

## Desvenlafaxine succinate

Pristiq™

### 50 mg and 100 mg Extended-Release Tablets

Antidepressants increase the risk of suicidal thinking and behavior (suicidality) in short term studies in children and adolescents with major depressive disorder (MDD) and other psychiatric disorders. Anyone considering the use of these agents in children or adolescents must balance the risks with clinical need.<sup>17</sup>

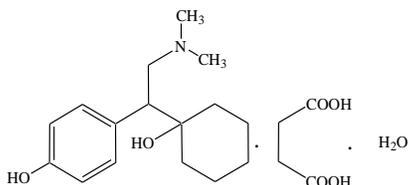
#### 1.0 THERAPEUTIC CATEGORY

Antidepressant/Dual-Acting Serotonin and Norepinephrine Reuptake Inhibitor (SNRI)<sup>1</sup>

#### 2.0 DESCRIPTION

Desvenlafaxine succinate monohydrate (Pristiq) is an extended-release tablet for once-a-day oral administration. The chemical name of Desvenlafaxine succinate monohydrate (Pristiq) is (*R,S*)-4-[2-(Dimethylamino)-1-(1-hydroxycyclohexyl)ethyl]phenol succinate monohydrate. The empirical formula is C<sub>16</sub>H<sub>25</sub>NO<sub>2</sub> (free base) and C<sub>16</sub>H<sub>25</sub>NO<sub>2</sub>•C<sub>4</sub>H<sub>6</sub>O<sub>4</sub>•H<sub>2</sub>O (succinate salt monohydrate). The molecular weight is 263.38 (free base) and 399.48 (succinate salt monohydrate).

The following represents the chemical structure of Desvenlafaxine succinate monohydrate (Pristiq):



Desvenlafaxine succinate monohydrate is a white to off-white powder that is soluble in water. The solubility of Desvenlafaxine succinate monohydrate is pH-dependent. Its octanol:aqueous system (at pH 7.0) partition coefficient is 0.21.

#### 3.0 FORMULATION

**Desvenlafaxine succinate (Pristiq) 50 mg extended-release tablet:** Each extended-release tablet contains Desvenlafaxine succinate equivalent to 50 mg desvenlafaxine.

**Desvenlafaxine succinate (Pristiq) 100 mg extended-release tablet:** Each extended-release tablet contains Desvenlafaxine succinate equivalent to 100 mg desvenlafaxine.

#### 4.0 CLINICAL PARTICULARS

##### 4.1 Therapeutic Indications

For the treatment of Major Depressive Disorder (MDD) and moderate-to-severe Vasomotor Symptoms (VMS) associated with menopause.

##### 4.2 Dosage and Administration

### **Major Depressive Disorder (MDD)**

The recommended dose for Desvenlafaxine is 50 mg once daily, with or without food. In clinical trials, doses of 50-400 mg/day were shown to be effective, although no additional benefit was demonstrated at doses greater than 50 mg/day. Based on clinical judgment, if dose increases are indicated for individual patients, they should occur gradually and at intervals of not less than 7 days. The maximum dose should not exceed 200 mg/day.

### **Vasomotor Symptoms (VMS) associated with Menopause**

The recommended dose for Desvenlafaxine is 100 mg once daily, with or without food. It is recommended to start at 50 mg/day for up to 7 days, to allow patients to adjust to the medicine before increasing to 100 mg/day. Patients should be periodically reassessed to determine the need to continue treatment.

### ***Use in Patients with Renal Impairment***

#### **Major Depressive Disorder (MDD)**

The recommended starting dose in patients with severe renal impairment (24-hr CrCl <30 mL/min) or end-stage renal disease (ESRD) is 50 mg every other day. Because of individual variability in clearance in these patients, individualization of dosage may be desirable.

Supplemental doses should not be given to patients after dialysis (see **Section 5.2 Pharmacokinetic Properties**).

#### **Vasomotor Symptoms (VMS) associated with Menopause**

The recommended dose in patients with severe renal impairment (24-hr CrCl <30 mL/min) or end-stage renal disease (ESRD) is 100 mg every other day. Supplemental doses should not be given to patients after dialysis. It is recommended to titrate from 50 mg every other day for up to 7 days, to 100 mg every other day to allow patients to adjust to the medicine. Because of individual variability in clearance in these patients, individualization of dosage may be desirable (see **Section 5.2 Pharmacokinetic Properties**).

### ***Use in Patients with Hepatic Impairment***

No dosage adjustment is necessary for patients with hepatic impairment (see **Section 5.2 Pharmacokinetic Properties**).

### ***Use in Children***

Safety and effectiveness in patients less than 18 years of age have not been established.

### ***Use in Elderly Patients***

No dosage adjustment is required solely on the basis of age; however, possible reduced renal clearance of Desvenlafaxine should be considered when determining dose (see **Section 4.4**

**Special Warnings and Precautions for Use - Geriatric Use** and **Section 5.2 Pharmacokinetic Properties**).

### ***Discontinuing Desvenlafaxine***

Symptoms associated with discontinuation of Desvenlafaxine, other SNRIs and SSRIs have been reported. Patients should be monitored for these symptoms when discontinuing treatment. A gradual reduction in the dose rather than abrupt cessation is recommended whenever possible. If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, then resuming the previously prescribed dose may be considered. Subsequently, the physician may continue decreasing the dose, but at a more gradual rate (see **Section 4.4 Special Warnings and Precautions for Use** and **Section 4.8 Undesirable Effects**).<sup>2</sup>

### ***Switching patients from other antidepressants to desvenlafaxine***

Discontinuation symptoms have been reported when switching patients from other antidepressants, including venlafaxine, to desvenlafaxine. Tapering of the initial antidepressant may be necessary to minimize discontinuation symptoms (see **Section 4.3 Contraindications**).

### 4.3 Contraindications

Hypersensitivity to Desvenlafaxine succinate or Venlafaxine hydrochloride.

Desvenlafaxine is an inhibitor of both norepinephrine and serotonin reuptake. Desvenlafaxine succinate must not be used in combination with a monoamine oxidase inhibitor (MAOI), or within at least 14 days of discontinuing treatment with an MAOI.<sup>3</sup> Based on the half-life of Desvenlafaxine succinate, at least 7 days should be allowed after stopping Desvenlafaxine succinate before starting an MAOI.

