PRODUCT MONOGRAPH

[Pr] pms-VENLAFAXINE XR

Venlafaxine Hydrochloride Extended-Release Capsules, House Standard

37.5 mg, 75 mg and 150 mg venlafaxine, as venlafaxine hydrochloride

Antidepressant

PHARMASCIENCE INC.
6111 Royalmount Ave, Suite 100
Montréal, Québec
H4P 2T4

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Venlafaxine Hydrochloride Extended Release Capsules, House Standard

37.5 mg, 75 mg and 150 mg

venlafaxine (as venlafaxine hydrochloride)

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	All Nonmedicinal Ingredients
Oral	Capsules, 37.5 mg, 75 mg and 150 mg	Dibutyl Sebecate, Ethyl Cellulose, Povidone and Sugar Spheres. Also contains: **37.5 mg**: Red iron oxide, yellow iron oxide, titanium dioxide, gelatin, black iron oxide. **75 mg**: Yellow iron oxide, red iron oxide, titanium dioxide, gelatin. **150 mg**: Yellow iron oxide, red iron oxide, titanium dioxide, gelatin.

INDICATIONS AND CLINICAL USE

Adults

pms-VENLAFAXINE XR (venlafaxine hydrochloride extended release capsules) is indicated for:

- *Depression:*
  pms-VENLAFAXINE XR is indicated for the symptomatic relief of major depressive disorder.

  The short-term efficacy of venlafaxine hydrochloride extended release Capsules has been demonstrated in placebo-controlled trials of up to 12 weeks.

  The efficacy of venlafaxine hydrochloride extended release Capsules in maintaining an antidepressant response for up to 26 weeks following response to 8 weeks of acute

treatment was demonstrated in a placebo-controlled trial (see **CLINICAL TRIALS, Depression**).

Long-term use of pms–VENLAFAXINE XR: The physician who elects to use pms-VENLAFAXINE XR for extended periods in the treatment of depression should periodically re-evaluate the long-term usefulness of the drug for the individual patient (See **DOSAGE AND ADMINISTRATION**).

Geriatrics (> *65* years of age): Caution should be exercised in treating the elderly. In Phase II and III clinical trials, 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.

Pediatrics (< 18 years of age): pms-VENLAFAXINE XR is not indicated for use in children under 18 years of age (see WARNINGS AND PRECAUTIONS**,** General, Potential Association with Behavioural and Emotional Changes, Including Self-Harm).

CONTRAINDICATIONS

- **Hypersensitivity**: Patients who are hypersensitive to this drug or to any ingredient in the formulation or component of the container.

- **Monoamine Oxidase Inhibitors (MAOIs)**:
  pms-VENLAFAXINE XR should not be used in combination with MAOIs or within two weeks of terminating treatment with MAOIs. Treatment with MAOIs should not be started until 2 weeks after discontinuation of pms-VENLAFAXINE XR therapy.

  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.

WARNINGS AND PRECAUTIONS

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 behavioral and emotional changes, including an increased risk of suicidal ideation and behavior 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 behavior 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. The risk of suicide attempt must be considered, especially in depressed patients (see OVERDOSAGE).

Discontinuation Symptoms
Patients currently taking pms-VENLAFAXINE XR should NOT be discontinued abruptly, due to risk of discontinuation symptoms (See WARNINGS and PRECAUTIONS, Discontinuation Symptoms). At the time that a medical decision is

made to discontinue an SSRI or other newer antidepressant drug, a gradual reduction in the dose wherever possible, rather than an abrupt cessation, is recommended.

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 venlafaxine hydrochloride extended release capsules. 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 venlafaxine hydrochloride extended release capsules, cannot be excluded, and may be a potential concern for patients with osteoporosis or major risk factors for bone fractures.

General
Allergic Reactions
Patients should be advised to notify their physician if they develop a rash, hives or a related allergic phenomenon.

Hypertension
General
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 (see Acute Severe Hypertension below).

Caution should be exercised in patients whose underlying conditions might be compromised by increases in blood pressure.

Acute Severe Hypertension: Cases of severe elevated blood pressure requiring immediate treatment have been reported in postmarketing experience, including reports of hypertensive crisis and malignant hypertension. The reports included normotensives and treated-hypertensive patients as well. Pre-existing hypertension should be controlled before treatment with venlafaxine. All patients should have their blood pressure evaluated before starting venlafaxine and monitored regularly during treatment. 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 1). Sustained increases in blood pressure could have adverse

consequences. Therefore, it is recommended that patients have their blood pressure monitored before starting venlafaxine and then regularly during treatment. 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.

Sustained hypertension, defined as treatment-emergent supine diastolic blood pressure (SDBP) ≥ 90 mm Hg and ≥ 10 mm Hg above baseline for 3 consecutive visits, showed the following incidence and dose relationship:

TABLE 1: PROBABILITY OF SUSTAINED ELEVATION IN SDBP

Probability of Sustained Elevation in SDBP (Pool of Premarketing Depression Studies with Venlafaxine HCl)	
Treatment Group	(%) Incidence of Sustained Elevation in SDBP
Venlafaxine	Extended Release Venlafaxine Hydrochloride Capsules
< 100 mg/day	3
101-200 mg/day	2
201-300 mg/day	4
> 300 mg/day	NE*
Placebo	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 mm Hg, SDBP.

Venlafaxine Hydrochloride Extended-Release Capsules
Depression: In placebo-controlled premarketing depression studies with venlafaxine hydrochloride extended release capsules, a final on-therapy mean increase in supine diastolic pressure (SDBP) of < 1.2 mm Hg was observed for venlafaxine hydrochloride extended release capsules-treated patients compared with a mean decrease of 0.2 mm Hg 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 mm Hg and ≥ 10 mm Hg 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 premarketing depression studies discontinued treatment because of elevated blood pressure compared with 0.4% of placebo-treated patients.

Serotonin Syndrome
As with other serotonergic agents, serotonin syndrome, a potentially life threatening condition, may occur with venlafaxine treatment, particularly with concomitant use of other agents that may affect the serotonergic neurotransmitter systems (please see ***Serotonin Syndrome/Neuroleptic Malignant Syndrome*** and **DRUG INTERACTIONS**, ***Serotonergic Drugs*****)**.

Discontinuation Symptoms
Discontinuation symptoms have been assessed in patients with depression. 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, vertigo, and vomiting. Where such symptoms occurred they were usually self-limiting but in a few patients continued for several weeks. In premarketing studies, the majority of discontinuation reactions were mild and resolved without treatment.

Discontinuation effects are well known to occur with antidepressants, and, therefore, it is recommended that the dosage be tapered gradually whenever possible and the patient monitored. Time to event onset after dose reduction or discontinuation can vary in individual patients and range from the same day to several weeks. (See also **ADVERSE EVENTS, Discontinuation Symptoms; DOSAGE AND ADMINISTRATION, Discontinuing Venlafaxine.**)

Venlafaxine Treatment during Pregnancy-Effects on Newborns
Post-marketing reports indicate that some neonates exposed to venlafaxine, SSRIs (Selective Serotonin Reuptake Inhibitors), or other newer anti-depressants late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding. Such complications can arise immediately upon delivery. When treating a pregnant woman with pms-VENLAFAXINE XR during the third trimester, the physician should carefully consider the potential risks and benefits of treatment (see **WARNINGS AND PRECAUTIONS, Special Populations, Pregnant Woman; DOSAGE AND ADMINISTRATION, Special Patient Populations-Treatment of Pregnant Women During the Third Trimester**).

Psychomotor Impairment
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.

The following additional precautions are listed alphabetically.

Carcinogenesis and Mutagenesis
For animal data see **TOXICOLOGY**.

Cardiovascular
Hypertension
See **WARNINGS AND PRECAUTIONS, General, Hypertension.**

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.

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 (QT_C) for venlafaxine-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-treated patients in phase III studies experienced QT_C prolongation to 500 msec during treatment. Baseline QT_C was >450 msec for all 3 patients.

No case of sudden unexplained death or serious ventricular arrhythmia, which are possible clinical sequelae of QT_C 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*.

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.

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 also **WARNINGS AND PRECAUTIONS, General, Hypertension**). 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.

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 central nervous system (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 premarketing 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).

Endocrine and Metabolism
Serum Cholesterol Elevation
Clinically relevant increases in total serum cholesterol were recorded in 5.3% of venlafaxine-treated patients and 0.0% of placebo-treated patients treated for at least 3 months in placebo-controlled trials in Major Depressive Disorders. (See **Monitoring Laboratory Changes, 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.

