serum cholesterol concentration of approximately 8.8 mg/dL (0.227 mmol/L),

increases in HDL cholesterol of 2.3 mg/dL (0.059 mmol/L), and increases in LDL cholesterol of 5.4 mg/dL (0.139 mmol/L). Patients treated with Venlafaxine Hydrochloride Extended-Release Capsules 75 mg/day for up to 6 months in a pre-marketing placebo-controlled social anxiety disorder trial had a mean final on-therapy decrease in total serum cholesterol concentration of approximately 0.5 mg/dL (0.013 mmol/L), decrease in HDL cholesterol of 1 mg/dL (0.025 mmol/L), and increase in LDL cholesterol of 0.2 mg/dL (0.006 mmol/L). Patients treated with Venlafaxine Hydrochloride Extended-Release Capsules 150-225 mg/day for up to 6 months in the same pre-marketing placebo-controlled social anxiety disorder trial had a mean final on-therapy increase in total serum cholesterol concentration of approximately 12.5 mg/dL (0.322 mmol/L), increase in HDL cholesterol of 1 mg/dL (0.026 mmol/L), and increase in LDL cholesterol of 8.2 mg/dL (0.213 mmol/L).

Patients treated with Venlafaxine Hydrochloride Extended-Release Capsules for up to 12 weeks in pre-marketing placebo-controlled panic disorder trials had a mean final on-therapy increases in total serum cholesterol concentration of approximately 5.8 mg/dL (0.149 mmol/L), increases in HDL cholesterol of 1.9 mg/dL (0.050 mmol/L), and increases in LDL cholesterol of 2.9 mg/dL (0.076 mmol/L). A dose-dependence effect in serum cholesterol concentration was noted in the 2 fixed-dose studies. In one study, a mean decrease of 2.9 mg/dL (0.07 mmol/L) was observed in the placebo group, and mean increases of 2.1 mg/dL (0.05 mmol/L) and 5.1 mg/dL (0.13 mmol/L) were observed in the Venlafaxine Hydrochloride Extended-Release Capsules 75 mg and 150 mg dosage groups, respectively. In another study, a mean decrease of 4.8 mg/dL (0.12 mmol/L) was observed in the placebo group, and mean increases of 2.3 mg/dL (0.06 mmol/L) and 11.5 mg/dL (0.30 mmol/L) were observed in the Venlafaxine Hydrochloride Extended-Release Capsules 75 mg and 225 mg dosage groups, respectively.

ECG Changes

The QT effect of venlafaxine was evaluated in a thorough QTc study. In healthy subjects, venlafaxine did not prolong the QTc interval at a dose of 450 mg/day (given as 225 mg twice a day).

In an analysis of ECGs obtained in 769 patients treated with venlafaxine immediate release tablets and 450 patients treated with placebo in controlled clinical trials in depression, the only statistically significant difference observed was for heart rate, i.e., a mean increase from baseline of 4 beats per minute for venlafaxine immediate release tablets.

An analysis of ECGs was obtained in 357 patients treated with Venlafaxine Hydrochloride Extended-Release Capsules and 285 patients treated with placebo in controlled clinical trials in depression, in 815 patients who received Venlafaxine Hydrochloride Extended-Release Capsules and 379 patients who received placebo for up to 6 months in double-blind, placebo-controlled trials in GAD, 593 patients who received Venlafaxine Hydrochloride Extended-Release Capsules and 534 patients who received placebo for up to 12 weeks in double-blind, placebo-controlled trials in social anxiety disorder, and in 661 patients who received Venlafaxine Hydrochloride Extended-Release Capsules and 395 patients who received placebo for up to 12 weeks in double-blind, placebo- controlled trials in panic disorder were analyzed. The mean change from baseline in corrected QT interval (QTc) for Venlafaxine Hydrochloride Extended-Release Capsules-treated patients was increased relative to that for placebo-treated patients in the clinical trials for

depression, social anxiety disorder and panic disorder (see 7 WARNINGS AND PRECAUTIONS, Cardiovascular, Cardiac Disease).

In North American clinical trials for generalized anxiety disorder, mean reductions in PR interval (3-6 msec decrease) were reported during Venlafaxine Hydrochloride Extended-Release Capsules treatment which represented statistically significant differences from the corresponding placebo groups (1-3 msec increase). The clinical significance of these changes is not definitively known.

8.3 Less Common Clinical Trial Adverse Reactions

During the pre-marketing assessment of venlafaxine immediate release tablets, multiple doses were administered to 2897 patients in phase II-III depression studies. Multiple doses of Venlafaxine Hydrochloride Extended-Release Capsules were administered to 705 patients in phase III depression studies (as well as 96 patients on venlafaxine immediate release tablets), to 1381 patients in phase III GAD studies, 819 patients in phase III social anxiety disorder studies and 1314 patients in phase III panic disorder studies. The conditions and duration of exposure to venlafaxine in both development programs varied greatly, and included (in overlapping categories) open and double-blind studies, uncontrolled and controlled studies, inpatient (venlafaxine immediate release tablets only) and outpatient studies, fixed-dose and titration studies. Untoward events associated with this exposure were recorded by clinical investigators using terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of untoward events into a smaller number of standardized event categories.

In the tabulations that follow, reported adverse events were classified using a standard COSTART-based Dictionary terminology. The frequencies presented, therefore, represent the proportion of the 7212 patients exposed to multiple doses of either formulation of venlafaxine who experienced an event of the type cited on at least one occasion while receiving venlafaxine. All reported events are included except those already listed in 4 (MDD), 5 (MDD dose related), 6 (GAD NA), 7 (GAD 378), 8 (SAD ST), 9 (SAD LT), and 10 (PD), and those events for which a drug cause was remote. If the COSTART term for an event was so general as to be uninformative, it was replaced with a more informative term. It is important to emphasize that, although the events reported occurred during treatment with venlafaxine, they were not necessarily caused by it.

Events are further categorized by body system and listed in order of decreasing frequency according to the following definitions: frequent adverse events are those occurring on one or more occasions in at least 1/100 patients; infrequent adverse events are those occurring in 1/100 to 1/1000 patients; rare adverse events are those occurring in fewer than 1/1000 patients.

Body as a whole: Frequent: chest pain substernal. **Infrequent**: angioedema, face edema, intentional injury, malaise, moniliasis, neck rigidity, overdose, pelvic pain, photosensitivity reaction, suicide attempt. **Rare**: anaphylaxis, appendicitis, bacteremia, body odour, carcinoma, cellulitis, granuloma, halitosis.

Cardiovascular system: Frequent: palpitations. **Infrequent**: angina pectoris, arrhythmia, bradycardia, extrasystoles, hypotension, peripheral vascular disorder (mainly cold feet and/or cold hands), syncope. **Rare**: aortic aneurysm, arteritis, first degree atrioventricular block,

bigeminy, bundle branch block, capillary fragility, cardiovascular disorder (includes mitral valve and circulatory disturbances), cerebral ischemia, coronary artery disease, heart arrest, congestive heart failure, hematoma, mucocutaneous hemorrhage, myocardial infarct, pallor, QT and QTc interval prolonged, sinus arrhythmia, thrombophlebitis, varicose vein, venous insufficiency.

Digestive system: Frequent: increased appetite. **Infrequent**: bruxism, colitis, dysphagia, tongue edema, eructation, esophagitis, gastritis, gastroenteritis, gastrointestinal ulcer, gingivitis, glossitis, rectal hemorrhage, hemorrhoids, melena, oral moniliasis, stomatitis, mouth ulceration. **Rare**: abdominal distension, biliary pain, cheilitis, cholecystitis, cholelithiasis, duodenitis, esophageal spasms, hematemesis, gastroesophageal reflux disease, gum hemorrhage, hepatitis, ileitis, jaundice, intestinal obstruction, liver tenderness, parotitis, periodontitis, proctitis, rectal disorder, increased salivation, salivary gland enlargement, soft stools, tongue discoloration.

Endocrine system: Rare: galactorrhea, goiter, hyperthyroidism, hypothyroidism, thyroid nodule, thyroiditis.

Hemic and lymphatic system: Infrequent: anemia, gastrointestinal hemorrhage, leukocytosis, leukopenia, lymphadenopathy, thrombocythemia, mucous membrane bleeding. **Rare**: basophilia, bleeding time increased, cyanosis, eosinophilia, lymphocytosis, multiple myeloma, purpura, thrombocytopenia.

Metabolic and nutritional: Frequent: edema, serum cholesterol increase. **Infrequent**: alkaline phosphatase increased, dehydration, hypercholesterolemia, hyperglycemia, hypokalemia, SGOT (AST) increased, SGPT (ALT) increased, thirst, SIADH. **Rare**: alcohol intolerance, bilirubinemia, BUN increased, creatinine increased, diabetes mellitus, glycosuria, gout, healing abnormal, hemochromatosis, hypercalcinuria, hyperkalemia, hyperphosphatemia, hyperuricemia, hypocholesterolemia, hypoglycemia, hyponatremia, hypophosphatemia, hypoproteinemia, uremia.

Musculoskeletal system: Infrequent: arthritis, arthrosis, bone spurs, bursitis, myasthenia. **Rare**: bone pain, muscle cramp, muscle spasm, musculoskeletal stiffness, pathological fracture, myopathy, osteoporosis, osteosclerosis, plantar fasciitis, rheumatoid arthritis, tendon rupture.