### 4.4 Special Warnings and Precautions for Use

#### ***Clinical Worsening of Depressive Symptoms, Unusual Changes in Behavior, and Suicidality***

Desvenlafaxine succinate is an SNRI, a class of medicines that may be used to treat depression. All patients treated with desvenlafaxine should be monitored appropriately and observed closely for clinical worsening and suicidality. 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 behavior, 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, and the smallest quantity of drug, consistent with good patient management, should be provided to reduce the risk of overdose.

Suicide is a known risk of depression and certain other psychiatric disorders, and these disorders themselves are strong predictors of suicide. Pooled analyses of short-term placebo-controlled trials of antidepressant medicines (SSRIs and others) showed that these medicines increase the risk of suicidality in children, adolescents, and young adults (ages 18 to 24 years) with major depression and other psychiatric disorders. Short-term trials did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond the age of 24 years; there was a reduction in the risk of suicidality with antidepressants compared to placebo in adults age 65 years and older.<sup>4,5,6,7</sup>

#### ***Mania/Hypomania***

In clinical trials, mania was reported for 0.1% of patients treated with desvenlafaxine. Activation of 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, desvenlafaxine should be used cautiously in patients with a history or family history of mania or hypomania (see **Section 4.8 Undesirable Effects**).<sup>8</sup>

#### ***Serotonin Syndrome or Neuroleptic Malignant Syndrome (NMS)-like reactions***

As with other serotonergic agents, the development of a potentially life-threatening serotonin syndrome or Neuroleptic Malignant Syndrome may occur with desvenlafaxine treatment, particularly with concomitant use of other serotonergic drugs (including SSRIs, SNRIs and triptans) and with drugs that impair metabolism of serotonin (including MAOIs), or with antipsychotics or other dopamine antagonists.<sup>9</sup> Serotonin syndrome symptoms may include mental status changes (e.g., agitation, hallucinations, and coma), autonomic instability (e.g., tachycardia, labile blood pressure, and hyperthermia), neuromuscular aberrations (e.g., hyperreflexia, incoordination) and/or gastrointestinal symptoms (e.g., nausea, vomiting, and

diarrhea).<sup>9</sup> Serotonin syndrome, in its most severe form, can resemble NMS, which includes hyperthermia, muscle rigidity, autonomic instability with possible rapid fluctuation of vital signs, and mental status changes<sup>9</sup> (see **Section 4.5 Interactions with Other Medicinal Products and Other Forms of Interaction**).

If concomitant treatment with desvenlafaxine 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 desvenlafaxine with serotonin precursors (such as tryptophan supplements) is not recommended.

#### ***Narrow-angle Glaucoma***

Mydriasis has been reported in association with desvenlafaxine; therefore, patients with raised intraocular pressure or those at risk of acute narrow-angle glaucoma (angle-closure glaucoma) should be monitored (see **Section 4.8 Undesirable Effects**).

#### ***Co-administration of Drugs containing Venlafaxine and/or Desvenlafaxine***

Desvenlafaxine is the major active metabolite of venlafaxine, a medication used to treat major depressive, generalized anxiety, social anxiety and panic disorders. Products containing desvenlafaxine succinate should not be used concomitantly with products containing venlafaxine hydrochloride or other products containing desvenlafaxine succinate.

#### ***Effects on Blood Pressure***

Increases in blood pressure were observed in some patients in clinical trials, particularly with higher doses. Pre-existing hypertension should be controlled before treatment with desvenlafaxine. Patients receiving desvenlafaxine should have regular monitoring of blood pressure. Cases of elevated blood pressure requiring immediate treatment have been reported with desvenlafaxine. Sustained blood pressure increases could have adverse consequences. For patients who experience a sustained increase in blood pressure while receiving desvenlafaxine, either dose reduction or discontinuation should be considered. Caution should be exercised in treating patients with underlying conditions that might be compromised by increases in blood pressure (see **Section 4.8 Undesirable Effects**).

#### ***Cardiovascular/Cerebrovascular***

Caution is advised in administering desvenlafaxine to patients with cardiovascular, cerebrovascular, or lipid metabolism disorders. Increases in blood pressure and heart rate were observed in clinical trials with desvenlafaxine. Desvenlafaxine has not been evaluated systematically in patients with a recent history of myocardial infarction, unstable heart disease, uncontrolled hypertension, or cerebrovascular disease. Patients with these diagnoses, except for cerebrovascular disease, were excluded from clinical trials (see **Section 4.8 Undesirable Effects**).

#### ***Serum Lipids***

Dose-related elevations in fasting serum total cholesterol, LDL (Low Density Lipoprotein) cholesterol, and triglycerides were observed in clinical trials. Measurement of serum lipids should be considered during treatment with desvenlafaxine (see **Section 4.8 Undesirable Effects**).

#### ***Seizures***

Cases of seizure were reported in pre-marketing clinical trials with desvenlafaxine. Desvenlafaxine has not been systematically evaluated in patients with a seizure disorder. Patients with a history of seizures were excluded from pre-marketing clinical trials. Desvenlafaxine should be prescribed with caution in patients with a seizure disorder (see **Section 4.8 Undesirable Effects**).

### ***Discontinuation Effects***

During marketing of SNRIs (Serotonin and Norepinephrine Reuptake Inhibitors), and SSRIs (Selective Serotonin Reuptake Inhibitors), there have been spontaneous reports of adverse events occurring upon discontinuation of these drugs, particularly when abrupt, including the following: dysphoric mood, irritability, agitation, dizziness, sensory disturbances (e.g., paraesthesias such as electric shock sensations), anxiety, confusion, headache, lethargy, emotional lability, insomnia, hypomania, tinnitus, and seizures. While these events are generally self-limiting, there have been reports of serious discontinuation symptoms.<sup>10</sup>

Patients should be monitored when discontinuing treatment with desvenlafaxine. A gradual reduction in the dose rather than abrupt cessation is recommended whenever possible. If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, then resuming the previously prescribed dose may be considered (see **Section 4.2 Dosage and Administration** and **Section 4.8 Undesirable Effects**).

### ***Abnormal Bleeding***

Drugs that inhibit serotonin uptake in platelets may lead to abnormalities of platelet aggregation.<sup>11,12</sup> As with other agents that inhibit serotonin-reuptake, desvenlafaxine should be used cautiously in patients predisposed to bleeding, including patients on anti-coagulants and platelet inhibitors.