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 trials. Significant weight loss, especially in underweight depressed 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 **DRUG INTERACTIONS**, **Serotonergic Drugs**.)

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.

Genitourinary

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.

Hematologic

Abnormal Bleeding

SSRIs and SNRIs, including venlafaxine hydrochloride extended release capsules, 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.

Patients should be cautioned about the risk of bleeding associated with the concomitant use of pms-VENLAFAXINE XR and NSAIDs, ASA, or other drugs that affect coagulation (see **DRUG INTERACTIONS, Drugs Affecting Platelet Function**). 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-desmethyl venlafaxine (ODV) are significantly altered. **Dosage adjustment is necessary in these patients** (See **Recommended Dose, Patients with Hepatic Impairment, Patients with Renal Impairment**).

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.

Neurologic

Seizures

pms-VENLAFAXINE XR capsules 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 also **WARNINGS AND PRECAUTIONS, Discontinuation Symptoms; ADVERSE REACTIONS, Discontinuation Symptoms; DOSAGE AND ADMINISTRATION, Discontinuing Venlafaxine**).

During premarketing depression studies no seizures were seen in 705 venlafaxine hydrochloride extended release capsule-treated patients. However, patients with a history of convulsive disorders were excluded from the study. pms-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 (NMS)

On rare occasions serotonin syndrome or neuroleptic malignant syndrome-like events have occurred in association with treatment with SSRIs, including venlafaxine, particularly when given in combination with other serotonergic drugs (including SSRIs, SNRIs and triptans), with drugs that may impair metabolism of serotonin (including MAOIs (including linezolid, an antibiotic, and methylene blue)), neuroleptics/antipsychotics or other dopamine antagonist drugs. As these syndromes may result in potentially life-threatening conditions, treatment with venlafaxine should be discontinued if patients develop a combination of symptoms possibly including hyperthermia, rigidity, myoclonus, autonomic instability (e.g., tachycardia, labile blood pressure) with possible rapid fluctuations of vital signs, neuromuscular aberrations (e.g., hyperreflexia, incoordination), and/or gastrointestinal symptoms (e.g., nausea, vomiting, and diarrhea), mental status changes including confusion, irritability, extreme agitation progressing to delirium and coma and supportive symptomatic treatment should be initiated. Serotonin syndrome, in its most severe form, can resemble neuroleptic malignant syndrome (NMS). Due to the risk of serotonergic syndrome or NMS venlafaxine should not be used in combination with MAO inhibitors or serotonin-precursors (such as L-tryptophan, oxitriptan) and should be used with caution in patients receiving other serotonergic drugs (triptans, lithium, tramadol, St. John's Wort, most tricyclic antidepressants) or neuroleptics/antipsychotics (see **CONTRAINDICATIONS** and **DRUG INTERACTIONS, Serotonergic Drugs**).

If concomitant treatment with venlafaxine and other agents that may affect the serotonergic and/or dopaminergic neurotransmitter systems is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases.

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

Ophthalmologic

Glaucoma

As with other SSRIs/SNRIs, **venlafaxine hydrochloride extended release Capsules** can cause mydriasis and should be used with caution in patients with raised intraocular pressure or those with narrow angle glaucoma.

Psychiatric

Suicide

The possibility of a suicide attempt in seriously depressed patients is inherent to the illness and may persist until significant remission occurs. Close supervision of patients should accompany initial drug therapy, and consideration should be given to the need for hospitalization of high risk patients.

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.

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. (See **WARNINGS AND PRECAUTIONS: POTENTIAL ASSOCIATION WITH BEHAVIORAL 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 **ADVERSE REACTIONS**) in a depression study, as shown in Table 2.

TABLE 2: INCIDENCE OF INSOMNIA AND NERVOUSNESS IN PLACEBO-CONTROLLED DEPRESSION

	Depression	
Symptom	Venlafaxine HCl (extended release) n=357	Placebo n=285
Insomnia	17%	11%
Nervousness	10%	5%

Insomnia and nervousness each led to drug discontinuation in 0.9% of the patients treated with venlafaxine hydrochloride extended release capsules in depression studies.

Activation of Mania/Hypomania

During Phase II and III trials, mania or hypomania occurred in 0.5% of venlafaxine hydrochloride extended release capsule-treated patients and in 0.3% and 0% of pmsVENLAFAXINE XR Capsule-treated patients in depression study. 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, pms-

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

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 **DOSAGE AND ADMINISTRATION,** Patients with Renal Impairment and **Recommended Dose,** Patients with Renal Impairment).

Sexual Function/Reproduction

See **ADVERSE REACTIONS** and **PART II: SCIENTIFIC INFORMATION, TOXICOLOGY, Reproductive Toxicity.**

Special Populations

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.

Post-marketing reports indicate that some neonates exposed to venlafaxine, SSRIs (Selective Serotonin Reuptake Inhibitors), 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 **WARNINGS and PRECAUTIONS, Serotonin Syndrome/Neuroleptic Malignant Syndrome**). When treating a pregnant woman with pms-VENLAFAXINE XR during the third trimester, the physician should carefully consider the potential risks and benefits of treatment. (See **DOSAGE AND ADMINISTRATION, Treatment of Pregnant Women During the Third Trimester**).

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

Pediatrics (<18 years of age): pms-VENLAFAXINE XR is not indicated for use in children under 18 years of age (see WARNINGS AND PRECAUTIONS, Potential Association with Behavioural and Emotional Changes, Including Self-Harm).

Geriatrics (>65 years of age): Forty three (4%) of the patients in premarketing depression trials with venlafaxine hydrochloride extended release capsules were 65 years of age or older. 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.

Monitoring and Laboratory Tests

Self-Harm

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 **WARNINGS AND PRECAUTIONS, POTENTIAL ASSOCIATION WITH BEHAVIOURAL AND EMOTIONAL CHANGES, INCLUDING SELF-HARM**).

Sustained Hypertension and Acute Severe Hypertension

Venlafaxine treatment has been associated with sustained hypertension. Also, cases of severe elevated blood pressure requiring immediate treatment have been reported in postmarketing experience, including hypertensive crisis and malignant hypertension. The reports included normotensives and treated-hypertensive patients as well. It is recommended that patients receiving venlafaxine have their blood pressure evaluated before starting venlafaxine and monitored regularly during treatment.

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. 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. (See also **WARNINGS AND PRECAUTIONS, General, Hypertension.**)

Serum Cholesterol Elevation

Clinically relevant increases in total serum cholesterol were recorded in 5.3% of venlafaxine-treated patients and 0.0% of placebo-treated patients treated for at least 3 months in placebo-controlled trials in Major Depressive Disorder. (See **ADVERSE REACTIONS, Laboratory Changes - Cholesterol**).

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.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Commonly Observed Adverse Reactions
During depression trials, the most commonly observed adverse events associated with the use of 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 venlafaxine hydrochloride extended release capsules at least twice that for placebo), derived from the 2% incidence Table 4A, were:

Venlafaxine XR: abnormal dreams, anorexia, dizziness, dry mouth, nausea, nervousness, somnolence, sweating, and tremor as well as abnormal ejaculation/orgasm in men.

Adverse Events that Led to Discontinuation of Treatment in Clinical Trials
Twelve percent (88/705) of venlafaxine XR-treated patients in Phase II and III depression studies discontinued treatment due to an adverse reaction. The more common events (>1%) associated with discontinuation of treatment in the trial 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 3.