Nervous system: Frequent: hypesthesia. **Infrequent:** akathisia/psychomotor restlessness, ataxia, circumoral paresthesia, CNS stimulation, emotional lability, euphoria, hallucinations, hostility, hyperesthesia, hyperkinesias, hypotonia, impaired coordination and balance, manic reaction, myoclonus, neuralgia, neuropathy, psychosis, serotonergic syndrome, seizure, abnormal speech, stupor, suicidal ideation. **Rare:** abnormal/changed behaviour, adjustment disorder, akinesia, alcohol abuse, aphasia, bradykinesia, buccoglossal syndrome, cerebrovascular accident, convulsion, feeling drunk, loss of consciousness, delusions, dementia, dystonia, energy increased, facial paralysis, abnormal gait, Guillain-Barré Syndrome, homicidal ideation, hyperchlorhydria, hysteria, impulse control difficulties, hypokinesia, motion sickness, neuritis, nystagmus, paranoid reaction, paresis, psychotic depression, reflexes decreased, reflexes increased, torticollis.

Respiratory system: Infrequent: chest congestion, epistaxis, hyperventilation, laryngismus, laryngitis, pneumonia, voice alteration. **Rare:** atelectasis, hemoptysis, hiccup, hypoventilation, hypoxia, larynx edema, pleurisy, pulmonary embolus, sleep apnea, sputum increased.

Skin and appendages: Frequent: pruritis. **Infrequent:** acne, alopecia, dry skin, maculopapular

rash, psoriasis. **Rare:** brittle nails, erythema nodosum, exfoliative dermatitis, lichenoid dermatitis, hair discoloration, skin discoloration, furunculosis, hirsutism, leukoderma, miliaria, petechial rash, pruritic rash, pustular rash, vesiculobullous rash, seborrhea, skin atrophy, skin hypertrophy, skin striae, sweating decreased.

Special senses: Infrequent: diplopia, dry eyes, eye pain, otitis media, parosmia, photophobia, taste loss. **Rare:** blepharitis, cataract, chromatopsia, conjunctival edema, corneal lesion, deafness, exophthalmos, eye hemorrhage, glaucoma, hyperacusis, retinal hemorrhage, subconjunctival hemorrhage, keratitis, labyrinthitis, miosis, papilledema, decreased pupillary reflex, otitis externa, scleritis, uveitis, visual field defect, vitreous disorder.

Urogenital system: Frequent: erectile dysfunction. **Infrequent:** albuminuria, cystitis, hematuria, leukorrhea[1], kidney calculus, kidney pain, kidney function abnormal, nocturia, breast pain, prostatic disorder (includes prostatitis, enlarged prostate, and prostate irritability)[1], polyuria, pyuria, urinary incontinence, urinary retention, urinary urgency, vaginal hemorrhage[1], vaginitis[1]. **Rare:** abortion[1], anuria, balanitis[1], bladder pain, breast discharge, breast engorgement, breast enlargement, endometriosis[1], fibrocystic breast, calcium crystalluria, cervicitis[1], ovarian cyst[1], prolonged erection[1], female lactation[1], gynecomastia[1], hypomenorrhea[1], mastitis[1], menopause[1], oliguria, orchitis, pyelonephritis, salpingitis[1], urolithiasis, uterine hemorrhage[1], vaginal dryness[1].

[1] Based on the number of men and women, as appropriate.

8.5 Post-Market Adverse Reactions

Voluntary reports of adverse events other than those above, temporally associated with the use of venlafaxine, that have been received since market introduction and that may have no causal relationship with the use of venlafaxine include the following:

Body as a whole: anaphylaxis, congenital anomalies, neuroleptic malignant syndrome-like events (including the case of a 10-year old boy who may have been taking methylphenidate, was treated and recovered), serotonin syndrome

Cardiovascular System: congestive heart failure, deep vein thrombosis, heart arrest, hemorrhage, myocardial infarction, ECG abnormalities (such as atrial fibrillation, bigeminy, supraventricular tachycardia, ventricular extrasystole, ventricular fibrillation and ventricular tachycardia, including torsades de pointes), stress cardiomyopathy (Takotsubo cardiomyopathy), hypertensive crisis, malignant hypertension, QTc prolongation, Torsade de Pointes, ventricular tachycardia, sudden death

Digestive system: bruxism, diarrhoea, gastrointestinal bleeding, hepatic events (including GGT elevation; abnormalities of unspecified liver function tests; fatty liver, liver damage, necrosis or failure, fulminant hepatitis, including rare fatalities), pancreatitis, diarrhoea

Endocrine system: prolactin increased

Hemic and lymphatic system: agranulocytosis, aplastic anemia, neutropenia, pancytopenia

Injury, poisoning and procedural complications: bone fracture.

Metabolic and nutritional: CPK increased, dehydration, hepatitis, LDH increased, syndrome of inappropriate antidiuretic hormone secretion, weight loss

Musculoskeletal: rhabdomyolysis

Nervous system: abnormal gait, agitation, catatonia, delirium, extrapyramidal symptoms (including dyskinesia, dystonia, tardive dyskinesia), grand mal seizures, increased muscle tonus, involuntary movements, panic, paresthesia, neuroleptic malignant syndrome, sedation, shock-like electrical sensations (in some cases, subsequent to the discontinuation of venlafaxine or tapering of dose), aggressive ideation and acts, including harm to others.

Respiratory system: interstitial lung disease (including pulmonary eosinophilia).

Skin and appendages: toxic epidermal necrolysis/Stevens-Johnson syndrome, erythema multiform, sweating including night sweats

Special senses: angle closure glaucoma, eye hemorrhage, tinnitus

Urogenital system: renal failure.

9 DRUG INTERACTIONS

9.1 Serious Drug Interactions

Serious Drug Interactions
• **Monoamine Oxidase Inhibitors: See 2 CONTRAINDICATIONS**

9.2 Drug Interactions Overview

Venlafaxine is not highly bound to plasma proteins; therefore, administration of venlafaxine to a patient taking another drug that is highly protein bound should not cause increased free concentrations of the other drug.

The risk of using venlafaxine in combination with other CNS-active drugs has not been systematically evaluated. Consequently, caution is advised if the concomitant administration of venlafaxine and such drugs is required.

As with all drugs, the potential for interaction by a variety of mechanisms is a possibility.

9.3 Drug-Behavioural Interactions

Patients should be advised not to use alcohol while taking venlafaxine as this may result in additive psychomotor impairment and/or severe poisoning which may require complex emergency treatment and monitoring. In post-marketing experience, overdose with venlafaxine has been reported in combination with alcohol and/or other drugs (such as methylphenidate, opioids, benzodiazepines), including cases with fatal outcomes (5 OVERDOSAGE).

Therefore, in the event of a suspected alcohol overdose involving venlafaxine, promptly contact your regional poison control centre.

9.4 Drug-Drug Interactions

The drugs listed in this table are based on either drug interaction case reports or studies, or potential interactions due to the expected magnitude and seriousness of the interaction (i.e.

those identified as contraindicated).

Table 12 – Established or Potential Drug-Drug Interactions

Proper/Common name	Source of Evidence	Effect	Clinical comment
Monoamine Oxidase Inhibitors	C	See 2 CONTRAINDICATIONS	M-VENLAFAXINE XR is contraindicated in patients taking concomitant MAOIs. At least 14 days should elapse between discontinuation of an MAOI and initiation of therapy with M-VENLAFAXINE XR. In addition, at least 14 days should be allowed after stopping M-VENLAFAXINE XR before starting an MAOI.
CNS-Active Drugs	T	*In vitro* studies revealed that venlafaxine has virtually no affinity for opiate, benzodiazepine, phencyclidine (PCP), or N-methyl-D-aspartic acid (NMDA) receptors. It has no significant CNS stimulant activity in rodents. In primate drug discrimination studies, venlafaxine showed no significant stimulant or depressant abuse liability.	The risk of using venlafaxine in combination with other CNS-active drugs has not been systematically evaluated. Consequently, caution is advised if the concomitant administration of venlafaxine and such drugs is required.
Serotonergic Drugs • triptans (e.g., almotriptan, sumatriptan, rizatriptan, naratriptan, zolmitriptan); • SSRIs; • other SNRIs; linezolid (an antibiotic which is a reversible non-selective MAOI);	T	Rare post-marketing reports describe patients with symptoms suggestive of, or diagnostic of, serotonin syndrome, following the combined use of a SSRI with 5HT1-agonists (triptans) or lithium.	Based on the mechanism of action of venlafaxine and the potential for serotonin syndrome, caution is advised when M-VENLAFAXINE XR is co- administered with other drugs or agents that may affect the serotonergic neurotransmitter systems. If concomitant treatment with M-VENLAFAXINE XR and a serotonergic drug is clinically warranted, appropriate

Proper/Common name	Source of Evidence	Effect	Clinical comment
• amphetamines; • lithium; • opioids (including buprenorphine, fentanyl and its analogues, dextromethorphan, tramadol, tapentadol, meperidine, methadone and pentazocine); • methylene blue (a surgical dye); • serotonin precursors, such as tryptophan supplements.			observation of the patient for acute and long-term adverse events is advised. (see 7 WARNINGS AND PRECAUTIONS, Endocrine and Metabolism, Changes in Appetite and Weight; and 7 WARNINGS AND PRECAUTIONS, Neurologic, Serotonin Syndrome/Neuroleptic Malignant Syndrome)
Drugs that Prolong the QT Interval • class IA antiarrhythmics (e.g., quinidine, procainamide, disopyramide); • class III antiarrhythmics (e.g., amiodarone, sotalol, ibutilide, dronedarone); • class IC antiarrhythmics (e.g., flecainide, propafenone); • antipsychotics (e.g., chlorpromazine, pimozide, haloperidol, droperidol, ziprasidone); • antidepressants	T		Pharmacokinetic and pharmacodynamic studies of venlafaxine combined with other medicinal products that prolong the QT interval have not been performed. An additive effect of venlafaxine and these medicinal products cannot be excluded. Therefore, co-administration of venlafaxine with medicinal products that have a clear QT interval prolonging effect is discouraged.