### ***Hyponatremia***

Cases of hyponatremia and/or the Syndrome of Inappropriate Antidiuretic Hormone (SIADH) secretion have been described with SNRIs and SSRIs, usually in volume-depleted or dehydrated patients, including elderly patients and patients taking diuretics (see **Section 4.8 Undesirable Effects**).<sup>13,14</sup>

### ***Pediatric Use***

Safety and effectiveness in patients less than 18 years of age have not been established.

### ***Geriatric Use***

No dosage adjustment is required solely on the basis of age; however, possible reduced renal clearance of desvenlafaxine should be considered when determining dose (see **Section 4.2 Dosage and Administration** and **Section 5.2 Pharmacokinetic Properties**)

Greater sensitivity to desvenlafaxine in some older patients cannot be ruled out.

### ***Major Depressive Disorder (MDD)***

Of the 3,292 patients in pre-marketing clinical trials with desvenlafaxine, 5% of patients were 65 years of age or older. No overall differences in safety or efficacy were observed between these patients and younger patients; however, in the short-term placebo-controlled trials, there was a higher incidence of systolic orthostatic hypotension in patients  $\geq 65$  years of age compared to patients < 65 years of age with desvenlafaxine.

### ***Vasomotor Symptoms (VMS) associated with Menopause***

Of the 1,432 patients in pre-marketing VMS clinical trials, 2.5 % were 65 years of age or older, and 6.7% were 60 years of age or older. No overall differences in safety or efficacy were observed between older patients ( $\geq 60$  years) and younger patients.

### ***Physical and Psychological Dependence***

Although desvenlafaxine has not been systematically studied in preclinical or clinical trials for its potential for abuse, no indication of drug-seeking behavior was seen in the clinical trials.

## **4.5 Interactions with Other Medicinal Products and Other Forms of Interaction**

### ***Monoamine Oxidase Inhibitors (MAOI)***

Adverse reactions, some of which were serious, have been reported in patients who have recently been discontinued from a monoamine oxidase inhibitor (MAOI) and started on antidepressants with pharmacological properties similar to desvenlafaxine (SNRIs or SSRIs), or who have recently had SNRI or SSRI therapy discontinued prior to initiation of an MAOI. Concomitant use of desvenlafaxine in patients taking monoamine oxidase inhibitors (MAOIs) is contraindicated (see **Section 4.4 Special Warnings and Precautions for Use**).

### ***Central Nervous System (CNS) – active agents***

The risk of using desvenlafaxine in combination with other CNS-active drugs has not been systematically evaluated. Consequently, caution is advised when desvenlafaxine is taken in combination with other CNS-active drugs.

### ***Serotonin Syndrome***

As with other serotonergic agents, serotonin syndrome, a potentially life-threatening condition, may occur with desvenlafaxine treatment, particularly with concomitant use of other agents that may affect the serotonergic neurotransmitter system (including triptans, SSRIs, other SNRIs, lithium, sibutramine, tramadol, or St. John's Wort [*Hypericum perforatum*]), with drugs that impair metabolism of serotonin (such as MAOIs, including linezolid [an antibiotic which is a reversible non-selective MAOI], see **Section 4.3 Contraindications**), or with serotonin precursors (such as tryptophan supplements).<sup>9</sup>

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

### ***Ethanol***

A clinical trial has shown that desvenlafaxine does not increase the impairment of mental and motor skills caused by ethanol. However, as with all CNS-active drugs, patients should be advised to avoid alcohol consumption while taking desvenlafaxine.

### ***Potential for Other Drugs to affect Desvenlafaxine***

#### ***Inhibitors of CYP3A4***

CYP3A4 is minimally involved in desvenlafaxine elimination. In a clinical trial, ketoconazole (200 mg twice a day) increased the area under the concentration vs. time curve (AUC) of desvenlafaxine (400 mg single dose) by approximately 43%, a weak interaction and  $C_{max}$  by about 8%. Concomitant use of desvenlafaxine with potent inhibitors of CYP3A4 may result in higher exposure to desvenlafaxine.

#### ***Inhibitors of other CYP Enzymes***

Based on *in vitro* data, drugs that inhibit CYP isozymes 1A1, 1A2, 2A6, 2D6, 2C8, 2C9, 2C19, and 2E1 are not expected to have significant impact on the pharmacokinetic profile of desvenlafaxine.

### ***Potential for Desvenlafaxine to affect Other Drugs***

#### ***Drugs metabolized by CYP2D6***

Clinical trials have shown that desvenlafaxine does not have a clinically relevant effect on CYP2D6

metabolism at a dose of 100 mg daily. When desvenlafaxine succinate was administered at a dose of 100 mg daily in conjunction with a single 50 mg dose of desipramine, a CYP2D6 substrate, the AUC of desipramine increased approximately 17%. When 400 mg was administered, the AUC of desipramine increased approximately 90%. When desvenlafaxine succinate was administered at a dose of 100 mg daily in conjunction with a single 60 mg dose of codeine, a CYP2D6 substrate metabolized to morphine, the AUC of codeine was unchanged, the AUC of morphine decreased approximately 8%. Concomitant use of desvenlafaxine with a drug metabolized by CYP2D6 may result in increased concentrations of that drug and decreased concentrations of its CYP2D6 metabolites.

#### **Drugs metabolized by CYP3A4**

*In vitro*, desvenlafaxine does not inhibit, or induce the CYP3A4 isozymes. In a clinical trial, desvenlafaxine (400 mg daily) decreased the AUC of midazolam (single 4 mg dose), a CYP3A4 substrate, by approximately 31%. In a second study, desvenlafaxine 50 mg daily was co administered with a single 4 mg dose of midazolam. The AUC of midazolam decreased by approximately 29 %. Concomitant use of desvenlafaxine with a drug metabolized by CYP3A4 may result in lower exposures to that drug.

#### **Drugs metabolized by a combination of both CYP2D6 & CYP3A4 (tamoxifen and aripiprazole)**

Clinical studies have shown that desvenlafaxine (100 mg daily) does not have a clinically relevant effect on drugs metabolized by a combination of both CYP2D6 and CYP3A4 enzymes.