TABLE 3: ADVERSE REACTIONS (PERCENTAGE) LEADING TO DISCONTINUATION OF TREATMENT

	Venlafaxine Hydrochloride Extended Release Capsules Depression Indication (n=705)	PLACEBO Depression Indication (n=285)
CNS		
Somnolence	2	<1
Insomnia	<1	<1
Dizziness	2	1
Nervousness	<1	1
Anxiety	<1	<1
Tremor	<1	<1
Gastrointestinal		
Dry Mouth	<1	0
Anorexia	<1	<1
Nausea	4	<1
Vomiting	1	0
Urogenital		
Abnormal Ejaculation*	<1	<1
Impotence*	0	0
Other		
Headache	2 #	1
Asthenia	<1	1
Sweating	<1	0

* : percentages based on the number of males
\# : greater than 1% but active drug rate not twice rate for placebo

Incidence in Controlled Trials

The table that follows (Table 4A) 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 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 4A: TREATMENT-EMERGENT ADVERSE EXPERIENCE INCIDENCE IN PLACEBO-CONTROLLED CLINICAL TRIALS (PERCENTAGE)[1] IN DEPRESSED PATIENTS

Body System	Preferred Term	Venlafaxine HCl Extended Release (n = 357)	Placebo (n = 285)
Body as a whole	Headache	26 #	33
	Asthenia	8	7
	Infection	6 #	9
	Chills	<1	1
Cardiovascular	Vasodilatation	4	2
	Increased blood pressure/ hypertension	4	1
	Tachycardia	<1	<1
Dermatological	Sweating	14	3
	Rash	1	1
Gastrointestinal	Nausea	31	12
	Constipation	8	5
	Anorexia	8	4
	Diarrhoea	8 #	9
	Vomiting	4	2
	Dyspepsia	7 #	9
	Flatulence	4	3
Metabolic	Weight loss	3	0
Nervous	Somnolence	17	8
	Dry mouth	12	6
	Dizziness	20	9
	Insomnia	17	11
	Nervousness	10	5
	Anxiety	2 #	5
	Tremor	5	2
	Abnormal dreams	7	2
	Hypertonia	1	0
	Paraesthesia	3	1
	Libido decreased	3	<1
	Agitation	3	1
	Depression	3	<1
	Thinking abnormal	<1	1

TABLE 4A: TREATMENT-EMERGENT ADVERSE EXPERIENCE INCIDENCE IN PLACEBO-CONTROLLED CLINICAL TRIALS (PERCENTAGE)[1] IN DEPRESSED PATIENTS

Body System	Preferred Term	Venlafaxine HCl Extended Release (n = 357)	Placebo (n = 285)
Respiration	Pharyngitis	7	6
	Yawn	3	0
Special Senses	Abnormal vision	4	<1
	Taste perversion	1	<1
Urogenital system	Abnormal ejaculation/ orgasm	16[2]	<1[2]
	Impotence	4[2]	<1[2]
	Anorgasmia	3[3]	<1[3]
	Urinary frequency	1	1
	Urination impaired	<1	0

[1] Events reported by at least 2% of patients treated with venlafaxine hydrochloride extended release capsules are included, and are rounded to the nearest %. Events for which the 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 hydrochloride extended release capsules: n = 126, Placebo: n = 108)

[3] Incidence based on number of female patients (For venlafaxine hydrochloride extended release capsules: n = 231, Placebo: n = 177)

Adaptation to Certain Adverse Events

In premarketing experience with 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).

Discontinuation Symptoms

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. Symptoms associated with discontinuation include but are not limited to: 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, vertigo, and vomiting. Where such symptoms occurred they were usually self-limiting but in a few

patients continued for several weeks. In premarketing studies, the majority of discontinuation reactions were mild and resolved without treatment.

Patients should be monitored for these or any other symptoms when discontinuing treatment, regardless of the indication for which venlafaxine hydrochloride is being prescribed. If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, dose titration should be managed on the basis of the patient's clinical response (See **WARNINGS AND PRECAUTIONS, Discontinuation Symptoms,** and **DOSAGE AND ADMINISTRATION, Discontinuing Venlafaxine** for details).

Vital Sign Changes

Treatment with venlafaxine hydrochloride extended release capsules for up to 12 weeks in premarketing *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 mm Hg, compared with mean decreases ranging from 0.5 to 1.4 mm Hg for placebo.

Laboratory Changes - Cholesterol

Clinically and statistically relevant increases in cholesterol levels have been noted in studies using venlafaxine hydrochloride extended release capsules (see **WARNINGS AND PRECAUTIONS, Serum Cholesterol Elevation**).

Venlafaxine hydrochloride extended release capsules treatment for up to 12 weeks in premarketing 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.

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.

ECG Changes

An analysis of ECGs obtained in 357 patients treated with venlafaxine hydrochloride extended release capsules and 285 patients treated with placebo in controlled clinical trials in depression were analyzed. The mean change from baseline in corrected QT interval (QT_C) for venlafaxine hydrochloride extended release-treated patients was increased relative to that for placebo-treated patients in the clinical trials for depression (see **WARNINGS AND PRECAUTIONS, Cardiac Disease**).

Other Events Observed During the Premarketing Evaluation of Venlafaxine

Multiple doses of venlafaxine hydrochloride extended release capsules were administered to 705 patients in phase III depression 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, 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 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 4A (MDD), 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: 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:
Common: 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 QT_C 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 mellitis, 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*, kidney calculus, kidney pain, kidney
function abnormal, nocturia, breast pain, prostatic disorder (includes prostatitis, enlarged prostate, and prostate irritability)*, polyuria, pyuria, urinary incontinence, urinary retention, urinary urgency, vaginal hemorrhage*, vaginitis*.
Rare: abortion*, anuria, balanitis*, bladder pain, breast discharge, breast engorgement, breast
enlargement, endometriosis*, fibrocystic breast, calcium crystalluria, cervicitis*, ovarian cyst*,
prolonged erection*, female lactation*, gynecomastia*, hypomenorrhea*, mastitis*, menopause*, oliguria, orchitis, pyelonephritis, salpingitis*, urolithiasis, uterine hemorrhage*, vaginal dryness*.

* Based on the number of men and women, as appropriate.

Post-Market Adverse Drug Reactions Not Listed as Clinical Trial Adverse Event
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)
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 necrosis/Stevens-Johnson syndrome, erythema multiform, sweating including night sweats
Special senses: angle closure glaucoma, eye hemorrhage, tinnitus
Urogenital system: renal failure.

DRUG INTERACTIONS

Serious Drug Interactions

- **Monoamine Oxidase Inhibitors: See CONTRAINDICATIONS**

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.

Drug-Drug Interactions

- ***Monoamine Oxidase Inhibitors:*** **See CONTRAINDICATIONS and DOSAGE AND ADMINISTRATION, Switching Patients to or from a Monoamine Oxidase Inhibitor.**

- ***Other CNS-Active Drugs***

  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***

  Based on the known mechanism of action of venlafaxine and the potential for serotonin syndrome, a potentially life threatening condition, caution is advised when venlafaxine is co-administered with other drugs that may affect the serotonergic neurotransmitter systems (such as triptans, selective serotonin reuptake inhibitors, other SNRIs, linezolid (an antibiotic which is a reversible non-selective MAOI; see **CONTRAINDICATIONS**, lithium, sibutramine or fentanyl (and its analogues, dextromethorphan, tramadol, tapentadol, meperidine, methadone and pentazocine) or with serotonin precursors, such as tryptophan supplements). Rare postmarketing reports describe patients with symptoms suggestive of, or diagnostic of, serotonin syndrome, following the combined use of a selective serotonin reuptake inhibitor (SSRI) with 5HT1-agonists (triptans) or lithium. If concomitant treatment with venlafaxine hydrochloride extended release capsules and a triptan (e.g., almotriptan, sumatriptan, rizatriptan, naratriptan, zolmitriptan), tricyclic antidepressants, or other drugs or agents with serotonergic activity (including but not limited to St. John's Wort) is clinically warranted, appropriate observation of the patient for acute and long-term adverse events is advised. (See also **WARNINGS AND PRECAUTIONS, Endocrine and Metabolism, Changes in Appetite and Weight; and WARNINGS AND PRECAUTIONS, Neurologic, Serotonin Syndrome/Neuroleptic Malignant Syndrome**.)

- ***Alcohol***

  The possibility of additive psychomotor impairment should be considered if venlafaxine is used in combination with alcohol. Patients should be advised to avoid alcohol while taking venlafaxine.

- ***Lithium***

  The steady-state pharmacokinetics of venlafaxine 150 mg administered as 50 mg every 8 hours was not affected when a single 600 mg oral dose of lithium was administered to 12 healthy male subjects. ODV was also unaffected. Venlafaxine had no effect on the pharmacokinetics of lithium. (Also see ***Other CNS-Active Drugs***).

- ***Diazepam***

  The steady-state pharmacokinetics of venlafaxine 150 mg administered as 50 mg every 8 hours was not affected when a single 10 mg oral dose of diazepam was administered to 18 healthy male subjects. ODV was also unaffected. Venlafaxine had no effect on the pharmacokinetics of diazepam or its active metabolite, desmethyldiazepam. Additionally, venlafaxine administration did not affect the psychomotor and psychometric effects induced by diazepam.

- ***Cimetidine***

  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***

  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 AUC. In addition, the haloperidol C_{max} increased 88% when coadministered with venlafaxine, but the haloperidol elimination half-life ($t_{1/2}$) was unchanged. The mechanism explaining this finding is unknown.

- ***Imipramine***

  Venlafaxine did not affect the pharmacokinetics of imipramine and 2-OH-imipramine. However, AUC, C_{max} and C_{min} 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 ql2h). The clinical significance of elevated 2-OH-desipramine levels is unknown.