Proper/Common name	Source of Evidence	Effect	Clinical comment
(e.g., citalopram, fluoxetine, sertraline), tricyclic/tetracyclic antidepressants (e.g., amitriptyline, imipramine, maprotiline); • opioids (e.g., methadone); • macrolide antibiotics and analogues (e.g., erythromycin, clarithromycin, telithromycin, tacrolimus); • quinolone antibiotics (e.g., moxifloxacin, levofloxacin, ciprofloxacin); • antimalarials (e.g., quinine, chloroquine); • azole antifungals (e.g., ketoconazole, fluconazole, voriconazole); • domperidone; • 5-HT3 receptor antagonists (e.g., dolasetron, ondansetron); • tyrosine kinase inhibitors (e.g., vandetanib, sunitinib, nilotinib, lapatinib); • histone deacetylase inhibitors (e.g., vorinostat); • beta-2 adrenoceptor			

Proper/Common name	Source of Evidence	Effect	Clinical comment
agonists (e.g., salmeterol, formoterol)			
Drugs that Affect Electrolytes • loop, thiazide, and related diuretics; • laxatives and enemas; • amphotericin B; • high dose corticosteroids	T		The concomitant use of venlafaxine with drugs that can disrupt electrolyte levels is discouraged.
Cimetidine	CT	Concomitant administration of cimetidine and venlafaxine in a steady-state study for both drugs in 18 healthy male subjects resulted in inhibition of first- pass metabolism of venlafaxine. The oral clearance of venlafaxine was reduced by about 43%, and the exposure (AUC) and maximum concentration (C_{max}) of the drug were increased by about 60%. However, there was no effect on the pharmacokinetics of ODV.	The overall pharmacological activity of venlafaxine plus ODV is expected to increase only slightly, and no dosage adjustment should be necessary for most normal adults. However, for patients with pre-existing hypertension, for elderly patients and for patients with hepatic or renal dysfunction, the interaction associated with the concomitant use of cimetidine and venlafaxine is not known and potentially could be more pronounced. Therefore, caution is advised with such patients.
Haloperidol	CT	Venlafaxine administered under steady-state conditions at 150 mg/day in 24 healthy subjects decreased total oral-dose clearance (Cl/F) of a single 2 mg dose of haloperidol by 42%, which resulted in a 70% increase in haloperidol	The mechanism explaining this finding is unknown.

Proper/Common name	Source of Evidence	Effect	Clinical comment
		AUC. In addition, the haloperidol C_{max} increased 88% when coadministered with venlafaxine, but the haloperidol elimination half- life (t½) was unchanged.	
Imipramine	CT	Venlafaxine did not affect the pharmacokinetics of imipramine and 2-OH-imipramine. However, AUC, Cmax and Cmin of desipramine (the active metabolite of imipramine) increased by approximately 35% in the presence of venlafaxine. The 2-OH-desipramine AUCs increased by at least 2.5 fold (with venlafaxine 37.5 mg q12h) and by 4.5 fold (with venlafaxine 75 mg q12h). Imipramine partially inhibited the CYP2D6-mediated formation of ODV. However, the total concentration of active compounds (venlafaxine plus ODV) was not affected by coadministration with imipramine.	The clinical significance of elevated 2-OH-desipramine levels is unknown. No dosage adjustment is required.
Metoprolol	CT	Concomitant administration of venlafaxine (50 mg every 8 hours for 5 days) and metoprolol (100 mg every 24 hours for 5 days) to healthy volunteers in a pharmacokinetic interaction study for both	The clinical relevance of this finding is unknown. Caution and monitoring of blood pressure is recommended (see 7 WARNINGS AND PRECAUTIONS, Cardiovascular, Hypertension).

Proper/Common name	Source of Evidence	Effect	Clinical comment
		drugs resulted in an increase of plasma concentrations of metoprolol by approximately 30-40% without altering the plasma concentrations of its active metabolite, α-hydroxymetoprolol. Metoprolol did not alter the pharmacokinetic profile of venlafaxine or its active metabolite, ODV.	
Risperidone	CT	Venlafaxine administered under steady-state conditions at 150 mg/day slightly inhibited the CYP2D6-mediated metabolism of risperidone (administered as a single 1 mg oral dose) to its active metabolite, 9-hydroxyrisperidone, resulting in an approximate 32% increase in risperidone AUC. However, venlafaxine co-administration did not significantly alter the pharmacokinetic profile of the total active moiety (risperidone plus 9-hydroxyrisperidone).	No dosage adjustment is required.

Proper/Common name	Source of Evidence	Effect	Clinical comment
Indinavir	CT	In a study of 9 healthy volunteers, venlafaxine administered under steady-state conditions at 150 mg/day resulted in a 28% decrease in the AUC of a single 800 mg oral dose of indinavir and a 36% decrease in indinavir C_{max}. Indinavir did not affect the pharmacokinetics of venlafaxine and ODV.	The clinical significance of this finding is unknown.
Ketoconazole	CT	A pharmacokinetic study with ketoconazole in extensive (EM) and poor metabolizers (PM) of CYP2D6 resulted in higher plasma concentrations of both venlafaxine and ODV in subjects following administration of ketoconazole. Venlafaxine C_{max} increased by 26% in EM subjects and 48% in PM subjects. C_{max} values for ODV increased by 14% and 29% in EM and PM subjects, respectively. Venlafaxine AUC increased by 21% in EM subjects and 70% in PM subjects. AUC values for ODV increased by 23% and 33% in EM and PM subjects, respectively.	Caution is recommended.
Drugs Affecting Platelet Function (e.g., Warfarin, NSAIDS, ASA and other anticoagulants)	CT	Altered anticoagulant effects, including increased bleeding, have been reported when SSRIs or SNRIs are co-administered with warfarin. There have been reports of	Serotonin release by platelets plays an important role in hemostasis. Epidemiological studies of the case-control and cohort design that have demonstrated an association between use of psychotropic

Proper/Common name	Source of Evidence	Effect	Clinical comment
		increases in prothrombin time, partial thromboplastin time, or INR when venlafaxine was given to patients receiving warfarin therapy.	drugs that interfere with serotonin reuptake and the occurrence of upper gastrointestinal bleeding have also shown that concurrent use of an NSAID, ASA or other anticoagulants may potentiate the risk of bleeding. Patients receiving warfarin therapy should be carefully monitored when M-VENLAFAXINE XR is initiated or discontinued (see 7 WARNINGS AND PRECAUTIONS, Hematologic, Abnormal Bleeding).
CYP2D6-Inhibitors	CT	*In vitro* and *in vivo* studies indicate that venlafaxine is metabolized to its active metabolite, ODV, by CYP2D6, the isoenzyme that is responsible for the genetic polymorphism seen in the metabolism of many antidepressants. Therefore, the potential exists for a drug interaction between drugs that inhibit CYP2D6 mediated metabolism and venlafaxine.	Drug interactions that reduce the metabolism of venlafaxine to ODV (see Imipramine above) potentially increase the plasma concentrations of venlafaxine and lower the concentrations of the active metabolite. Concomitant use of CYP2D6 inhibitors and venlafaxine may reduce the metabolism of venlafaxine to ODV, resulting in increased plasma concentrations of venlafaxine and decreased concentrations of ODV. As venlafaxine and ODV are both pharmacologically active, no dosage adjustment is required when venlafaxine is coadministered with a CYP2D6 inhibitor.

Proper/Common name	Source of Evidence	Effect	Clinical comment
CYP3A3/4 Inhibitors	CT	*In vitro* studies indicate that venlafaxine is likely metabolized to a minor, less active metabolite, N-desmethylvenlafaxine, by CYP3A3/4.	Concomitant use of CYP3A4 inhibitors and venlafaxine may increase levels of venlafaxine and ODV (see Ketoconazole, above). Therefore, caution is advised when combining venlafaxine with a CYP3A4 inhibitor.
CYP2D6 and 3A4 Inhibitors	T	Concomitant use would be expected to increase venlafaxine plasma concentrations.	Because the two primary metabolic pathways for venlafaxine are through CYP2D6 and, to a lesser extent, CYP3A3/4, concomitant intake of inhibitors of both of these isoenzymes is not recommended during treatment with venlafaxine.
Clozapine	C	There have been reports of elevated clozapine levels that were temporally associated with adverse events including seizures, following the addition of venlafaxine.	Caution is recommended.

Legend: C = Case Study; CT = Clinical Trial; T = Theoretical

9.5 Drug-Food Interactions

Food has no significant effect on the absorption of venlafaxine or on the subsequent formation of ODV.