A single 40 mg dose of tamoxifen, which is metabolized to active metabolites 4-hydroxy-tamoxifen and endoxifen primarily by CYP2D6 with minor contributions to metabolism by CYP3A4, was administered in conjunction with desvenlafaxine succinate (100 mg daily). The AUC increased by 3% with concomitant administration of desvenlafaxine succinate. The AUC of 4-hydroxy-tamoxifen increased by 9%. Endoxifen AUC was decreased by 12%.

Desvenlafaxine succinate was administered at a dose of 100 mg daily in conjunction with a single 5 mg dose of aripiprazole, a CYP2D6 and CYP3A4 substrate metabolized to the active metabolite dehydro-aripiprazole. The AUC of aripiprazole increased by 6%, with concomitant administration of desvenlafaxine succinate. The AUC of dehydro-aripiprazole increased by 3%, with concomitant administration.

#### **Drugs Metabolized by CYP1A2, 2A6, 2C8, 2C9 and 2C19**

*In vitro*, desvenlafaxine does not inhibit CYP1A2, 2A6, 2C8, 2C9, and 2C19 isozymes and would not be expected to affect the pharmacokinetics of drugs that are metabolized by these CYP isozymes.

#### ***P-glycoprotein Transporter***

*In vitro*, desvenlafaxine is not a substrate or an inhibitor for the P-glycoprotein transporter.

#### ***Electroconvulsive Therapy***

There are no clinical data establishing the risks and/or benefits of electroconvulsive therapy combined with desvenlafaxine treatment for MDD.

## **4.6 Pregnancy and Lactation**

### ***Pregnancy***

The safety of desvenlafaxine in human pregnancy has not been established. Desvenlafaxine must only be administered to pregnant women if the expected benefits outweigh the possible risks. If desvenlafaxine is used until, or shortly before birth, discontinuation effects in the newborn should be considered.

Complications, including the need for respiratory support, tube feeding or prolonged hospitalization, have been reported in neonates exposed to SNRIs or SSRIs late in the third trimester. Such complications can arise immediately upon delivery.<sup>10</sup>

### ***Lactation***

Desvenlafaxine (O-desmethylvenlafaxine) is excreted in human milk.<sup>15</sup> Because of the potential for serious adverse reactions in nursing infants from desvenlafaxine, a decision should be made whether or not to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. Only administer desvenlafaxine to lactating women if the expected benefits outweigh the possible risks.

## **4.7 Effects on Ability to Drive and Use Machines**

The results of a clinical trial that assessed the effects of desvenlafaxine on behavioral performance of healthy individuals revealed no clinically significant impairment of psychomotor, cognitive, or complex behavior performance. However, since any CNS-active drug may impair judgment, thinking, or motor skills, patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that desvenlafaxine therapy does not adversely affect their ability to engage in such activities.

## **4.8 Undesirable Effects**

### ***Clinical Trials Experience***

The pre-marketing safety of desvenlafaxine was established in a total of 4,724 patients who were exposed to at least one dose of desvenlafaxine ranging from 50 to 400 mg/day in MDD and VMS clinical trials (3,292 in MDD trials; 1,432 in VMS trials). Long-term safety was evaluated in 1,576 patients (1,070 in MDD and 506 in VMS) who were exposed to desvenlafaxine for at least 6 months and with 575 (274 in MDD and 301 in VMS) patients exposed for 1 year.

### ***Combined MDD and VMS Adverse Reactions***

The following list of adverse reactions were reported by patients treated with desvenlafaxine throughout the dose range studied (50 to 400 mg) during both short- and long-term pre-marketing trials. In general, the adverse reactions were most frequent in the first week of treatment.

Adverse reactions are categorized by body system and listed in order of decreasing frequency using the following definitions:

Very common	≥10 %
Common	≥1 % and <10 %
Uncommon	≥0.1 % and <1 %
Rare	≥0.01 % and <0.1 %
Very rare	<0.01 %
Not known	Cannot be estimated from the available data

### ***System Organ Class***

### ***Adverse Reactions***

#### ***Cardiac disorders***

Common Palpitations, Tachycardia

***Ear and labyrinth disorders***

Common Tinnitus, vertigo†

***Eye disorders***

Common Vision blurred, Mydriasis

***Gastrointestinal disorders***

Very Common Nausea, Dry mouth, Constipation

Common Diarrhea, Vomiting

***General disorders and administration site conditions***

Very Common Fatigue

Common Chills, Asthenia, Feeling jittery, Irritability

Uncommon Drug Withdrawal Syndrome

***Immune System Disorders***

Uncommon Hypersensitivity

***Investigations***

Common Weight increased, Blood pressure increased, Weight decreased, Blood cholesterol increased

Uncommon Blood triglycerides increased, Liver function test abnormal, Blood prolactin increased

***Metabolism and nutritional disorders***

Common Decreased appetite

***Musculoskeletal, connective tissue and bone disorders***

Common Musculoskeletal stiffness

***Nervous system disorders***

Very Common Headache, Dizziness

Common Somnolence, Tremor, Paraesthesia, Dysgeusia, Disturbance in attention

Uncommon Syncope

Rare Convulsion, Extrapyrarnidal disorder

***Psychiatric disorders***

Very common Insomnia

Common Anxiety, Abnormal dreams, Nervousness, Libido decreased, Anorgasmia, Orgasm abnormal

Uncommon Depersonalization, Hypomania

***Renal and urinary disorders***

Common Urinary hesitation

Rare Proteinuria

***Reproductive system and breast disorders***

Common Erectile dysfunction, Ejaculation delayed, Ejaculation disorder\*, Ejaculation failure\*

Uncommon Sexual dysfunction

### ***Respiratory, thoracic and mediastinal disorders***

Common	Yawning
Uncommon	Epistaxis

### ***Skin and subcutaneous tissue disorders***

Very common	Hyperhidrosis
Common	Rash
Not known	Angioedema†

### ***Vascular disorders***

Common	Hot flush
Uncommon	Orthostatic hypotension

\* Frequency is calculated based on men only.

† Adverse reaction identified during post-approval use.

### ***Ischemic Cardiac Adverse Events***

In clinical trials, there were uncommon reports of ischemic cardiac adverse events, including myocardial ischemia, myocardial infarction, and coronary occlusion requiring revascularization; these patients had multiple underlying cardiac risk factors. More patients experienced these events during desvenlafaxine treatment as compared to placebo (see **Section 4.4 Special Warnings and Precautions for Use**).