  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, and no dosage adjustment is required.

- ***Metoprolol***

  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 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. The clinical relevance of this finding is unknown. Metoprolol did not alter the pharmacokinetic profile of venlafaxine or its active metabolite, ODV. (See also **WARNINGS AND PRECAUTIONS, General, Hypertension**).

- ***Risperidone***

  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).

- ***Indinavir***

  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***

  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.

- ***Drugs Affecting Platelet Function (e.g. NSAIDS, ASA and other anticoagulants)***

  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 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.

  Altered anticoagulant effects, including increased bleeding, have been reported when SSRIs or SNRIs are co-administered with warfarin. Patients receiving warfarin therapy should be carefully monitored when pms-VENLAFAXINE XR

is initiated or discontinued. (See **WARNINGS AND PRECAUTIONS**, **Hematologic, Abnormal Bleeding.**)

- ***Drugs Highly Bound to Plasma Proteins***

  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.

- ***Drugs Metabolized by Cytochrome P450 Isoenzymes***

  The metabolic pathways for venlafaxine include CYP2D6 and CYP3A4. Venlafaxine is primarily metabolized to its active metabolite, ODV, by the cytochrome P450 enzyme CYP2D6. CYP3A4 is a minor pathway relative to CYP2D6 in the metabolism of venlafaxine.

  In vitro studies indicate that venlafaxine is a relatively weak inhibitor of CYP2D6. These findings have been confirmed *in vivo* by a clinical drug interaction study comparing the effect of venlafaxine with that of fluoxetine on the CYP2D6-mediated metabolism of dextromethorphan to dextrorphan.

Drugs that Inhibit Cytochrome P450 Isoenzymes

- **CYP2D6-Inhibitors:**

  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.

- **CYP3A3/4 Inhibitors:**

  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:***

  Interactions between concomitant intake of inhibitors of both CYP2D6 and CYP3A3/4 with venlafaxine have not been studied. However, this 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.

- **CYP3A4**

  Venlafaxine did not inhibit CYP3A4 *in vitro*. This finding was confirmed *in vivo* by clinical drug interaction studies in which venlafaxine did not inhibit the metabolism of several CYP3A4 substrates, including alprazolam, diazepam, and terfenadine.

- **CYP1A2**

  Venlafaxine did not inhibit CYP1A2 *in vitro*. This finding was confirmed *in vivo* by a clinical drug interaction study in which venlafaxine did not inhibit the metabolism of caffeine, a CYP1A2 substrate

CYP2C9

Venlafaxine did not inhibit CYP2C9 *in vitro*. This finding was confirmed *in vivo* by a clinical drug interaction study in which venlafaxine did not inhibit the metabolism of tolbutamide, a CYP2C9 substrate.

. **CYP2C19**

Venlafaxine did not inhibit the metabolism of diazepam, which is partially metabolized by CYP2C19 (see Diazepam above).

Postmarketing Reports of Drug-Drug Interactions

There have been reports of elevated clozapine levels that were temporally associated with adverse events including seizures, following the addition of venlafaxine. There have been reports of increases in prothrombin time, partial thromboplastin time, or INR when venlafaxine was given to patients receiving warfarin therapy.

Electroconvulsive Therapy

There are no clinical data on the use of electroconvulsive therapy combined with venlafaxine hydrochloride extended release capsules treatment.

Drug-Food Interactions

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

Drug-Herb Interactions

St. John's Wort

In common with SSRI's, pharmacodynamic interactions between venlafaxine hydrochloride extended release capsules and the herbal remedy St. John's Wort may occur and may result in an increase in undesirable effects.

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.

Drug-Lifestyle Interactions

Interference with Cognitive and Motor Performance

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.

Drug Abuse and Dependence

Physical and Psychological Dependence

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 their potential for abuse, there was no indication of drug-seeking behavior in the clinical trials. However, it is not possible to predict on the basis of premarketing 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 behavior).

DOSAGE AND ADMINISTRATION

Dosing Considerations

General

- **pms-VENLAFAXINE XR is not indicated for use in children under 18 years of age (see WARNINGS AND PRECAUTIONS, Potential Association with Behavioural and Emotional Changes, Including Self-Harm).**

- **Discontinuing Venlafaxine**
  When discontinuing venlafaxine 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 in patients with depression. 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. Reported symptoms include but are not limited to the following: aggression, agitation, anorexia, anxiety, asthenia, confusion, convulsions, impaired coordination and balance , diarrhoea, dizziness, dry mouth, dysphoric mood, fasciculation, fatigue, headache, hypomania, insomnia, nausea, nightmares, nervousness, paresthesia, electric shock sensations, sensory disturbances (including shock like electrical sensations), sleep disturbances, somnolence, sweating, tinnitus, vertigo, and vomiting. Where such symptoms occurred they were usually self-limiting but in a few patients continued for several weeks. It is therefore recommended that the dosage of pms-VENLAFAXINE XR capsules be tapered gradually whenever possible and the patient monitored. The period required for tapering 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 (see **WARNINGS AND PRECAUTIONS**, **POTENTIAL ASSOCIATION WITH BEHAVIORAL AND EMOTIONAL CHANGES, INCLUDING SELF-HARM,** and also **Discontinuation Symptoms; ADVERSE REACTIONS , Discontinuation Symptoms).**

- **Patients With Hepatic or Renal Impairment:**
  Dosage adjustments are required (see **DOSAGE AND ADMINISTRATION, Special Patient Populations** below).

- **Switching Patients to or from a Monoamine Oxidase Inhibitor:**
  At least 14 days should elapse between discontinuation of an MAOI and initiation of therapy with pms-VENLAFAXINE XR. In addition, at least 14 days should be allowed after stopping pms-VENLAFAXINE XR before starting an MAOI (see **CONTRAINDICATIONS**).

- **Switching Patients from Immediate Release Tablets:**
  Depressed patients who are currently being treated at a therapeutic dose with immediate release tablets may be switched to venlafaxine hydrochloride extended release capsules at

the nearest equivalent dose (mg/day), e.g., 37.5 mg immediate release two-times-a-day to 75 mg venlafaxine hydrochloride extended release capsules once daily. However, individual dosage adjustments may be necessary.

Recommended Dose and Dosage Adjustment

ADULTS:

Patients with Major Depressive Disorder

The recommended dose for pms-VENLAFAXINE XR capsules 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 pms-VENLAFAXINE XR 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.

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 pms-VENLAFAXINE XR for depression.

During long-term therapy for any indication, the pms-VENLAFAXINE XR dosage should be maintained at the lowest effective dose and the need for continuing treatment should be periodically reassessed.

Depression:

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 **CLINICAL TRIALS, Depression**).

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.

Special Patient Populations:

Treatment of Pregnant Women During the Third Trimester
Post-marketing reports indicate that some neonates exposed to venlafaxine hydrochloride extended release, SSRIs (Selective Serotonin Reuptake Inhibitors), or other newer antidepressants late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding. (See **WARNINGS AND PRECAUTIONS, Special Populations, Pregnant Women**). When treating a pregnant woman with pms-VENLAFAXINE XR during the third trimester, the physician should carefully consider the potential risks and benefits of treatment.

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

Elderly Patients
No dose adjustment is recommended for elderly patients solely on the basis of their age. As with any antidepressant, caution should be exercised in treating the elderly. When individualizing the dosage, extra care should be taken when increasing the dose.

Pediatrics
pms-VENLAFAXINE XR is not indicated for use in children under 18 years of age (see **WARNINGS AND PRECAUTIONS, Potential Association with Behavioural and Emotional Changes, Including Self-Harm).**

Patients with 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 **ACTION AND CLINICAL PHARMACOLOGY, Hepatic Insufficiency**), 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.

Patients with 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 **ACTION AND CLINICAL PHARMACOLOGY, Renal Insufficiency**), the total daily dose must 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.

Missed Dose
If a dose is missed, it should not be made up for it by doubling up on the dose next time. The next dose should be taken as scheduled.

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

OVERDOSAGE

Among the patients included in the premarketing evaluation of venlafaxine 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.

Postmarketing Experience with Venlafaxine Hydrochloride (Dosage Form Unknown)

In postmarketing experience, overdose with venlafaxine was reported predominantly in combination with alcohol and/or other drugs. 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. According to post-marketing overdose reports with venlafaxine (where overdose amounts were provided) fatal acute overdoses have been reported with venlafaxine alone at doses as low as approximately 1 gram.