9.6 Drug-Herb Interactions

St. John's Wort

In common with SSRI's, pharmacodynamic interactions between M-VENLAFAXINE XR and the herbal remedy St. John's Wort may occur and may result in an increase in undesirable effects.

9.7 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.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Venlafaxine is a phenethylamine bicyclic derivative, chemically unrelated to tricyclic, tetracyclic or other available antidepressant or anxiolytic agents.

The mechanism of venlafaxine's antidepressant action in humans is believed to be associated with its potentiation of neurotransmitter activity in the CNS. Preclinical studies have shown that venlafaxine and its active metabolite, O-desmethylvenlafaxine (ODV), are potent inhibitors of neuronal serotonin and norepinephrine reuptake and weak inhibitors of dopamine reuptake.

10.2 Pharmacodynamics

Venlafaxine and ODV have no significant affinity for muscarinic, histaminergic, or a_1-adrenergic receptors *in vitro*. Pharmacologic activity at these receptors is hypothesized to be associated with the various anticholinergic, sedative, and cardiovascular effects seen with other psychotropic drugs.

Venlafaxine and ODV do not possess monoamine oxidase (MAO) inhibitory activity.

Results of testing in healthy volunteers demonstrated differences in the gastrointestinal tolerability of different formulations of venlafaxine. Data from healthy volunteers showed reduced incidence and severity of nausea with Venlafaxine Hydrochloride Extended-Release Capsules, compared with immediate release tablets.

10.3 Pharmacokinetics

Absorption

Venlafaxine Hydrochloride Extended-Release Capsules: After administration of Venlafaxine Hydrochloride Extended-Release Capsules, the peak plasma concentrations of venlafaxine and ODV are attained within 6 ±1.5 and 8.8 ±2.2 hours, respectively. The rate of absorption of venlafaxine from the Venlafaxine Hydrochloride Extended-Release Capsules is slower than its rate of elimination. Therefore, the apparent elimination half-life of venlafaxine following administration of Venlafaxine Hydrochloride Extended-Release Capsules (15 ±6 hours) is actually the absorption half-life instead of the true disposition half-life (5 ±2) hours observed following administration of a venlafaxine hydrochloride immediate release tablet. On the basis of mass balance studies, at least 92% of a single dose of venlafaxine is absorbed.

Steady-state concentrations of both venlafaxine and ODV in plasma are attained within 3 days of oral multiple dose therapy. The clearance of venlafaxine is slightly (15%) lower following multiple

doses than following a single dose.

Venlafaxine and ODV exhibited approximately linear kinetics over the dose range of 75 to 450 mg/day.
The mean ±SD steady-state plasma clearances of venlafaxine and ODV are 1.3 ±0.6 and 0.4 ±0.2 L/h/kg, respectively; apparent elimination half-life is 5 ±2 and 11 ±2 hours, respectively; and apparent (steady- state) volume of distribution is 7.5 ±3.7 and 5.7 ±1.8 L/kg, respectively.

When equal daily doses of venlafaxine were administered as either an immediate release tablet or the extended-release capsule, the exposure (AUC, area under the concentration curve) to both venlafaxine and ODV was similar for the two treatments, and the fluctuation in plasma concentrations was slightly lower following treatment with the extended-release capsule. Therefore, the Venlafaxine Hydrochloride Extended-Release Capsules provide a slower rate of absorption, but the same extent of absorption (i.e., AUC), as the venlafaxine immediate release tablet.

Food has no significant effect on the absorption of venlafaxine or on the subsequent formation of ODV.

Distribution

Following intravenous administration, the steady-state volume of distribution of venlafaxine is 4.4 ±1.9L/kg, indicating that venlafaxine distributes well beyond the total body water. Venlafaxine and ODV are 27 and 30% bound to human plasma proteins, respectively. Therefore, administration of venlafaxine to a patient taking another drug that is highly protein-bound should not cause increased free concentrations of the other drug.

Metabolism

Following absorption, venlafaxine undergoes extensive presystemic metabolism in the liver. The absolute bioavailability of venlafaxine is approximately 45%. The primary metabolite of venlafaxine is ODV, which is an active metabolite. ODV peak plasma levels occur approximately 4 hours after dosing. Venlafaxine is also metabolized to N-desmethylvenlafaxine, N,O-didesmethylvenlafaxine, and other minor metabolites. *In vitro* studies indicate that the formation of ODV is catalysed by CYP2D6 and that the formation of N-desmethylvenlafaxine is catalysed by CYP3A3/4. The results of the *in vitro* studies have been confirmed in a clinical study with subjects who are CYP2D6 poor and extensive metabolizers. However, despite the metabolic differences between the CYP2D6 poor and extensive metabolizers, the total exposure to the sum of the two active species (venlafaxine and ODV, which have comparable activity) was similar in the two metabolizer groups.

Elimination

Approximately 87% of a single dose of venlafaxine is recovered in the urine within 48 hours as either unchanged venlafaxine (5%), unconjugated ODV (29%), conjugated ODV (26%), or other minor inactive metabolites (27%), and 92% of the radioactive dose is recovered within 72 hours. Therefore, renal elimination of venlafaxine and its metabolites is the primary route of excretion.

Venlafaxine and ODV renal clearances are 49 ± 27 and 94 ± 56 mL/h/kg, respectively, which correspond to 5 ± 3% and 25 ± 13% of an administered venlafaxine dose recovered in urine as

venlafaxine and ODV, respectively.

Special Populations and Conditions

- **Pediatrics:** Safety and efficacy in children below the age of 18 have not been established. Therefore, Health Canada has not authorized an indication for pediatric use.
- **Geriatrics:** Population pharmacokinetic analyses of 547 venlafaxine-treated patients from three studies involving both venlafaxine immediate release tablets and Venlafaxine Hydrochloride Extended-Release Capsules showed that age does not significantly affect the pharmacokinetics of venlafaxine. A 20% reduction in clearance was noted for ODV in subjects over 60 years old; this was possibly caused by the decrease in renal function that typically occurs with aging. Dosage adjustment based upon age is generally not necessary.
- **Sex:** Population pharmacokinetic analyses of 547 venlafaxine-treated patients from three studies involving both venlafaxine immediate release tablets and Venlafaxine Hydrochloride Extended-Release Capsules showed that sex does not significantly affect the pharmacokinetics of venlafaxine. Dosage adjustment based upon gender is generally not necessary.
- **Genetic Polymorphism:** Plasma concentrations of venlafaxine were higher in CYP2D6 poor metabolizers than extensive metabolizers. Because the total exposure (AUC) of venlafaxine and ODV was similar in poor and extensive metabolizer groups, there is no need for different venlafaxine dosing regimens for these two groups.
- **Hepatic Insufficiency:** In 9 patients with hepatic cirrhosis, the pharmacokinetic disposition of both venlafaxine and ODV was significantly altered. Venlafaxine elimination half-life was prolonged by about 30%, and clearance was decreased by about 50% in cirrhotic patients compared to normal subjects. ODV elimination half-life was prolonged by about 60% and clearance decreased by about 30% in cirrhotic patients compared to normal subjects.
  A large degree of inter-subject variability was noted. Three patients with more severe cirrhosis had a more substantial decrease in venlafaxine clearance (about 90%) compared to normal subjects.
  Dosage adjustment is necessary in patients with hepatic impairment (see 4.2 Recommended Dose and Dosage Adjustment).
- **Renal Insufficiency:** In patients with moderate to severe impairment of renal function (GFR = 10- 70 mL/min), venlafaxine elimination half-life was prolonged by 50%, and clearance was decreased by about 24% compared to normal subjects. ODV elimination half-life was prolonged by about 40%, but clearance was unchanged.

  In dialysis patients, venlafaxine elimination half-life was prolonged by about 180% and clearance was decreased by about 57%. In dialysis patients, ODV elimination half-life was prolonged by about 142%, and clearance was reduced by about 56% compared to normal subjects.

  A large degree of inter-subject variability was noted.

  Dosage adjustment is necessary in patients with renal impairment (see 4.2 Recommended Dose and Dosage Adjustment).

11 STORAGE, STABILITY AND DISPOSAL

Store at room temperature (15 - 30°C), in a dry place.