### ***Discontinuation Symptoms***

#### Major depressive disorder (MDD)

Adverse drug reactions reported in association with abrupt discontinuation, dose reduction or tapering of treatment in MDD clinical trials at a rate of  $\geq 5\%$  include: dizziness, nausea, headache, irritability, diarrhea, anxiety, abnormal dreams, fatigue, and hyperhidrosis. In general, discontinuation symptoms occurred more frequently with longer duration of therapy (see **Section 4.2 Dosage and Administration** and **Section 4.4 Special Warnings and Precautions for Use**).

#### Vasomotor Symptoms (VMS) associated with Menopause

Adverse drug reactions reported in association with abrupt discontinuation, dose reduction or tapering of treatment in VMS clinical trials at a rate of  $> 2\%$  include: dizziness, nausea, headache, insomnia, hot flush, diarrhea, tinnitus, vomiting, vertigo, fatigue, abnormal dreams, irritability. In general, discontinuation symptoms occurred more frequently with longer duration of therapy. The majority of symptoms were mild and resolved without treatment (see **Section 4.2 Dosage and Administration** and **Section 4.4 Special Warnings and Precautions for Use**).

### ***Orthostatic hypotension***

Of the 3,292 patients in pre-marketing clinical trials with desvenlafaxine, 5% of patients were 65 years of age or older. No overall differences in safety or efficacy were observed between these patients and younger patients; however, in the short-term placebo-controlled trials, there was a higher incidence of systolic orthostatic hypotension in patients  $\geq 65$  years of age compared to patients  $< 65$  years of age treated with desvenlafaxine.

### ***Adverse Reactions Leading to Discontinuation of Therapy***

#### Major Depressive Disorder (MDD)

The most common adverse reactions leading to discontinuation in at least 2% of the desvenlafaxine-treated patients in the short-term trials, up to 8 weeks, were: nausea (4%); dizziness and vomiting (2% each); in the long-term trial, up to 9 months, the most common was

vomiting (2%).

#### Vasomotor Symptoms (VMS) associated with Menopause

The most common adverse reactions that led to discontinuation (i.e., leading to discontinuation in at least 1% of the 100 mg desvenlafaxine-treated subjects) were: palpitations, dry mouth, insomnia, vomiting, fatigue, somnolence and anxiety.

#### ***Adverse reactions reported with other SNRIs***

Although the following are not considered adverse reactions for desvenlafaxine succinate, they are adverse reactions for other SNRIs and may also occur with desvenlafaxine succinate: gastrointestinal bleeding, hallucinations, photosensitivity reactions, and severe cutaneous reactions (such as Stevens-Johnson Syndrome, toxic epidermal necrolysis, and/or erythema multiforme).

### **4.9 Overdosage**

There is limited clinical experience with desvenlafaxine succinate overdosage in humans.

Among the patients included in the pre-marketing major depressive disorder trials of desvenlafaxine succinate, there were four adults who ingested doses greater than 800 mg of desvenlafaxine succinate (4000 mg [desvenlafaxine alone], 900, 1800 and 5200 mg [in combination with other drugs]); all patients recovered. In addition, one patient's 11-month-old child accidentally ingested 600 mg of desvenlafaxine succinate, was treated, and recovered.

No specific antidotes for desvenlafaxine are known. Induction of emesis is not recommended. Because of the moderate volume of distribution of this drug, forced diuresis, dialysis, hemoperfusion, and exchange transfusion are unlikely to be of benefit.

Treatment should consist of those general measures employed in the management of overdosage with any SSRI/SNRI. Ensure an adequate airway, oxygenation, and ventilation. Monitor cardiac rhythm and vital signs. General supportive and symptomatic measures are also 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.

## **5.0 PHARMACOLOGICAL PROPERTIES**

### **5.1 Mode of Action**

Non-clinical trials have shown that desvenlafaxine is a selective serotonin and norepinephrine reuptake inhibitor (SNRI).<sup>1</sup> The clinical efficacy of desvenlafaxine is thought to be related to the potentiation of these neurotransmitters in the central nervous system.

Desvenlafaxine lacked significant affinity for numerous receptors, including muscarinic-cholinergic, H<sub>1</sub>-histaminergic, or  $\alpha_1$ -adrenergic receptors *in vitro*. Pharmacologic activity at these receptors has been hypothesized to be associated with the various anticholinergic, sedative, and cardiovascular effects seen with other psychotropic drugs.<sup>16</sup> In the same comprehensive binding profile assay, desvenlafaxine also lacked significant affinity for various ion channels, including calcium, chloride, potassium and sodium ion channels and also lacked monoamine oxidase (MAO) inhibitory activity. Desvenlafaxine lacked significant activity in the *in vitro* cardiac potassium channel (hERG) assay.

In preclinical rodent models, desvenlafaxine demonstrated activity predictive of antidepressant,

anxiolytic and thermoregulatory actions, and pain inhibitory properties.

## 5.2 Pharmacodynamic Properties

### Major Depressive Disorder (MDD)

The efficacy of desvenlafaxine as a treatment for depression was established in four, 8-week, randomized, double-blind, placebo-controlled, fixed-dose trials in adult outpatients who met the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) criteria for major depressive disorder. In the first trial, patients received 100 mg (n = 114), 200 mg (n = 116), or 400 mg (n = 113) of desvenlafaxine once daily, or placebo (n = 118). In a second trial, patients received either 200 mg (n = 121) or 400 mg (n = 124) of desvenlafaxine once daily, or placebo (n = 124). In two additional trials, patients received 50 mg (n = 150 and n = 164) or 100 mg (n = 147 and n = 158) of desvenlafaxine once daily, or placebo (n = 150 and n = 161).

Desvenlafaxine showed superiority over placebo as measured by improvement in the 17-item Hamilton Rating Scale for Depression (HAM-D<sub>17</sub>) total score in four trials and, as measured by the Clinical Global Impressions Scale - Improvement (CGI-I), in three of the four trials. There was no clear evidence that doses greater than 50 mg/day conferred any additional benefit.