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 tircyclic 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 overdosages as opposed to some characteristics of venlafaxine-treated patients is not clear. Prescriptions for venlafaxine should be written for the smallest quantity of drug consistent with good patient management, in order to reduce the risk of overdose.

Overdosage Management
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. Gastric lavage with a large bore orogastric tube with appropriate airway protection, if needed, may be indicated if performed soon after ingestion or in symptomatic patients. 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. The physician should consider contacting a poison control centre for information on the treatment of any overdose.

For Management of a Suspected Overdose, Please Contact Your Regional Poison Control Centre immediately.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action
Venlafaxine is a phenethylamine bicyclic derivative, chemically unrelated to tricyclic, tetracyclic or other available antidepressant 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.

Pharmacodynamics
Venlafaxine and ODV have no significant affinity for muscarinic, histaminergic, or α_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.

Pharmacokinetics
After administration of venlafaxine hydrochloride extended release capsules, the peak plasma concentrations of venlafaxine and ODV are attained within 6.0 ± 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.

Multiple-Dose Pharmacokinetic Profile

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.

Venlafaxine and ODV renal clearances are 49 ± 27 and 94 ± 56 mL/h/kg, respectively, which correspond to 5 ± 3.0% and 25 ± 13% of an administered venlafaxine dose recovered in urine as venlafaxine and ODV, 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.

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.

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. Following intravenous administration, the steady-state volume of distribution of venlafaxine is 4.4 ± 1.9 L/kg, indicating that venlafaxine distributes well beyond the total body water.

Absorption: Venlafaxine is well absorbed; after administration of venlafaxine hydrochloride extended release capsules, the peak plasma concentrations of venlafaxine and ODV are attained within 6.0 ±1.5 and 8.8 ±2.2 hours, respectively. The rate of absorption of venlafaxine from the venlafaxine hydrochloride extended release capsule 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.

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 ±1.9 L/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. 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.

Excretion: 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.

Special Populations and Conditions

Pediatrics: Safety and efficacy in children below the age of 18 have not been established. pms-VENLAFAXINE XR (venlafaxine hydrochloride) extended release is not indicated for use in children under 18 years of age.

Geriatrics: Population pharmacokinetic analyses of 547 venlafaxine-treated patients from three studies involving venlafaxine 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.

Gender: Population pharmacokinetic analyses of 547 venlafaxine-treated patients from three studies involving venlafaxine extended release capsules showed that sex does not

significantly affect the pharmacokinetics of venlafaxine. Dosage adjustment based upon gender is generally not necessary.

Hepatic Impairment: 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 intersubject 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 **DOSAGE AND ADMINISTRATION, Special Patient Populations**).

Renal Impairment: 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 intersubject variability was noted.

Dosage adjustment is necessary in patients with renal impairment (see **DOSAGE AND ADMINISTRATION, Special Patient Populations**).

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.

STORAGE AND STABILITY

Store between 15°C and 30°C, in a dry place.

SPECIAL HANDLING INSTRUCTIONS

None.

DOSAGE FORMS, COMPOSITION AND PACKAGING

pms-VENLAFAXINE XR (venlafaxine hydrochloride extended release) capsules are available in bottles of 100 capsules and 500 capsules, in the following dosage strengths (*potency is expressed in terms of venlafaxine base*):

37.5 mg Hard gelatin capsule with light grey opaque cap and peach opaque body, with "37.5" on the body, in red ink

75 mg Hard gelatin capsule with peach opaque cap and body, with "75" on the body, in red ink.

150 mg Hard gelatin capsule with dark orange opaque cap and body, with "150" on the body, in white ink.

Composition of Product

Venlafaxine hydrochloride is the active ingredient. The capsules also contain the following inactive ingredients: sugar spheres, povidone, ethyl cellulose , dibutyl sebecate.

Composition of Capsule

37.5 mg Red iron oxide, yellow iron oxide, titanium dioxide, gelatin, black iron oxide.
75 mg Yellow iron oxide, red iron oxide, titanium dioxide, gelatin.
150 mg Yellow iron oxide, red iron oxide, titanium dioxide, gelatin.

Composition of Inks:

White Ink: Shellac, dehydrated alcohol, isopropyl alcohol, butyl alcohol, propylene glycol, sodium hydroxide, povidone, titanium dioxide.
Red Ink: Shellac glaze, iron oxide red, N-Butyl alcohol, isopropyl alcohol, propylene glycol, ammonium hydroxide, simethicone.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

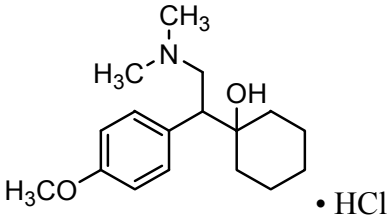
Proper name: Venlafaxine Hydrochloride

Chemical name: (R/S)-l –[2-(dimethylamino)-1-(4-methoxyphenyl)ethyl] cyclohexanol hydrochloride;
or
(±)-1-[α[dimethylamino)methyl]-p-methoxy-benzyl] cyclohexanol hydrochloride.

Molecular formula: $C_{17}H_{27}NO_2$, HCl

Molecular mass: 313.87 g/Mol

Structural formula:



Physicochemical properties:

Physical Form: White to off-white crystalline solid

Solubility:

Water: 540, 542, 501 and 21.6 mg/mL at pH 1.0, 5.38, 7.09 and 7.97
Ethanol: 91.7mg/mL
Propylene Glycol: 200 mg/mL
Glycerin: 115 mg/mL

pKa value: 9.4

pms-VENLAFAXINE XR capsules, the extended release formulation of venlafaxine, contains spheroids which release the drug slowly into the digestive tract. The insoluble portion of these spheroids is eliminated and may be seen in the stools.

CLINICAL TRIALS

Comparative Bioequivalence Study (150 mg strength) - Fasting

A comparative bioavailability study using 20 healthy adult male volunteers under fasting conditions was performed between pms-VENLAFAXINE XR 150 mg capsules, manufactured by Pharmascience Inc., and EFFEXOR® XR 150 mg capsules manufactured by Wyeth Canada Inc, the CRP. The study showed that pms-VENLAFAXINE XR capsules are bioequivalent to EFFEXOR® XR capsules. Results are tabulated below.

Summary Table of the Comparative Bioavailability Data

pms-VENLAFAXINE XR (1 x 150 mg Capsules) From measured data Uncorrected for potency				
Parameter	Geometric Mean Arithmetic Mean (CV%)		% Ratio of Geometric Means	90 % Confidence Interval
	Test pms -VENLAFAXINE XR	Reference EFFEXOR® XR †		
AUC_T (ng.h/mL)	1116.31 1335.60 (72.9)	1112.89 1395.82 (85.7)	100.31	94.32 – 106.67
AUC□ (ng.h/mL)	1181.51 1401.32 (71.4)	1177.47 1463.52 (85.0)	100.34	94.65 – 106.38
C_{MAX} (ng/mL)	81.97 90.03 (47.2)	73.38 80.22 (47.2)	111.72	
T_{MAX}§ (h)	6.00 (5.00-8.00)	6.75 (5.50-9.00)		
$T_{½}$□ (h)	9.46 (24.7)	8.78 (20.4)		

* pms-VENLAFAXINE XR Capsules, Pharmascience Inc.

† EFFEXOR® XR Capsules is manufactured by Wyeth Canada Inc., and was purchased in Canada.

§ Expressed as the median (range) only.

□ Expressed as the arithmetic mean (CV%) only.

Comparative Bioequivalence Study (150 mg strength) – Fed

A comparative bioavailability study using 20 healthy adult male volunteers under fed conditions was performed between pms-VENLAFAXINE XR 150 mg capsules, manufactured by Pharmascience Inc., and EFFEXOR® XR 150 mg capsules manufactured by Wyeth Canada Inc, the CRP. The study showed that pms-VENLAFAXINE XR capsules are bioequivalent to EFFEXOR® XR capsules. Results are tabulated below.

Summary Table of the Comparative Bioavailability Data

pms-VENLAFAXINE XR (1 x 150 mg Capsules) From measured data Uncorrected for potency				
Parameter	Geometric Mean Arithmetic Mean (CV%)		% Ratio of Geometric Means	90 % Confidence Interval
	Test pms -VENLAFAXINE XR	Reference EFFEXOR® XR †		
AUC_T (ng.h/mL)	1506.38 1724.62 (55.4)	1391.23 1627.15 (58.4)	108.28	102.69 – 114.17
AUC□ (ng.h/mL)	1589.15 1795.06 (52.9)	1463.36 1698.23 (56.8)	108.60	102.75 – 114.77
C_{MAX} (ng/mL)	108.37 112.55 (26.8)	98.07 103.29 (29.6)	110.50	
T_{MAX}§ (h)	5.50 (4.50-10.00)	5.50 (4.50-10.00)		
$T_{½}$□ (h)	8.76 (20.6)	9.53 (22.4)		

* pms-VENLAFAXINE XR Capsules, Pharmascience Inc.