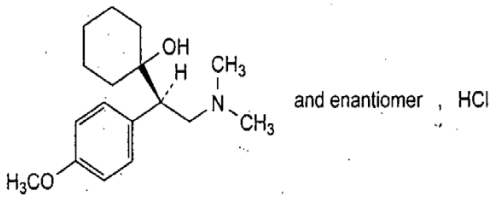
12 SPECIAL HANDLING INSTRUCTIONS

None.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

Proper name:	Venlafaxine Hydrochloride
Chemical name:	Cyclohexanol,1-[2-(dimethylamino)-1-(4 methoxyphenyl)ethyl]-,hydrochloride;(±)-1-[α-[(dimethylamino)methyl]-p-methoxybenzyl]cyclohexanol hydrochloride Or 1-[(1RS)-2-(dimethylamino)-1-(4-methoxyphenyl)ethyl]-cyclohexanol hydrochloride
Molecular formula and molecular mass:	$C_{17}H_{27}NO_2 \cdot HCl$; 313.86 g/mol
Structural formula:	 and enantiomer , HCl
Physicochemical properties:	
Appearance:	White or almost white powder.
Solubility:	Freely soluble in water and in methanol, soluble in anhydrous ethanol, slightly soluble or practically insoluble in acetone.
Melting point:	210-218°C

14 CLINICAL TRIALS

14.1 Clinical Trials by Indication

Major Depressive Disorder

Summary of Patient Demographics and Study Results for Clinical Trials in Major Depressive Disorder

Venlafaxine Hydrochloride Extended-Release Capsules: The efficacy of Venlafaxine Hydrochloride Extended-Release Capsules as a treatment for depression was established in two placebo-controlled, short-term, flexible-dose studies in adult outpatients meeting DSM-III-R or DSM-IV criteria for major depression. An 8-week study utilizing Venlafaxine Hydrochloride Extended-Release Capsules doses in a range 75-225 mg/day (mean dose for completers was 177 mg/day) and a 12-week study utilizing Venlafaxine Hydrochloride Extended-Release Capsules doses in a range 75-150 mg/day (mean dose for completers was 136 mg/day) both demonstrated superiority of Venlafaxine Hydrochloride Extended-Release Capsules over placebo on the HAM-D total score, the HAM-D Depressed Mood Item, the MADRS total score, the CGI Severity of illness scale, and the CGI Global Improvement scale. In both studies, Venlafaxine Hydrochloride Extended-Release Capsules was also significantly better than placebo for certain factors of the HAM-D, including the anxiety/somatization factor, the cognitive disturbance factor, and the retardation factor, as well as for the psychic anxiety score.

In the 12-week study comparing immediate release tablets with Venlafaxine Hydrochloride Extended-Release Capsules, once daily, Venlafaxine Hydrochloride Extended-Release Capsules was significantly more effective at weeks 8 and 12, compared with immediate release tablets given twice daily for treating major depression. Analysis of safety data from this trial showed that the incidence of treatment-emergent nausea and nausea severity over time were lower with Venlafaxine Hydrochloride Extended-Release Capsules than with immediate release tablets. Additionally, the incidence of vomiting was lower with Venlafaxine Hydrochloride Extended-Release Capsules.

In one longer term study, outpatients meeting DSM-IV criteria for major depressive disorder who had "responded"[2] during an 8-week open trial on venlafaxine hydrochloride extended-release (75, 150, or 225 mg, in the morning (qAM) were randomized to continuation of their same venlafaxine hydrochloride extended-release dose or to placebo, for up to 26 weeks of observation for "relapse"[2]. Patients receiving continued venlafaxine hydrochloride extended-release treatment experienced significantly lower "relapse"[2] rates compared with those on placebo.

[2]*For the purposes of this study:*
"Responded" *during the open phase was defined as a CGI Severity of Illness item score < 3 and a HAM-D-21 total score of < 10 at the day 56 evaluation.*
"Relapse" *during the double-blind phase was defined as follows:*
(1) a reappearance of major depressive disorder as defined by DSM-IV criteria and a CGI Severity of Illness item score of > 4 (moderately ill),
(2) 2 consecutive CGI Severity of Illness item scores of > 4, or
(3) a final CGI Severity of Illness item score of > 4 for any patient who withdrew from the study

for any reason.

Generalized Anxiety Disorder (GAD)

Summary of Patient Demographics and Study Results for Clinical Trials in Generalized Anxiety Disorder

The efficacy of Venlafaxine Hydrochloride Extended-Release Capsules in the treatment of GAD has been demonstrated in three fixed dose studies and one flexible dose study for time periods ranging from 8 to 28 weeks. In these studies, Venlafaxine Hydrochloride Extended-Release Capsules was shown to have a statistically significant superiority over placebo on the following three measures: Hamilton Anxiety Rating Scale (total score), Hamilton anxious mood item, and Clinical Global Impression of Severity of Illness rating.

In the three fixed dose studies, response rates at week 8 of treatment, as defined by the proportion of patients achieving Clinical Global Impression of Improvement Scores of "much" or "very much improved", were as follows (last observation carried forward):

Table 13 –Results of Studies 210 US, 378 EU and 214 US in Generalized Anxiety Disorder

Study #	Placebo		37.5 mg		75 mg		150 mg		225 mg	
	n	%	n	%	n	%	n	%	n	%
210 US	96	49%			86	57%	81	58%	86	65%
378 EU	130	45%	138	59%	130	69%	131	78%		
214 US	98	39%			87	62%	87	49%		

For the two long-term studies, response rates at month 6 were as follows for last observation carried forward (LOCF):

Table 14 –Results of Studies 378 US and 218 US in Generalized Anxiety Disorder

Study #		Placebo		37.5 mg		75 mg		150 mg		75-225 mg	
		n	%	n	%	n	%	n	%	n	%
378 EU	LOCF	123	33%							115	67%
218 US	LOCF	130	48%	138	66%	130	75%	131	81%		

Social Anxiety Disorder (Social Phobia)

Summary of Patient Demographics and Study Results for Clinical Trials in Social Anxiety Disorder

The efficacy of Venlafaxine Hydrochloride Extended-Release Capsules as a treatment for social anxiety disorder (also known as social phobia) was demonstrated in four 12-week, multi-center, placebo-controlled, flexible-dose studies and one 6- month, fixed/flexible-dose study in adult outpatients meeting DSM-IV criteria for social anxiety disorder. These studies evaluating Venlafaxine Hydrochloride Extended-Release Capsules doses in a range of 75-225 mg/day demonstrated that Venlafaxine Hydrochloride Extended-Release Capsules was significantly more effective than placebo for the Liebowitz Social Anxiety Scale Total score, Clinical Global Impressions of Severity of Illness rating, and Social Phobia Inventory.

Examination of subsets of the population studied did not reveal any differential responsiveness on the basis of age or gender.

Panic Disorder

Summary of Patient Demographics and Study Results for Clinical Trials in Panic Disorder

Panic disorder (DSM-IV) is characterized by recurrent, unexpected panic attacks, i.e., a discrete period of intense fear or discomfort, in which four (or more) of the following symptoms develop abruptly and reach a peak within 10 minutes: 1) palpitations, pounding heart, or accelerated heart rate; 2) sweating; 3) trembling or shaking; 4) sensations of shortness of breath or smothering; 5) feeling of choking; 6) chest pain or discomfort; 7) nausea or abdominal distress; 8) feeling dizzy, unsteady, light-headed, or faint; 9) derealization (feelings of unreality) or depersonalization (being detached from oneself); 10) fear of losing control; 11) fear of dying; 12) paresthesias (numbness or tingling sensations); 13) chills or hot flushes.

Two fixed-dose and two flexible-dose placebo-controlled studies have been performed to investigate the efficacy of Venlafaxine Hydrochloride Extended-Release Capsules as a treatment for panic disorder. In the two double-blind, 12-week, multi- center, placebo-controlled studies in adult outpatients meeting DSM-IV criteria for panic disorder, with or without agoraphobia, patients received fixed doses of 75 or 150 mg/day in one study and 75 or 225 mg/day in the other study. In these two trials, Venlafaxine Hydrochloride Extended-Release Capsules doses of 75 mg, 150 mg and 225 mg were significantly more effective than placebo for the primary outcome, the percentage of patients free of full-symptom panic attacks on the Panic and Anticipatory Anxiety Scale (PAAS), and for the two key secondary outcomes: 1) mean change from baseline to endpoint on the panic disorder Severity Scale (PDSS) total score, and (2) percentage of patients rated as responders (much improved or very much improved) in the Clinical Global Impressions (CGI) Improvement scale.

In one flexible-dose study (75 mg to 225 mg daily doses), the primary outcome, the percentage of patients free of full-symptom panic attacks, approached significance (p=0.056). In this study, Venlafaxine Hydrochloride Extended-Release Capsules was significantly more effective than placebo for the two key secondary outcomes, (1) mean change from baseline to endpoint on the panic disorder Severity Scale (PDSS) total score, and (2) percentage of patients rated as responders (much improved or very much improved) in the Clinical Global Impressions (CGI) Improvement scale.

In another flexible-dose study (dose range 75 mg-225 mg/day), Venlafaxine Hydrochloride Extended-Release Capsules was not significantly more effective than placebo for the primary outcome, the percentage of patients free of full-symptom panic attacks, but it was significantly more effective than placebo for the secondary outcome: percentage of patients rated as responders (much improved or very much improved) in the Clinical Global Impressions (CGI) Improvement scale.

Examination of subsets of the population studied did not reveal any differential responsiveness on the basis of gender. There was insufficient information to determine the effect of age or race on outcome in these studies.

In a longer-term study, adult outpatients meeting DSM-IV criteria for panic disorder who had

responded at the end of a 12-week open phase with Venlafaxine Hydrochloride Extended-Release Capsules (75 to 225 mg/day) were randomly assigned to continue the same Venlafaxine Hydrochloride Extended-Release Capsules dose (75, 150, or 225 mg) or switch to placebo for observation for relapse during a 6-month double-blind phase. Response during the open phase was defined as ≤ 1 full-symptom panic attack per week during the last 2 weeks of the open phase and a CGI Improvement score of 1 (very much improved) or 2 (much improved) during that same 2-week period. Relapse during the double-blind phase was defined as having 2 or more full-symptom panic attacks per week for 2 consecutive weeks or having discontinued due to loss of effectiveness as determined by the investigator. Patients receiving continued Venlafaxine Hydrochloride Extended-Release Capsules treatment experienced significantly longer time to relapse over the subsequent 6 months compared with those receiving placebo.