In a long-term trial, adult outpatients meeting DSM-IV criteria for major depressive disorder and who responded to 12 weeks of acute treatment with desvenlafaxine were assigned randomly to the same dose (200 or 400 mg/day) they had received during acute treatment or to placebo for up to 26 weeks of observation for relapse. Response during the open phase was defined as a HAM-D<sub>17</sub> total score of ≤11 at the day 84 evaluation. Relapse during the double-blind phase was defined as follows: (1) a HAM-D<sub>17</sub> total score of ≥16 at any office visit, (2) a CGI-I score of ≥6 (versus day 84) at any office visit, or (3) discontinuation from the trial due to unsatisfactory response. Patients receiving continued desvenlafaxine treatment experienced significantly lower relapse rates over the subsequent 26 weeks compared with those receiving placebo.

Analyses of the relationships between treatment outcome and age and treatment outcome and gender did not suggest any differential responsiveness on the basis of these patient characteristics. There was insufficient information to determine the effect of race on outcome in these trials.

### Vasomotor Symptoms (VMS) associated with Menopause

The efficacy of desvenlafaxine as a treatment for vasomotor symptoms associated with menopause was established in three randomized, double-blind, placebo-controlled, fixed dose trials in postmenopausal women who had moderate-to-severe hot flashes. Women with current episodes of major depressive disorder, bipolar disorder, psychotic disorder or generalized anxiety disorder, requiring therapy were excluded from these trials.

A total of 2,158 patients were evaluated for efficacy and safety. In the first trial of 12-month duration, a total of 689 postmenopausal women were randomly assigned to one of the five treatment groups, receiving either placebo (n = 77) or desvenlafaxine 50 mg (n = 149), 100 mg (n = 155), 150 mg (n = 157), or 200 mg (n = 151). In the second trial of 6-month duration, a total of 541 postmenopausal women were randomly assigned to one of the three treatment groups, receiving either placebo (n=180) or desvenlafaxine 100 mg (n = 182) or 150 mg (n = 179). In the third trial of 3-month duration, a total of 452 postmenopausal women were randomly assigned to one of the 3 treatment groups, receiving either placebo (n = 151) or desvenlafaxine 100 mg (n = 150) or 150 mg (n = 151).

Efficacy for vasomotor symptoms was assessed during the first 12 weeks of treatment by measuring the change from baseline in the number and severity of moderate to severe hot

flushes. In all three trials, desvenlafaxine 100 mg demonstrated efficacy in reducing the number and severity of hot flushes at weeks 4 and 12. Efficacy was seen within the first week of therapy. A composite score for moderate to severe hot flushes demonstrated a significant reduction (up to 70%) from baseline with the desvenlafaxine 100 mg dose. In all three trials, desvenlafaxine 100 mg showed a significant reduction in the number of awakenings due to hot flushes (see **Section 4.2 Dosage and Administration**).

## 5.2 Pharmacokinetic Properties

The single-dose pharmacokinetics of desvenlafaxine are linear and dose-proportional in a dose range of 100 to 600 mg/day. The mean terminal half-life,  $t_{1/2}$ , is approximately 11 hours. With once-daily dosing, steady-state plasma concentrations are achieved within approximately 4-5 days. At steady state, multiple-dose accumulation of desvenlafaxine is linear and predictable from the single-dose pharmacokinetic profile.

The pharmacokinetics of desvenlafaxine have been thoroughly evaluated in women and men. There are minimal differences based on gender; data from all subjects are presented below.

### ***Absorption and Distribution***

Desvenlafaxine succinate is well absorbed, with an absolute oral bioavailability of 80%. Mean time to peak plasma concentrations ( $T_{max}$ ) is about 7.5 hours after oral administration. AUC and  $C_{max}$  of 6,747 ng·hr/mL and 376 ng/mL, respectively, are predicted after a single dose of 100 mg.

### ***Effects of Food***

A food-effect trial involving administration of desvenlafaxine to healthy subjects under fasting and fed conditions (high-fat meal) indicated that the  $C_{max}$  was increased about 16% in the fed state, while the AUCs were similar. This difference is not clinically significant; therefore, desvenlafaxine can be taken without regard to meals.

The plasma protein binding of desvenlafaxine is low (30%) and is independent of drug concentration. Desvenlafaxine's volume of distribution at steady-state following intravenous administration is 3.4 L/kg, indicating distribution into nonvascular compartments.

### ***Metabolism and Elimination***

Approximately 45% of desvenlafaxine is excreted unchanged in urine. Desvenlafaxine is primarily metabolized by conjugation (mediated by UGT isoforms, including UGT1A1, UGT1A3, UGT2B4, UGT2B15, and UGT2B17) and to a minor extent through oxidative metabolism. Approximately 19% of the administered dose is excreted as the glucuronide metabolite and <5% as the oxidative metabolite (N,O-didesmethylvenlafaxine) in urine. CYP3A4 is the predominant cytochrome P450 isozyme mediating the oxidative metabolism (N-demethylation) of desvenlafaxine.

### ***Geriatric Patients***

In a trial of healthy subjects administered doses up to 300 mg, there was an age-dependent decrease in desvenlafaxine clearance, resulting in a 32% increase in  $C_{max}$  and a 55% increase in AUC values in subjects greater than 75 years of age, as compared with subjects 18 to 45 years of age. No dosage adjustment is required solely on the basis of age; however, possible reduced renal clearance of desvenlafaxine should be considered when determining dose (see **Section 4.2 Dosage and Administration** and **Section 4.4 Special Warnings and Precautions for Use - Geriatric Use**).

### ***Pediatric Patients***

Safety and effectiveness in patients less than 18 years of age have not been established.

### ***Patients with Renal Impairment***

The pharmacokinetics of desvenlafaxine succinate 100 mg were studied in subjects with mild (n = 9), moderate (n = 8), severe (n = 7) and end-stage renal disease (ESRD) requiring dialysis (n = 9) and in healthy, age-matched control subjects (n = 8). Elimination was significantly correlated with creatinine clearance. Total body clearance was reduced by 29% in mild, 39% in moderate, 51% in severe renal impairment and 58% in ESRD compared to healthy subjects. This reduced clearance resulted in increases in AUCs of 42% in mild (24-hr CrCl = 50-80 mL/min), 46% in moderate (24-hr CrCl = 30-50 mL/min), 108% in severe (24-hr CrCl <30 mL/min), and 116% in ESRD subjects.

The mean terminal half-life ( $t_{1/2}$ ) was prolonged from 11.1 hours in the healthy subjects to 13.5, 15.5, 17.6, and 22.8 hours in mild, moderate, severe renal impairment and ESRD subjects, respectively.