† EFFEXOR® XR Capsules is manufactured by Wyeth Canada Inc., and was purchased in Canada.

§ Expressed as the median (range) only.

□ Expressed as the arithmetic mean (CV%) only.

Comparative Bioequivalence Study (150 mg strength) – Steady State

A comparative bioavailability study using 28 healthy adult male volunteers under fasting conditions at Steady State was performed between pms-VENLAFAXINE XR 150 mg capsules, manufactured by Pharmascience Inc., and EFFEXOR® XR 150 mg capsules manufactured by Wyeth Canada Inc, the CRP. The study showed that pms-VENLAFAXINE XR capsules are bioequivalent to EFFEXOR® XR capsules. Results are tabulated below.

Summary Table of the Comparative Bioavailability Data

pms-VENLAFAXINE XR (1 x 150 mg Capsules) From measured data Uncorrected for potency				
Parameter	Geometric Mean Arithmetic Mean (CV%)		% Ratio of Geometric Means	90 % Confidence Interval
	Test pms -VENLAFAXINE XR	Reference EFFEXOR® XR †		
AUC_{TAU} (ng.h/mL)	1217.288 1429.021 (63.572)	1184.859 1431.807 (70.832)	102.74%	97.61% - 108.13%
C_{MAX} (ng/mL)	104.927 116.353 (50.205)	98.912 113.647 (61.095)	106.08%	
C_{MIN} (ng/mL)	19.082 25.539 (88.193)	19.992 27.319 (91.740)	95.45%	
T_{MAX}‡ (h)	5.750 (4.500 – 10.000)	5.500 (4.500 - 7.500)		

* pms-VENLAFAXINE XR Capsules, Pharmascience Inc.

† EFFEXOR® XR Capsules is manufactured by Wyeth Canada Inc., and was purchased in Canada.

‡ Expressed as the median (range) only.

Study results

DEPRESSION

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 than with immediate release tablets.

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

**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.

DETAILED PHARMACOLOGY

Venlafaxine (Wy-45,030) is a novel bicyclic 2-phenyl-2-(1-hydroxy-cycloalkyl) ethylamine racemate whose enantiomers are configured as R (-) venlafaxine and S (+) venlafaxine. The major human metabolite of venlafaxine is the racemate Wy-45,233 (O-desmethyl-venlafaxine) whose enantiomers are configured as R (-) Wy-45,233 and S (+) Wy-45,233.

Venlafaxine is a potent inhibitor of both norepinephrine and serotonin uptake that has demonstrated antidepressant activity in a number of preclinical models. Wy-45,233, the major human metabolite of venlafaxine, has a pharmacological profile quite similar to that of venlafaxine since it also inhibits norepinephrine and serotonin uptake and produces rapid noradrenergic desensitization. This indicates that Wy-45,233 is a biologically active metabolite of venlafaxine. While the enantiomers of Wy-45,233 effectively inhibit monoamine uptake, they were less effective in *in vivo* models of antidepressant activity.

Ancillary pharmacological effects of venlafaxine and Wy-45,233 were quite similar. In neuropharmacological studies, both compounds lacked activity at a wide range of CNS receptors and had a low abuse liability potential. The effects of venlafaxine and Wy-45,233 on arterial pressure and heart rate in animals are most likely related to the inhibition of monoamine uptake and are similar to those produced by tricyclic antidepressants. Lastly, venlafaxine and Wy-45,233 produced only limited effects in immunological, gastrointestinal and endocrine studies which were generally at doses greater than those required to produce antidepressant effects in animals.

Venlafaxine is rapidly absorbed and excreted from laboratory animals and man. Differences in biotransformation pathways among species result in different pharmacokinetic profiles. Tissue uptake occurs, but without notable accumulation. Elimination of venlafaxine and its metabolites occurs via renal pathway in all species. O-Demethylation to a bioactive metabolite is the major transformation in man, dog and mouse, but further transformations occur in the animals. Other transformation pathways predominate in rat and rhesus monkey. While venlafaxine HCl is a racemic mixture, the animals in drug safety evaluation studies were exposed to similar or greater amounts of each venlafaxine enantiomer, as well as each Wy-45,233 enantiomer, than when humans received venlafaxine HCl at the highest recommended therapeutic dose. Stereoselective transformations, which were recognized in rats and rhesus monkeys, were not significant in humans.

TOXICOLOGY

The toxicologic 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.

Acute Toxicity
Venlafaxine showed low acute toxicity with $LD_{50s} \geq 405$ 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.

Long Term Toxicity/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.

Mutagenicity
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, but elicited a clastogenic response in the *in vivo* chromosomal aberration assay in rat bone marrow.

Reproductive Toxicity
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 epididymides, 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.

REFERENCES

1. Ballenger JC. Clinical Evaluation of Venlafaxine. J Clin Psychopharmacol 1996;16 (3, Suppl 2):29S-35S.

2. Ballenger JC. Clinical Evaluation of Venlafaxine: Commentary. J Clin Psychopharmacol 1996; 16(3, Suppl 2):35S-36S.

3. Ballus C, Quiros G, De Flores T, de la Torre J, Palao D, Rojo L, et al. The efficacy and tolerability of venlafaxine and paroxetine in outpatients with depressive disorder or dysthymia. International Clinical Psychopharmacology 2000; 15(1):43-48.

4. Benkert O, Grunder G, Wetzel H, Hackett D. A Randomized, Double-Blind Comparison of a Rapidly Escalating Dose of Venlafaxine and Imipramine in Patients with Major Depression and Melancholia. J Psychiat Res 1996:30(6):441-451.

5. Clerc GE, Ruimy P, Verdeau-Palles J. A Double-Blind Comparison of Venlafaxine and Fluoxetine in Patients Hospitalized for Major Depression and Melancholia. International Clinical Psychopharmacology 1994; 9:139-143.

6. Costa e Silva J. Randomized, double-blind comparison of venlafaxine and fluoxetine in outpatients with major depression. J Clin Psychiatry 1998; 59:352-357.

7. Cunningham LA, Borison RL, Carman JS, Chouinard G, Crowder JE, Diamond BI. et al. A Comparison of Venlafaxine, Trazodone, and Placebo in Major Depression. J Clin Psychopharmacol 1994; 14(2):99-106.

8. Dierick M. An Open Label Evaluation of the Long-Term Safety of Oral Venlafaxine in Depressed Elderly Patients. Annals of Clin Psychiatry, 1996; 8(3):169-178.

9. Entsuah R, Upton GV, Rudolph R. Efficacy of Venlafaxine Treatment in Depressed Patients with Psychomotor Retardation or Agitation: A Meta-Analysis. Human Psychopharmacol 1995; 10:195-200.

10. Entsuah R, Rudolph R, Chitra R. Effectiveness of Venlafaxine Treatment in a Broad Spectrum of Depressed Patients: A Meta-Analysis. Psychopharmacol Bull 1995; 31(4):759-766.

11. Ereshefsky L. Drug-Drug Interactions Involving Antidepressants: Focus on Venlafaxine. J Clin Psychopharmacol 1996; 16(3) Suppl 2: 37S-49S.

12. Feighner JP. The Role of Venlafaxine in Rational Antidepressant Therapy. J Clin Psychiatry 1994;55 (9, Suppl A):62-68.

13. Guelfi JD, White C, Hackett D, Guichoux JY, Magni G. Effectiveness of Venlafaxine in Patients Hospitalized for Major Depression and Melancholia. J Clin Psych 1995;56(10): 450-458.

14. Khan A, Fabre LF, Rudolph R. Venlafaxine in Depressed Outpatients. Psychopharmacol Bull 1991; 27(2):141-144

15. Kuzel RJ. Treating Comorbid Depression and Anxiety. J Family Practice 1996;43(6, Suppl):S45-S53.

16. Lecrubier Y, Bourin M, Moon CA, Schifano F, Blanchard C, Danjou P. et al. Efficacy of venlafaxine in depressive illness in general practice. Acta Psychiatr Scand 1997;95:485-493.

17. Mehtonen O-P, Sogaard J, Roponen P, Behnke K. Randomized, double-blind comparison of venlafaxine and sertraline in outpatients with major depressive disorder. J Clin Psychiatry 2000; 61(2):95-100.