14.2 Comparative Bioavailability Studies

Fasting study

A randomized, single-dose, two-way, crossover comparative bioavailability study of M-VENLAFAXINE XR 150 mg extended-release capsules (Mantra Pharma Inc.) and EFFEXOR® XR 150 mg extended-release capsules (Upjohn Canada ULC) was conducted in 36 healthy, adult, male subjects under fasting conditions. A summary of the bioavailability data from 31 subjects that were included in the statistical analysis is presented in the following table:

SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA

Venlafaxine (1 × 150 mg) Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test[1]	Reference[2]	% Ratio of Geometric Means	90% Confidence Interval
AUC_T (ng·h/mL)	1715.77 1897.84 (41.29)	1678.15 1888.1 (46.27)	102.2	95.6 – 109.3
AUC_I (ng·h/mL)	1781.54 1960.32 (40.73)	1754.14 1958.06 (45.86)	101.6	95.0 – 108.6
C_{max} (ng/mL)	122.14 128.68 (28.31)	109.28 116.40 (32.45)	111.8	105.7 – 118.2
T_{max}[3] (h)	5.00 (4.00 – 7.50)	5.50 (4.50 – 7.50)		
$T_{1/2}$[4] (h)	8.81 (20.31)	8.77 (22.38)		

[1] M-VENLAFAXINE XR (venlafaxine as venlafaxine hydrochloride) extended-release capsules, 150 mg (Mantra Pharma Inc.)
[2] EFFEXOR® XR (venlafaxine as venlafaxine hydrochloride) extended-release capsules, 150 mg (Upjohn Canada ULC)
[3] Expressed as the median (range) only
[4] Expressed as the arithmetic mean (CV%) only

Fed Study

A randomized, single-dose, two-way, crossover comparative bioavailability study of M-VENLAFAXINE XR 150 mg extended-release capsules (Mantra Pharma Inc.) and EFFEXOR® XR 150 mg extended-release capsules (Upjohn Canada ULC) was conducted in 36 healthy, adult, male subjects under high-fat, high calorie fed conditions. A summary of the bioavailability data from 32 subjects that were included in the statistical analysis is presented in the following table:

SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA

Venlafaxine (1 × 150 mg) Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test[1]	Reference[2]	% Ratio of Geometric Means	90% Confidence Interval
AUC_T (ng·h/mL)	2256.08 2613.97 (60.82)	2223.46 2513.86 (54.34)	101.5	96.4 – 106.8
AUC_I (ng·h/mL)	2330.87 2712.24 (62.93)	2295.47 2606.58 (56.66)	101.5	96.6 – 106.8
C_{max} (ng/mL)	148.35 154.8 (27.08)	140.84 148.48 (29.09)	105.3	99.8 – 111.1
T_{max}[3] (h)	5.00 (4.50 – 6.50)	5.00 (4.50 – 16.00)		
$T_{1/2}$[4] (h)	9.36 (30.61)	9.1 (32.09)		

[1] M-VENLAFAXINE XR (venlafaxine as venlafaxine hydrochloride) extended-release capsules, 150 mg (Mantra Pharma Inc.)
[2] EFFEXOR® XR (venlafaxine as venlafaxine hydrochloride) extended-release capsules, 150 mg (Upjohn Canada ULC)
[3] Expressed as the median (range) only
[4] Expressed as the arithmetic mean (CV%) only

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

The toxicological profile of venlafaxine was evaluated for up to 18 months in mice, up to 2 years in rats, and up to 1 year in dogs. A single dose range finding study was done in monkeys. As part of its evaluation, the reproductive toxicologic potential of venlafaxine was evaluated in segment I, II, and III studies in rats and a segment II study in rabbits. The major findings in the acute, long-term, and reproductive toxicity studies are discussed below.

General Toxicology

Acute Toxicity: Venlafaxine showed low acute toxicity with LD_{50s} ≥ 405 mg/kg in mice and ≥ 336 mg/kg in rats; i.v. LD_{50s} in mice were ≥ 48 mg/kg. No drug-related macroscopic lesions were observed; microscopic examinations were not performed.

Carcinogenicity

Subchronic toxicity of venlafaxine was evaluated in mice, rats, dogs and monkeys (1-month range finding study only); chronic toxicity was evaluated in dogs; and chronic toxicity/carcinogenicity was evaluated in mice and rats.

Mice: Venlafaxine was administered to mice for 3 months at 0, 24, 96, 138, 180 and 240 mg/kg to establish doses for a subsequent 18 month carcinogenicity study. Drug-related tonic/clonic convulsions occurring in both 180 and 240 mg/kg groups were regarded as limiting for subsequent studies of longer duration due to anticipated mortality associated with convulsions of this magnitude. Based on these results, a maximum dose of 120 mg/kg was selected for chronic carcinogenicity studies, which was regarded to provide a minimal margin below the convulsive threshold which would limit survival in a chronic study. In the 18 month study, mice were thus dosed at 10, 35, and 120 mg/kg. No carcinogenic effect was noted in males or females. A slight decrease in survival occurred in the 120 mg/kg males, but was not associated with specific microscopic lesions. The cause of death in the 120 mg/kg mice could not be clearly established. Male and female mice receiving 120 mg/kg were noted to have increased motor activity.

Rats: Rats were dosed with venlafaxine at 0, 4.5, 40, 170, and 340 mg/kg in the 6 month toxicity study and at 0, 10, 35, and 120 mg/kg in the 2 year study. No drug-related histologic lesions occurred in either study. In the six month study, an increased mortality was seen at 170 and 340 mg/kg.

Deaths were generally associated with convulsions. Effects noted included decreased body weight and food consumption at 170 and 340 mg/kg and increased incidence of physical examination findings at 40 mg/kg and above. Due to mortality, body weight, and food consumption effects, the maximum tolerated dose for the chronic study was considered to be below 170 mg/kg. The rat carcinogenicity study was conducted at dosages of 0, 10, 35, and 120 mg/kg for 2 years. As with the mouse, no carcinogenic effect was observed. An increased mortality was seen at 120 mg/kg; however, no clear drug-related lesion was associated with mortality. Mortality at lower dosages was comparable to historical limits (50-65%).

Dogs: In dogs, venlafaxine was administered for 6 months at 0, 2, 7, and 22 mg/kg and for 12 months at 0, 4, 10, and 24 mg/kg. As with the other species tested, no drug-related histologic lesions occurred. In the 6 month dog study, slightly decreased heart rate occurred in two dogs (during weeks 6, 12, 18, and 25 in one dog and week 25 in the other dog) receiving 22 mg/kg. Although effects on cardiovascular parameters have been seen with other antidepressants, including ECG alterations consisting of T wave changes (inversions, bifid T wave), prolongation of conduction and sinus tachycardia seen with tricyclic antidepressants, these effects were not seen after administration of venlafaxine. Blood pressure and ECGs were measured periodically throughout treatment at multiple intervals after ECG abnormalities in these or any other dogs in

the 6 month or 1 year studies. A slight decrease in body weight gain was seen at the high dose in both studies. Mydriasis, a pharmacologic effect, occurred at all dosages.

Other minor drug-related effects were generally limited to the high dose.

Monkeys: In monkeys, a range finding assay was conducted using one monkey/sex at dosages of 0, 25, 80, 125, 170, and 260 mg/kg for up to 27 days. Deaths occurred in the first 5 days in one of two monkeys at 125 mg/kg and all monkeys at higher dosages. No drug-related histologic changes were found in these animals, and deaths were considered secondary to drug-induced convulsions.
Electrocardiograms were only measured on the 80 mg/kg monkeys and showed no drug-related effects. Due to pharmacokinetic considerations, additional monkey studies were not conducted.

Genotoxicity

Venlafaxine and the major human metabolite, O-desmethylvenlafaxine (ODV), were not mutagenic in the Ames reverse mutation assay in Salmonella bacteria or the Chinese hamster ovary/HGPRT mammalian cell forward gene mutation assay. Venlafaxine was also not mutagenic or clastogenic in the *in vitro* BALB/c-3T3 mouse cell transformation assay, the sister chromatid exchange assay in cultured Chinese hamster ovary cells, or in the *in vivo* chromosomal aberration assay in rat bone marrow. ODV was not clastogenic in the *in vivo* Chinese hamster ovary cell chromosomal aberration assay, or in the *in vivo* chromosomal aberration assay in rat bone marrow.

Reproductive and Developmental Toxicology

The reproductive toxicology of venlafaxine was studied in rats and rabbits. No teratogenic effect was observed and no deaths occurred.

Pharmacotoxic signs were seen in paternal and maternal rats given venlafaxine doses of 30 and 60 mg/kg/day (4 and 8 times the maximum recommended human dose, respectively), but no adverse effect was noted in fertility or general reproductive performance. Decreased fetal size and pup weight at birth with 60 mg/kg/day may be correlated with maternal toxicity. In a perinatal toxicity study, decreased fetal survival following birth was observed at 40 and 80 mg/kg/day (approximately 5 to 11 times the maximum recommended human dose, respectively) and was considered secondary to drug- related decreased maternal care. No teratogenic effect was seen. Evidence of carcinogenesis, mutagenesis, and impairment of fertility was not noted in preclinical toxicology studies.