Less than 5% of the drug in the body was cleared during a standard 4-hour hemodialysis procedure. Therefore, supplemental doses should not be given to patients after dialysis. Dosage adjustment is recommended in patients with significant impairment of renal function (see **Section 4.2 Dosage and Administration** and **Section 4.4 Special Warnings and Precautions for Use - Geriatric Use**).

### ***Patients with Hepatic Impairment***

The pharmacokinetics of desvenlafaxine succinate 100 mg were studied in subjects with mild (Child-Pugh A, n = 8), moderate (Child-Pugh B, n = 8), and severe (Child-Pugh C, n = 8) hepatic impairment and in healthy subjects (n = 12).

Average AUC was increased by approximately 31% and 35% in patients with moderate and severe hepatic impairment, respectively, as compared to healthy subjects. Average AUC values were comparable in subjects with mild hepatic impairment and healthy subjects (<5% difference).

Systemic clearance (CL/F) was decreased by approximately 20% and 36% in patients with moderate and severe hepatic impairment, respectively, as compared to healthy subjects. CL/F values were comparable in mild hepatic impairment and healthy subjects (<5% difference).

The mean  $t_{1/2}$  changed from approximately 10 hours in healthy subjects and subjects with mild hepatic impairment to 13 and 14 hours in moderate and severe hepatic impairment, respectively (see **Section 4.2 Dosage and Administration**).

### ***Thorough QTc Trial***

In a thorough QTc trial with prospectively determined criteria, in healthy women, desvenlafaxine did not cause QT prolongation. Additionally, no effect on QRS interval was observed.

## **5.3 Preclinical Safety Data**

### ***Carcinogenicity***

Desvenlafaxine succinate administered by oral gavage to mice and rats for 2 years did not increase the incidence of tumors in either trial.

### ***Vasomotor Symptoms (VMS) associated with Menopause***

Mice received desvenlafaxine at dosages up to 500/300 mg/kg/day (dosage lowered after 45 weeks of dosing). The 300 mg/kg/day dose was 180 times, on a mg/kg basis, the maximum recommended human dose (MRHD) of 100 mg/day, and 15 times the MRHD, on a mg/m<sup>2</sup> basis.

Rats received desvenlafaxine at dosages up to 300 mg/kg/day (males) or 500 mg/kg/day (females). The highest dose was 180 (males) or 300 (females) times, on a mg/kg basis, the MRHD of 100 mg/day, and 29 (males) or 48 (females) times the MRHD of 100 mg/day, on a mg/m<sup>2</sup> basis.

#### Major Depressive Disorder (MDD)

Mice received desvenlafaxine at dosages up to 500/300 mg/kg/day (dosage lowered after 45 weeks of dosing). The 300 mg/kg/day dose is 90 times, on a mg/kg basis, the maximum recommended human dose (MRHD) of 200 mg/day, and 7 times the MRHD, on a mg/m<sup>2</sup> basis.

Rats received desvenlafaxine at dosages up to 300 mg/kg/day (males) or 500 mg/kg/day (females). The highest dose was 90 (males) or 150 (females) times, on a mg/kg basis, the MRHD of 200 mg/day, and 15 (males) or 24 (females) times the MRHD of 200 mg/day, on a mg/m<sup>2</sup> basis.

#### **Mutagenicity**

Desvenlafaxine was not mutagenic in the *in vitro* bacterial mutation assay (Ames test) and was not clastogenic in an *in vitro* chromosome aberration assay in cultured CHO cells, an *in vivo* mouse micronucleus assay, or an *in vivo* chromosome aberration assay in rats. Additionally, desvenlafaxine was not genotoxic in the *in vitro* CHO mammalian cell forward mutation assay and was negative in the *in vitro* BALB/c-3T3 mouse embryo cell transformation assay.

#### **Impairment of Fertility**

Reduced fertility was observed in a preclinical trial in which both male and female rats received desvenlafaxine succinate.

#### Vasomotor Symptoms (VMS) associated with Menopause

This effect was noted at oral doses approximately 60 times, on a mg/kg basis, and 10 times the maximum human dose (MRHD) of 100 mg/day, on a mg/m<sup>2</sup> basis. There was no effect on fertility at oral doses approximately 18 times the MRHD on a mg/kg basis, and 3 times the MRHD on a mg/m<sup>2</sup> basis. The human relevance of this finding is unknown.

#### Major Depressive Disorder (MDD)

This effect was noted at oral doses approximately 30 times, on a mg/kg basis, and 5 times the maximum human dose (MRHD) of 200 mg/day on a mg/m<sup>2</sup> basis. There was no effect on fertility at oral doses approximately 9 times the MRHD on a mg/kg basis, and 1.5 times the MRHD on a mg/m<sup>2</sup> basis. The human relevance of this finding is unknown.

#### **Teratogenicity**

##### Vasomotor Symptoms (VMS) associated with Menopause

When desvenlafaxine was administered orally to pregnant rats and rabbits during the period of organogenesis, there was no evidence of teratogenicity in rats at any doses tested, up to 60 times on a mg/kg basis and up to 10 times the maximum recommended human dose (MRHD) of 100 mg/day (on a mg/m<sup>2</sup> basis) in rats. In rabbits, there was no evidence of teratogenicity at doses up to 45 times (on a mg/kg basis) the MRHD of 100 mg/day, or 15 times the MRHD (on a mg/m<sup>2</sup> basis). However, fetal weights were decreased in rats with a no-effect dose 60 times the MRHD (on a mg/kg basis) and 10 times the MRHD (on a mg/m<sup>2</sup> basis).

When desvenlafaxine succinate was administered orally to pregnant rats throughout gestation and lactation, there was a decrease in pup weights and increase in pup deaths during the first four days of lactation. The cause of these deaths is not known. The no-effect dose for rat pup mortality was 60 times on a mg/kg basis and 10 times the MRHD of 100 mg/day (on a mg/m<sup>2</sup> basis).

basis). Post-weaning growth and reproductive performance of the progeny were not affected by maternal treatment with desvenlafaxine at a dose 180 times the MRHD (on a mg/kg basis) and 29 times the MRHD (on a mg/m<sup>2</sup> basis).