18. Mendels J, Johnston R, Mattes J, Riesenberg R. Efficacy and Safety of BID Doses Of Venlafaxine In A Dose-Response Study. Psychopharmacol Bull 1993; 29(2):l69-l74.

19. Montgomery SA. Venlafaxine: A New Dimension in Antidepressant Pharmacotherapy. J Clin Psychiatry 1993; 54(3):119-126.

20. Muth EA, Moyer JA, Haskins JT, Andree TH, Husbands GEM. Biochemical, Neurophysiological, and Behavioral Effects of Wy-45,233 and Other Identified Metabolites of the Antidepressant Venlafaxine; Drug Development Research 1991; 23:191-199.

21. Nierenberg A, Feighner J, Rudolph R, Cole J, Sullivan J. Venlafaxine For Treatment-Resistant Unipolar Depression. J Clin Psychopharmacol 1994;14:419-423.

22. Rudolph RL, Entsuah R, Chitra R. A Meta-Analysis of Effects of Venlafaxine on Anxiety Associated with Depression. J Clin Psychopharmacol; 1998; 18:136-144.

23. Rudolph RI, Feiger AD. A double-blind, randomized, placebo-controlled trial of once- daily venlafaxine extended release (XR) and fluoxetine for the treatment of depression. J Affective Disorders 1999; 56:171-181.

24. Schweizer E, Weise C, Clary C, Fox I, Rickels K. Placebo-Controlled Trial of Venlafaxine for the Treatment of Major Depression. J Clin Psychopharmacol 1991; 11(4):233-236.

25. Schweizer E, Feighner J, Mandos LA, Rickels K. Comparison of Venlafaxine and Imipramine in the Acute Treatment of Major Depression in Outpatients. J Clin Psychiatry 1994; 55(3):104-108.

26. Shrivastava RK, Cohn C, Crowder J, Davidson J, Dunner D, Feighner J. et al. Long-Term Safety and Clinical Acceptability of Venlafaxine and Imipiramine in Outpatients with Major Depression. J Clin Psychopharmacol. 1994; 14(5):322-329.

27. Zajecka JM, Fawcett J, Guy C. Co-existing Major Depression and Obsessive - compulsive Disorder treated with Venlafaxine. J Clin Psychopharmacol 1990; 10(2): 152-153.

28. Wyeth Canada. Product Monograph EFFEXOR XR Capsules (Venlafaxine hydrochloride extended-release capsules, 37.5 mg, 75 mg and 150 mg). Date of revision: September 5, 2012, Control number: 156396.

PART III: CONSUMER INFORMATION

[Pr]pms-VENLAFAXINE XR
Venlafaxine Hydrochloride Extended Release Capsules, House Standard

This leaflet is part III of a three-part "Product Monograph" published when pms-VENLAFAXINE XR was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about pms-VENLAFAXINE XR. Contact your doctor or pharmacist if you have any questions about the drug.

Please read this information carefully before you start to take your medicine, even if you have taken this drug before. Do not throw away this leaflet until you have finished your medicine as you may need to read it again. For further information or advice, please see your doctor or pharmacist.

ABOUT THIS MEDICATION

What the medication is used for:
pms-VENLAFAXINE XR has been prescribed to you by your doctor to relieve your symptoms of the following conditions:
- Depression (feeling sad, a change in appetite or weight, difficulty concentrating or sleeping, feeling tired, headaches, unexplained aches and pain)

What it does:
pms-VENLAFAXINE XR belongs to a group of medicines called antidepressants. pms-VENLAFAXINE XR is thought to work by affecting two naturally occurring brain chemicals, serotonin and norepinephrine.

When it should not be used:
- Do not use **pms-VENLAFAXINE XR** if you are allergic to it or to any of the components of its formulation (see list of components at the end of this section). Stop taking the drug and contact your doctor immediately if you experience an allergic reaction or any severe or unusual side effects.
- Do not use pms-VENLAFAXINE XR if you are currently taking or have recently taken monoamine oxidase inhibitor antidepressants (e.g. phenelzine sulphate, moclobemide).

What the medicinal ingredient is:
Venlafaxine Hydrochloride.

What the nonmedicinal ingredients are:
Dibutyl Sebecate, Ethyl Cellulose, Povidone and Sugar Spheres. Also contains:
37.5 mg: gelatine, black iron oxide, red iron oxide, titanium dioxide, yellow iron oxide.
75 mg: gelatine, red iron oxide, titanium dioxide, yellow iron oxide.
150 mg: gelatine, red iron oxide, titanium dioxide, yellow iron oxide.

What dosage forms it comes in:
Extended Release Capsules: 37.5 mg, 75 mg and 150 mg.

WARNINGS AND PRECAUTIONS

During treatment with these types of medication it is important that you and your doctor have good ongoing communication about how you are feeling.

pms-VENLAFAXINE XR is not for use in children under 18 years of age.

New or Worsened Emotional or Behavioural Problems
Particularly in the first few weeks or when doses are adjusted, a small number of patients taking drugs of this type may feel worse instead of better. They may experience new or worsened feelings of agitation, hostility, anxiety, impulsivity or thoughts about suicide, self-harm or harm to others. Suicidal thoughts and actions can occur in any age group but may be more likely in patients 18 to 24 years old. Should this happen to you, or to those in your care, consult your doctor immediately. Close observation by a doctor is necessary in this situation. **Do not discontinue your medication on your own.**

You may be more likely to think like this if you have previously had thoughts about harming yourself.

You may find it helpful to tell a relative or close friend that you are depressed or have an anxiety disorder, and ask them to read this leaflet. You might ask them to tell you if they think your depression or anxiety is getting worse, or if they are worried about changes in your behaviour.

Taking pms-VENLAFAXINE XR may increase your risk of breaking a bone if you are elderly or 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.

Before taking pms-VENLAFAXINE XR tell your doctor or pharmacist:
- if you have ever had any allergic reaction to medications, food, etc;
- all your medical conditions, including a history of seizures, liver disease, kidney disease, heart problems or high cholesterol;
- if you have a bleeding disorder or have been told that you have low platelets.
- if you have blood pressure problems;
- any medications (prescription or non-prescription) which you are taking, especially monoamine oxidase (MAO) inhibitors (e.g. phenelzine sulfate, tranylcypromine sulfate, moclobemide or selegeline) or any other antidepressants, weight-loss medication, sleeping pills, antianxiety drugs, or medication to control blood pressure;
- if you are pregnant or thinking about becoming pregnant, or if you are breast feeding;
- your habits of alcohol and/or street drug consumption;
- any natural or herbal products you are taking (e.g., St. John's Wort).
- if you had a recent bone fracture or were told you have osteoporosis or risk factors for osteoporosis.

- if you drive a vehicle or perform hazardous tasks during your work.
- if you have glaucoma or increased pressure in your eyes.

Discontinuing pms –VENLAFAXINE XR
It is very important that you do NOT stop taking these medications without first consulting your doctor. See SIDE EFFECTS AND WHAT TO DO ABOUT THEM section for more information.

Effects on Pregnancy and Newborns
Post-marketing reports indicate that some newborns whose mothers took an SSRI (selective serotonin reuptake inhibitor) or other newer anti-depressants, such as venlafaxine hydrochloride extended release Capsules, during pregnancy have developed complications at birth requiring prolonged hospitalization, breathing support and tube feeding. Reported symptoms included feeding and/or breathing difficulties, seizures, tense or overly relaxed muscles, jitteriness and constant crying.

In most cases, the SSRI or other newer anti-depressant was taken during the third trimester of pregnancy. These symptoms are consistent with either a direct adverse effect of the antidepressant on the baby, or possibly a discontinuation syndrome caused by sudden withdrawal from the drug. These symptoms normally resolve over time. However, if your baby experiences any of these symptoms, contact your doctor as soon as you can.

If you are pregnant and taking an SSRI, or other newer anti-depressant, you should discuss the risks and benefits of the various treatment options with your doctor. It is very important that you do NOT stop taking these medications without first consulting your doctor. See SIDE EFFECTS AND WHAT TO DO ABOUT THEM section for more information.

INTERACTIONS WITH THIS MEDICATION

Do not use pms-VENLAFAXINE XR if you are taking or have recently taken monoamine oxidase inhibitors.

You should avoid taking St. John's Wort if you are taking pms-VENLAFAXINE XR.

Certain laboratory results may be affected by use of pms-VENLAFAXINE XR, discuss with your doctor if you receive any unusual lab reports.