Reproductive Toxicity with the Major Metabolite of Venlafaxine: Reduced fertility was observed in a study in which both male and female rats were exposed to the major metabolite of venlafaxine (ODV). This ODV exposure was approximately 2 to 3 times that which would result from a human dose of 225 mg/day of venlafaxine. The human relevance of this finding is unknown.

In this study, administration of ODV as the succinate salt in male and female rats resulted in disrupted estrous cycles and increased time-to-mating at ≥ 30 mg/kg/day; decreased fertility rates at ≥ 100 mg/kg/day; and increased preimplantation loss and decreased fetal weight at 300 mg/kg/day. There was decreased prostate weight at ≥ 30 mg/kg/day associated with prostate

atrophy at ≥ 100 mg/kg/day; however, there were no compound-related macroscopic or microscopic findings in the epididymis, seminal vesicles, or testes. The no-observed-adverse-effect level (NOAEL) for effects on fertility was 30 mg/kg/day and the developmental NOAEL was 100 mg/kg/day.

17 SUPPORTING PRODUCT MONOGRAPHS

1. EFFEXOR® XR (extended-release capsules, 37.5 mg, 75 mg and 150 mg), submission control 276199, Product Monograph, BGP Pharma ULC. (OCT 31, 2023)

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

[Pr]M-VENLAFAXINE XR

Venlafaxine Hydrochloride Extended-Release Capsules

Read this carefully before you start taking **M-VENLAFAXINE XR** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **M-VENLAFAXINE XR**.

Serious Warnings and Precautions

New or worsened emotional or behaviour problems:

- When you first start taking M-VENLAFAXINE XR or when your dose is adjusted, you may feel worse instead of better. You may feel new or worsened feelings of agitation, hostility, anxiety, or impulsivity.
- During your treatment with M-VENLAFAXINE XR, it is important that you and your healthcare professional talk regularly about how you are feeling. They will closely monitor you for signs of new or worsened emotions or behaviours while you are taking M-VENLAFAXINE XR.
- You may find it helpful to tell a relative or close friend that you are depressed. Ask them to read this leaflet. You might ask them to tell you if they:
    - think your depression is getting worse, or
    - are worried about changes in your behavior.
- If your depression worsens or you experience changes in your behavior, tell your healthcare professional right away. Do not stop taking your medicine as it takes time for M-VENLAFAXINE XR to work.

Self-harm or Suicide:

- Antidepressants, such as M-VENLAFAXINE XR, can increase the risk of suicidal thoughts or actions.
- If you have thoughts of harming or killing yourself at any time, tell your healthcare professional or go to a hospital right away. Close observation by your healthcare professional is necessary in this situation.

What is M-VENLAFAXINE XR used for?

M-VENLAFAXINE XR is used in adults to relieve the symptoms of:

- Major depressive disorder (feeling sad, a change in appetite or weight, difficulty concentrating or sleeping, feeling tired, headaches, unexplained aches and pain).
- Generalized anxiety disorder (anxiety or nervousness).
- Social anxiety disorder, also known as social phobia (avoidance and/or fear of social situations).

- Panic disorder (repeated, unexpected panic attacks).

How does M-VENLAFAXINE XR work?

M-VENLAFAXINE XR belongs to a group of medicines called serotonin and norepinephrine reuptake inhibitors (SNRIs). M-VENLAFAXINE XR is thought to work by increasing the levels of two chemicals in the brain, serotonin and norepinephrine. This helps to relieve your symptoms of major depressive disorder, generalized anxiety disorder, social anxiety disorder and/or panic disorder.

What are the ingredients in M-VENLAFAXINE XR?

Medicinal ingredient: Venlafaxine Hydrochloride

Non-medicinal ingredients: Microcrystalline cellulose, hypromellose, ethylcellulose, purified talc, capsule shell (gelatin, purified water, titanium dioxide, iron oxide black and iron oxide red) and printing ink (shellac, dehydrated alcohol, isopropyl alcohol, butyl alcohol, propylene glycol, strong ammonia solution, black iron oxide, potassium hydroxide and purified water).

M-VENLAFAXINE XR comes in the following dosage forms:

Extended-Release Capsules: 37.5 mg, 75 mg and 150 mg venlafaxine (as venlafaxine hydrochloride)

Do not use M-VENLAFAXINE XR if:

- You are allergic to venlafaxine hydrochloride or to any of the non-medicinal ingredients in M-VENLAFAXINE XR.
- You are taking or have recently taken monoamine oxidase inhibitors (MAOIs) such as phenelzine sulphate and moclobemide, within the last 14 days.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take M-VENLAFAXINE XR. Talk about any health conditions or problems you may have, including if you:

- Have ever had any allergic reaction to medications, food, etc;
- Have or have a history of:
  - Liver problems
  - Kidney problems
  - Seizures
  - Aggression
  - Heart problems;
- Have or have a family history of QT/QTc prolongation (abnormal electrical activity of the heart);
- Have a history or family history of bipolar disorder;
- Have a bleeding disorder or have been told that you have low platelets.
- Have blood pressure problems;
- Are taking any medications, especially:

- Other medicines used to treat depression,
- Medicines used to treat psychiatric disorders,
- Opioids (including those used to treat pain or drug dependence),
- Weight-loss medication,
- Sleeping pills,
- Medicines used to treat anxiety, or
- Medication used to control blood pressure;

- Are pregnant or thinking about becoming pregnant, or if you are breast feeding;
- Drink alcohol and/or use street drugs;
- Had a recent bone fracture or were told you have osteoporosis or risk factors for osteoporosis.

Other warnings you should know about:

During treatment with M-VENLAFAXINE XR, it is important that you and your healthcare professional talk regularly about how you are feeling.

Do NOT stop taking M-VENLAFAXINE XR without talking to your healthcare professional first, as it may cause unwanted side effects such as headache, insomnia, numbness, tingling, burning, or prickling, nervousness, anxiety, nausea, sweating, dizziness, jitteriness and weakness.

Activation of Mania: Some patients with bipolar disorder (also known as manic depression) may enter into a manic phase when they start taking M-VENLAFAXINE XR. Tell your healthcare professional if you experience symptoms of mania such as excessive physical activity, overactive behaviour or thoughts, increased energy, trouble sleeping, racing thoughts, reckless behaviour, excessive happiness or irritability, talking more or faster than usual.

Effects on Sexual Function: Taking medicines like M-VENLAFAXINE XR may cause symptoms of sexual dysfunction. In some cases these symptoms have continued after stopping M-VENLAFAXINE XR treatment. Talk to your healthcare professional if you experience symptoms such as a decrease in sexual desire, performance or satisfaction.

Pregnancy: Only take M-VENLAFAXINE XR during pregnancy if you and your healthcare professional have discussed the risks and have decided that you should. If you take M-VENLAFAXINE XR near the end of your pregnancy, you may be at a higher risk of heavy vaginal bleeding shortly after birth. If you become pregnant while taking M-VENLAFAXINE XR, tell your healthcare professional right away.

Effects on newborns: In some cases, babies born to a mother taking M-VENLAFAXINE XR during pregnancy may require hospitalization, breathing support and tube feeding. Be ready to seek medical help for your newborn if they:

- Have trouble breathing or feeding;
- Have muscle stiffness, or floppy muscles (like a rag doll);
- Have seizures (fits);

- Are shaking (jitteriness);
- Are constantly crying.

Serotonin toxicity (also known as Serotonin Syndrome): M-VENLAFAXINE XR can cause serotonin toxicity, a rare but potentially life-threatening condition. It can cause serious changes in how your brain, muscles and digestive system work. You may develop serotonin toxicity if you take M-VENLAFAXINE XR with certain antidepressants or migraine medications. Serotonin toxicity symptoms include:

- Fever, sweating, shivering, diarrhea, nausea, vomiting;
- Muscle shakes, jerks, twitches or stiffness, overactive reflexes, loss of coordination
- Fast heartbeat, changes in blood pressure;
- Confusion, agitation, restlessness, hallucinations, mood changes, unconsciousness, and coma.

Falls and fractures: Taking M-VENLAFAXINE XR may increase your risk of breaking a bone if you are elderly, have osteoporosis or have other major risk factors for breaking a bone. You should take extra care to avoid falls, especially if you get dizzy or have low blood pressure.

Driving and using machines: Until you know how M-VENLAFAXINE XR affects you, do not drive or operate a vehicle or potentially dangerous machinery.

Monitoring and tests: Your healthcare professional may do tests, including blood tests, before you take M-VENLAFAXINE XR and regularly during your treatment. These tests will monitor:

- Your blood pressure;
- Your level of cholesterol (a type of fat) in your blood.

Angle-closure Glaucoma
M-VENLAFAXINE XR can cause an acute attack of glaucoma. Having your eyes examined before you take M-VENLAFAXINE XR could help identify if you are at risk of having angle-closure glaucoma. Seek immediate medical attention if you experience:

- Eye pain;
- Changes in vision;
- Swelling or redness in or around the eye.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

Serious Drug Interactions

Do not use M-VENLAFAXINE XR if you are taking or have recently taken

- MAOIs, such as phenelzine, tranylcypromine, moclobemide, selegiline, linezolid, and methylene blue, within the last 14 days.