#### Major Depressive Disorder (MDD)

When desvenlafaxine was administered orally to pregnant rats and rabbits during the period of organogenesis, there was no evidence of teratogenicity in rats at any doses tested, up to 30 times on a mg/kg basis and up to 5 times the maximum recommended human dose (MRHD) of 200 mg/day (on a mg/m<sup>2</sup> basis) in rats. In rabbits, there was no evidence of teratogenicity at doses up to 23 times (on a mg/kg basis) the MRHD of 200 mg/day, or 7 times the MRHD (on a mg/m<sup>2</sup> basis). However, fetal weights were decreased in rats with a no-effect dose 30 times the MRHD (on a mg/kg basis) 5 times the MRHD (on a mg/m<sup>2</sup> basis).

When desvenlafaxine succinate was administered orally to pregnant rats throughout gestation and lactation, there was a decrease in pup weights and increase in pup deaths during the first four days of lactation. The cause of these deaths is not known. The no-effect dose for rat pup mortality was 30 times on a mg/kg basis and 5 times the MRHD of 200 mg/day (on a mg/m<sup>2</sup> basis). Post-weaning growth and reproductive performance of the progeny were not affected by maternal treatment with desvenlafaxine at a dose 90 times the MRHD (on a mg/kg basis) and 15 times the MRHD (on a mg/m<sup>2</sup> basis).

## 6.0 PHARMACEUTICAL PARTICULARS

### 6.1 Availability

**Desvenlafaxine succinate (Pristiq) 50 mg extended-release tablets:** Light pink, square (pyramid, one-sided), film-coated tablet, debossed "W" over "50" on the flat side. Available in blisters x 14 tablets (Boxes of 28's)

**Desvenlafaxine succinate (Pristiq) 100 mg extended-release tablets:** Reddish-orange, square (pyramid, one-sided), film-coated tablet, debossed "W" over "100" on the flat side. Available in blisters x 14 tablets (Boxes of 28's)

### 6.2 Storage

Store at a temperature not exceeding 30°C.

### 6.3 Other Information

#### ***Residual inert matrix tablet***

Patients receiving desvenlafaxine may notice an inert matrix tablet passing in the stool or via colostomy. Patients should be informed that the active medication has already been absorbed by the time the patient sees the inert matrix tablet.

#### **CAUTION**

Foods, Drugs, Devices and Cosmetics Act prohibits dispensing without prescription.

#### **KEEP OUT OF REACH OF CHILDREN.**

Manufactured by:

**WYETH PHARMACEUTICALS CO.**

State Road No. 3 (Km 142.1)

Guayama, Puerto Rico 00784

Packed by:

**PFIZER BIOTECH CORPORATION - HSIN CHU PLANT**

No. 290-1, Chung-Lun, Chung Lun Village,  
Hsinfeng, Hsin Chu, Taiwan, R.O.C.

Imported by:

**PFIZER, INC.**

23/F Ayala Life-FGU Center  
6811 Ayala Avenue, Makati City 1200  
Philippines

Revision no:	1.0
Revision date:	24 October 2011
Reference:	CDS version 10.0, CPR Amendment
Reference date:	4 August 2011, 19 July 2011

UNDER AUTHORITY OF PFIZER, INC., New York, NY, USA.

References:

- 1 Muth EA, Haskins JT, Moyer JA, et al. *Antidepressant biochemical profile of the novel bicyclic compound WY-45030, an ethyl cyclohexanol derivative. Biochem Pharmacol.* 1986;35(24):4493-4497.
- 2 US FDA Class Labeling. Regulatory Correspondence. FDA letter dated October 28, 2004. Available at: <http://www.fda.gov/cder/drug/antidepressants/SSRIlabelChange.htm>. Accessed 22-Aug-2007.
- 3 Tiller JWG. *Clinical overview on moclobemide. Prog Neuro-Psychopharmacol Biol Psychiat.* 1993;17:703-712.
- 4 US FDA Class Labeling. Regulatory Correspondence. FDA letter dated 01-Aug-2007, Revised Labeling for Antidepressants Regarding Suicidality.
- 5 Akiskal HS, Benazzi F, Perugi G, et al. *Agitated "unipolar" depression re-conceptualized as a depressive mixed state: Implications for the antidepressant-suicide controversy. Journal of Affective Disorders.* 2005;85:245-258.
- 6 Hansen L. *A critical review of akathisia, and its possible association with suicidal behaviour. Hum Psychopharmacol Clin Exp.* 2001;16:495-505.
- 7 Culpepper L, Davidson JRT, Dietrich AJ, et al. *Suicidality as a possible side effect of antidepressant treatment. Physicians Postgraduate Press, Inc.* 2004;79-88.
- 8 Yager J, Gitlin M. *Clinical manifestations of psychiatric disorders.* In: Sadock BJ, Sadock VA. Kaplan and Sadock's Comprehensive Textbook of Psychiatry. Vol 1.8th ed. Philadelphia, PA: Lippincott, Williams and Wilkins; 2005:964-1002.
- 9 Boyer EW, Shannon M. *The serotonin syndrome. N Engl J Med.* 2005;352:1112-1120.
- 10 Haddad PM. *Antidepressant discontinuation syndromes, clinical relevance, prevention and management. Drug Safety.* 2001;24(3):183-197.
- 11 Kohn S, Labbate LA. *Venlafaxine and ecchymosis. Can J Psychiatry.* 1997;42-91.
- 12 DeClerck FF, Herman AG. *5-hydroxytryptamine and platelet aggregation. Fed Proc.* 1983;149:228-232.
- 13 Kirby D, Ames D. *Hyponatremia and selective serotonin re-uptake inhibitors in elderly patients. Intern J of Geriatric Psychiatry.* 2001;16:484-493.
- 14 Kirby D, Harrigan S, Ames D. *Hyponatremia in elderly psychiatric patients treated with selective serotonin reuptake inhibitors and venlafaxine: a retrospective controlled study in an inpatient unit. Intern J of Geriatric Psychiatry.* 2002;17:231-237.
- 15 Illett KF, Hackett LP, Dusci LJ, et al. *Distribution and excretion of venlafaxine and O-desmethylvenlafaxine in human milk. Br J Clin Pharmacol.* 1998;45:459-462.
- 16 Richelson, E. *Pharmacology of antidepressants. Psychopathology.* 1987;20 (Suppl. 1):1-12.
- 17 Bureau of Food and Drugs. *BC # 05 s. 2005: Black Box Warning for all Antidepressant Drugs.* 3 January 2005