You should tell your doctor if you are taking or have recently taken any medications (prescription, non-prescription or natural/herbal), especially:
- other antidepressants, such as SSRIs and certain tricyclics
- other drugs that affect serotonin such as, lithium, linezolid, sibutramine, tryptophan, triptans used to treat migraines
- certain medicines used to treat pain, such as fentanyl (used in anaesthesia or to treat chronic paint), tramadol, tapentadol, meperidine, methadone, pentazocine
- certain medicines used to treat cough, such as dextromethorphan
- certain medicines used to treat schizophrenia
- certain medicines used to treat bipolar depression, such as lithium
- metoprolol or other medications used to treat high blood pressure and angina
- certain medicines which may affect blood clotting and increase bleeding, such as oral anti-coagulants (e.g. warfarin, dabigatran) acetylsalicylic acid and other non-steroidal anti-inflammatory drugs (e.g. ibuprofen)
- certain medicines used to treat epilepsy
- cimetidine
- In general, drinking alcoholic beverages should be kept to a minimum or avoided completely while taking pms – VENLAFAXINE XR.
- Ketoconazole

PROPER USE OF THIS MEDICATION

Usual dose:
- It is very important that you take pms-VENLAFAXINE XR exactly as your doctor has instructed.
- Never increase or decrease the amount of pms-VENLAFAXINE XR you, or those in your care if you are a caregiver or guardian, are taking unless your doctor tells you to and do not stop taking this medication without consulting your doctor.
- As with all antidepressants improvement with pms-VENLAFAXINE XR is gradual. You may not have noticeable effect in the first few days of treatment. Some symptoms may begin to improve within about 2 weeks but significant improvement can take several weeks.
- pms-VENLAFAXINE XR should be taken once a day with food, as prescribed; do not divide, crush or chew the capsules.

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 doctor or pharmacist.

Overdose:

In case of overdose, contact your doctor, the nearest hospital emergency department or your local poison control centre, even though you may not feel sick.

Missed Dose:
If you happen to miss a dose, do not try to make up for it by doubling up on the dose next time. Just take your next regularly scheduled dose and try not to miss any more.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like all medications, pms-VENLAFAXINE XR can cause some side effects. You may not experience any of them. For most patients these side effects are likely to be minor and temporary. However, some may be serious. Some of these side effects may be dose related. Consult your doctor if you experience these or other side effects, as the dose may have to be adjusted.

If you experience an allergic reaction (including red skin, hives, itching, swelling of the lips, face, tongue, throat, trouble

breathing, wheezing, shortness of breath, skin rashes, blisters of the skin, sores or pain in the mouth or eyes) or any severe or unusual side effects, stop taking the drug and contact your doctor immediately.

Some side effects of pms-VENLAFAXINE XR are:
- headache
- nausea
- dry mouth
- constipation
- loss of appetite
- vomiting
- sleepiness
- dizziness
- insomnia
- sexual problems
- weakness
- sweating
- nervousness
- abnormal vision
- abnormal dreams

Particularly in the first few weeks or when doses are adjusted, a small number of patients taking drugs of this type may feel worse instead of better; for example, they may experience unusual feelings of agitation, hostility or anxiety, or have impulsive or disturbing thoughts such as thoughts of self-harm or harm to others. Should this happen to you, or to those in your care if you are a caregiver or guardian, consult your doctor immediately; do not discontinue your medication on your own.

pms-VENLAFAXINE XR does not usually affect people's normal activities. However, some people feel sleepy while taking it, in which case they should not drive or operate machinery.

Although psychiatric disorders may be associated with decreases in sexual desire, performance and satisfaction, treatment with this medication may also affect sexual functioning.

pms-VENLAFAXINE XR may increase blood pressure in some people. You should have your blood pressure measured prior to starting pms-VENLAFAXINE XR and during treatment. High blood pressure should be controlled before starting pms-VENLAFAXINE XR. Blood pressure changes may sometimes be sudden and without warning. Consult your doctor if you have symptoms that may indicate a sudden rise in your blood pressure, such as headache (particularly in the back of head/neck when waking up); stronger, possibly more rapid, or irregular heart beat; chest pain; dizziness; excessive tiredness; or blurred vision.

pms-VENLAFAXINE XR may raise cholesterol levels in some patients. Blood cholesterol tests may be required by your doctor during treatment with pms-VENLAFAXINE XR.

Discontinuation Symptoms
Contact your doctor before stopping or reducing your dosage of pms-VENLAFAXINE XR. Symptoms such as anorexia (loss of appetite, loss of weight), anxiety, agitation (restlessness), aggression, confusion, convulsions, coordination problems, diarrhea, dizziness, dry mouth, fatigue, headache, hypomania (rapid mood swings), insomnia, nausea, nervousness, nightmares, paresthesia (sensation of tingling, burning or crawling of the skin), electric shock sensations, sleep disturbances, somnolence (drowsiness), sweating, tinnitus (ringing in the ears), vertigo (sensation that the world is spinning), vomiting and other symptoms have been reported after stopping treatment, reducing the dosage of pms-VENLAFAXINE XR, or when a dose is missed. These symptoms usually disappear without needing treatment. Tell your doctor immediately if you have these or any other symptoms. Your doctor may adjust the dosage of pms-VENLAFAXINE XR to alleviate the symptoms.

Effects on Newborns
Some newborns whose mothers took an SSRI (Selective Serotonin Reuptake Inhibitor) or other newer anti-depressant, such as pms-VENLAFAXINE XR, during pregnancy have shown such symptoms as breathing and feeding difficulties, jitteriness and constant crying. If your baby experiences any of these symptoms, contact your doctor as soon as you can. See WARNINGS AND PRECAUTIONS section for more information.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM				
Symptom/effect		**Talk with your doctor or pharmacist right away**		**Stop taking drug and seek immediate emergency medical attention**
		Only if severe	**In all cases**	
Common	Increased blood pressure that persists [see also Severe Hypertension below]		✓	
Common	Fast heartbeat		✓	
Uncommon	Allergic reactions [red skin, hives, itching, swelling of the lips, face, tongue, throat, trouble breathing, wheezing, shortness of breath, skin rashes, blisters of the skin, sores or pain in the mouth or eyes]			✓
Uncommon	Low sodium level in blood [symptoms of tiredness, weakness, confusion combined with achy, stiff or uncoordinated muscles]		✓	
Unknown	Low Platelets: Bruising or unusual bleeding from the skin or other areas		✓	
Uncommon	Mania/hypomania [elevated or irritable mood, decreased need for sleep, racing thoughts]		✓	
Uncommon	Akathisia [feeling restless and unable to sit or stand still]		✓	
Uncommon	Hallucinations [strange visions or sounds]		✓	
Uncommon	Uncontrollable movements of the body or face		✓	
Uncommon	Inability to urinate		✓	
Uncommon	Gastrointestinal bleeding [vomiting blood or passing blood in stools]			✓
Rare	Seizures [loss of consciousness with uncontrollable shaking "fit"]			✓
Rare	Serotonin syndrome [a combination of most or all of the following; confusion, restlessness, sweating, shaking, shivering, high fever, sudden jerking of the muscles, hallucinations, fast heartbeat]			✓
Rare	Liver disorder [symptoms include nausea, vomiting, loss of appetite combined with itching, yellowing of the skin or eyes, dark urine]		✓	
Rare	Glaucoma: Increased pressure in the eyes eye pain and blurred vision		✓	
See Warnings and Precautions	New or worsened emotional or behavioural problems		✓	
See Side Effects and What to Do About Them	Severe Hypertension [symptoms include headache, stronger and possibly faster heartbeat, chest pain, dizziness, excessive tiredness, blurred vision]			✓

This is not a complete list of side effects. For any unexpected effects while taking pms-VENLAFAXINE XR, contact your doctor or pharmacist.

HOW TO STORE IT

- Store pms-VENLAFAXINE XR between 15°C and 30°C, in a dry place.
- Keep container tightly closed.
- Keep all medicines out of the sight and reach of children.
- If your doctor tells you to stop taking pms-VENLAFAXINE XR please return any left over medicine to your pharmacist.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- Report online at www.healthcanada.gc.ca/medeffect
- Call toll-free at 1-866-234-2345
- Complete a Canada Vigilance Reporting Form and:
  - Fax toll-free to 1-866-678-6789, or
  - Mail to: Canada Vigilance Program
    Health Canada
    Postal Locator 0701E
    Ottawa, ON K1A 0K9

  Postage paid labels, Canada Vigilance Reporting Form and the adverse reactions reporting guidelines are available on the MedEffect™ Canada Website at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be obtained by contacting the sponsor, Pharmascience Inc., at: 1-888-550-6060

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Montreal Quebec
H4P 2T4

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