The following may interact with M-VENLAFAXINE XR:

- Other antidepressants, such as other SNRIs, selective serotonin reuptake inhibitors and certain tricyclics;
- Other drugs that affect serotonin such as, amphetamines, opioids, lithium, linezolid, sibutramine, tryptophan, triptans used to treat migraines;
- Medicines used to treat pain, such as fentanyl (used in anaesthesia or to treat chronic pain), tramadol, tapentadol, meperidine, methadone, pentazocine;
- Medicines used to treat cough, such as dextromethorphan;
- Medicines used to treat bipolar depression, such as lithium;
- Medicines used to treat high blood pressure such as metoprolol;
- Medicines used to treat heartburn and ulcers such as cimetidine;
- Medicines called triptans which are used to treat migraines, such as almotriptan, sumatriptan, rizatriptan, naratriptan, and zolmitriptan;
- Medicines that affect how your heart beats such as quinidine, procainamide, disopyramide, amiodarone, sotalol, ibutilide, dronedarone, flecainide, and propafenone;
- Medicines used to manage psychosis (antipsychotics) such as chlorpromazine, pimozide, haloperidol, droperidol, ziprasidone, risperidone and clozapine;
- Medicines to treat bacterial and fungal infections such as erythromycin, clarithromycin, telithromycin, tacrolimus, moxifloxacin, levofloxacin, and ciprofloxacin, ketoconazole, fluconazole, and voriconazole;
- Medicines used to treat malaria such as quinine, and chloroquine;
- Medicines used to treat nausea and vomiting such as domperidone, dolasetron, and ondansetron;
- Medicines used in cancer therapy such as vandetanib, sunitinib, nilotinib, lapatinib, and vorinostat;
- Medicines used to treat asthma such as salmeterol, and formoterol;
- Medicines that affect your electrolyte levels such as diuretics (“water pills”), laxatives and enemas, amphotericin B, and high dose corticosteroids (drugs that reduce inflammation);
- Medicines that can affect how your blood clots such as warfarin, acetylsalicylic acid (Aspirin), and non-steroidal anti-inflammatory drugs (NSAIDs);
- Herbal medicines such as St. John’s Wort;
- Alcohol, it is recommended to avoid drinking alcohol while taking M-VENLAFAXINE XR.

How to take M-VENLAFAXINE XR:

- It is very important that you take M-VENLAFAXINE XR exactly as your healthcare professional has instructed;
- Do not change your dose without talking to your healthcare professional;
- Your healthcare professional will tell you when to stop taking M-VENLAFAXINE XR. Always follow your healthcare professional’s instructions on how to lower your dose carefully and

safely to void experiencing withdrawal symptoms;

- Continue to take M-VENLAFAXINE XR even if you do not feel better, as it may take several weeks for your medicine to start working;
- Take with food either in the morning or the evening;
- Swallow the capsules whole with water. Do not divide, crush, chew or place the capsules in water.

REMEMBER: This medicine has been prescribed only for you. Do not give it to anybody else. If you have any further questions, please ask your healthcare professional or pharmacist.

Usual dose:

Major depressive disorder: The usual dose is 75 mg once daily. Your healthcare professional may decide to start you on a lower dose of 37.5 mg once daily. Based on how you respond and your tolerability, your healthcare professional may increase your dose. The maximum daily dose is 225 mg / day.

Generalized anxiety disorder: The usual starting dose is 37.5 mg once daily for 4 to 7 days. The usual maintenance dose is 75 mg once daily. Based on how you respond and your tolerability, your healthcare professional may increase your dose. The maximum daily dose is 225 mg / day.

Social anxiety disorder: The usual dose is 75 mg once daily. Your healthcare professional may decide to start you on a lower dose of 37.5 mg once daily. Based on how you respond and your tolerability, your healthcare professional may increase your dose. The maximum daily dose is 225 mg / day.

Panic disorder: The usual starting dose is 37.5 mg once daily for 7 days. The usual maintenance dose is 75 mg once daily. Based on how you respond and your tolerability, your healthcare professional may increase your dose. The maximum daily dose is 225 mg / day.
If you have liver or kidney problems, your healthcare professional may prescribe a lower dose.

Overdose:

If you think you, or a person you are caring for, have taken too much M-VENLAFAXINE XR, contact a healthcare professional, hospital emergency department, regional poison control centre or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669) immediately, even if there are no signs or symptoms.

Missed Dose:

If you missed a dose of this medication, you do not need to make up the missed dose. Skip the missed dose and continue with your next scheduled dose. Do not take two doses at the same time.

What are possible side effects from using M-VENLAFAXINE XR?

These are not all the possible side effects you may have when taking M-VENLAFAXINE XR. If you experience any side effects not listed here, tell your healthcare professional.
Some side effects of M-VENLAFAXINE XR are:

- Headache;

- Nausea;
- Dry mouth;
- Constipation;
- Loss of appetite;
- Vomiting;
- Sleepiness;
- Dizziness;
- Insomnia;
- Weakness;
- Sweating;
- Nervousness;
- Abnormal vision;
- Abnormal dreams;
- Tremors (shaking);
- Diarrhea;
- Discomfort or pain in the upper abdomen;
- Weight loss;
- Prickling of the skin;
- Rash.

Serious side effects and what to do about them

Frequency/Side Effect/Symptom	Talk to your healthcare professional		Stop taking this drug and get immediate medical help
	Only if severe	In all cases	
COMMON			
Increase in Blood Pressure: headache, stronger and possibly faster heartbeat, chest pain, dizziness, excessive tiredness, and blurred vision. Sometimes, the increase in blood pressure could be severe enough to require urgent medical attention		✓	
Tachycardia (abnormally fast heartbeat): dizziness, light headedness, shortness of breath, racing heart		✓	
UNCOMMON			

Frequency/Side Effect/Symptom	Talk to your healthcare professional		Stop taking this drug and get immediate medical help
	Only if severe	In all cases	
Akathisia (a type of movement disorder): feeling restless and unable to sit or stand still		✓	
Allergic Reaction: difficulty swallowing or breathing, wheezing, drop in blood pressure, feeling sick to your stomach and throwing up, hives or rash, swelling of the face, lips, tongue or throat			✓
Gastrointestinal Bleeding (bleeding in the stomach or bowels): black, tarry stool, blood in the stool, vomiting blood			✓
Hallucinations (seeing or hearing things that are not there)		✓	
Hyponatremia (low sodium in the blood): lethargy, confusion, muscular twitching, achy, stiff or uncoordinated muscles, seizure, coma		✓	
Low Platelets: Bruising or unusual bleeding from the skin or other areas		✓	
Mania: elevated or irritable mood, decreased need for sleep, racing thoughts		✓	
Uncontrollable movements of the body or face		✓	
Urinary retention (inability to urinate or empty or loss of control of the bladder): pain		✓	
Self-harm or Suicide: thoughts or actions about hurting or killing yourself		✓	
Sexual problems: milky discharge from breasts in women, abnormal ejaculation or impotence in men, decreases in sexual desire, performance and satisfaction		✓	

Frequency/Side Effect/Symptom	Talk to your healthcare professional		Stop taking this drug and get immediate medical help
	Only if severe	In all cases	
RARE			
Angle-closure Glaucoma: blurred vision, halos around lights, eye pain and redness, nausea and vomiting, severe headache			✓
Heart rhythm problems: dizziness, increased heart rate, palpitations, fainting or seizures			✓
Liver Disorder: yellowing of the skin or eyes, dark urine and pale stools, abdominal pain, nausea, vomiting, loss of appetite		✓	
New or worsened emotional or behavioural problems: agitation, anger, aggression, anxiety, suicidal or violent thoughts		✓	
Seizures (fit): uncontrollable shaking with or without loss of consciousness			✓
Serotonin toxicity: mental changes such as agitation, hallucinations, confusion, or other changes in mental status; coordination problems, uncontrolled muscle spasms, or muscle twitching (overactive reflexes); restlessness, shaking, shivering, racing or fast heartbeat, high or low blood pressure, sweating or fever, nausea, vomiting, or diarrhea, muscle rigidity (stiff muscles), tremor, loss of muscle control			✓
Symptoms after discontinuation or dose reduction: loss of appetite or weight, anxiety, restlessness, aggression, confusion, convulsions, coordination problems, diarrhea, dizziness, dry mouth, fatigue, headache, rapid	✓		

Frequency/Side Effect/Symptom	Talk to your healthcare professional		Stop taking this drug and get immediate medical help
	Only if severe	In all cases	
mood swings, nausea, nightmares, tingling of the skin, sleep disturbances, sweating, ringing in the ears or vomiting			
Syndrome of inappropriate antidiuretic hormone secretion (SIADH): concentrated urine (dark in colour), feel or are sick, have muscle cramps, confusion and fits (seizures) which may be due to inappropriate secretion of ADH (antidiuretic hormone)			✓

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (canada.ca/drug-device-reporting) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

- Store M-VENLAFAXINE XR at room temperature (15 - 30°C), in a dry place.
- Keep container tightly closed.
- Keep all medicines out of reach and sight of children.
- If your healthcare professional tells you to stop taking M-VENLAFAXINE XR please return any left over medicine to your pharmacist.

If you want more information about M-VENLAFAXINE XR:

- Talk to your healthcare professional.
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada Drug Product Database website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html; or by contacting Mantra Pharma Inc. at medinfo@mantrapharma.ca or at 1-833-248-7326.

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