



**Desvenlafaxine**  
**Pristiq SR<sup>®</sup>**  
**50 mg Extended-Release Tablets**

**WARNING: SUICIDAL THOUGHTS AND BEHAVIORS**

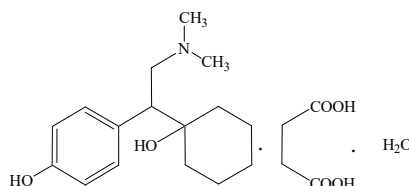
**Antidepressants increase the risk of suicidal thinking and behavior (suicidality) in children and adolescents with major depressive disorder (MDD) and other psychiatric disorders and those considering use of these agents must balance risk with the clinical need.**

**1.0 PHARMACOLOGIC CATEGORY**

Antidepressant/Serotonin and Norepinephrine Reuptake Inhibitor (SNRI).

**2.0 DESCRIPTION**

Desvenlafaxine succinate (Pristiq SR) is an extended-release tablet for oral administration that contains desvenlafaxine succinate, a structurally novel SNRI for the treatment of MDD. Desvenlafaxine (O-desmethylvenlafaxine) is the major active metabolite of the antidepressant venlafaxine, a medication used to treat major depressive disorder. Desvenlafaxine is designated (R,S)-4-[2-(Dimethylamino)-1-(1-hydroxycyclohexyl)ethyl]phenol and has the empirical formula of  $C_{16}H_{25}NO_2$  (free base) and  $C_{16}H_{25}NO_2 \cdot C_4H_6O_4 \cdot H_2O$  (succinate monohydrate). Desvenlafaxine succinate monohydrate has a molecular weight of 399.48. The structural formula is shown below:



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

Desvenlafaxine succinate (Pristiq SR) is available as a 50 mg extended release tablet for oral administration. The 50 mg tablet consists of light pink, square (pyramid, one sided), film-coated tablets debossed "W" over "50" on the flat side.

**3.0 FORMULATION**

Each extended-release tablet contains Desvenlafaxine succinate equivalent to 50 mg desvenlafaxine.

**4.0 CLINICAL PARTICULARS**

**4.1 Therapeutic Indications**

Desvenlafaxine succinate (Pristiq SR) is not indicated for use in any pediatric population.

Desvenlafaxine is indicated for the

- Treatment of adults with major depressive disorder (MDD).
- Acute and maintenance treatment of major depressive disorder (MDD).

## **4.2 Dosage and Method of Administration**

### **General Instructions for Use**

The recommended dose for Desvenlafaxine succinate (Pristiq SR) is 50 mg once daily, with or without food. The 50 mg dose is both a starting dose and the therapeutic dose. Desvenlafaxine succinate (Pristiq SR) should be taken at approximately the same time each day. Tablets must be swallowed whole with fluid and not divided, crushed, chewed, or dissolved.

In clinical studies, doses of 10 mg to 400 mg per day were studied. In clinical studies, doses of 50 to 400 mg/day were shown to be effective, although no additional benefit was demonstrated at doses greater than 50 mg per day and adverse reactions and discontinuations were more frequent at higher doses.

The 25 mg per day dose is intended for a gradual reduction in dose when discontinuing treatment. When discontinuing therapy, gradual dose reduction is recommended whenever possible to minimize discontinuation symptoms [see **Subsection Discontinuing Desvenlafaxine succinate (Pristiq SR)** and **Section 4.4. Special Warnings and Precautions for Use**].

### **Dosage Recommendations for Patients with Renal Impairment**

The maximum recommended dose in patients with moderate renal impairment (24-hr creatinine clearance [ $Cl_{Cr}$ ] = 30 to 50 mL/min, Cockcroft-Gault [C-G]) is 50 mg per day. The maximum recommended dose in patients with severe renal impairment ( $Cl_{Cr}$  15 to 29 mL/min, C-G) or end-stage renal disease (ESRD,  $Cl_{Cr}$  <15 mL/min, C-G) is 25 mg every day or 50 mg every other day. Supplemental doses should not be given to patients after dialysis.

Adjust the maximum recommended dosage in patients with moderate or severe renal impairment ( $Cl_{Cr}$  15 to 50 mL/min, C-G), or end-stage renal disease ( $Cl_{Cr}$  <15 mL/min, C-G) [see **Section 5.2 Pharmacokinetic Properties**].

### **Dosage Recommendations for Patients with Hepatic Impairment**

The recommended dose in patients with moderate to severe hepatic impairment (Child-Pugh score 7 to 15) is 50 mg per day. Dose escalation above 100 mg per day is not recommended [see **Section 5.2 Pharmacokinetic Properties**].

Adjust the maximum recommended dosage in patients with moderate to severe hepatic impairment (Child-Pugh score 7 to 15) [see **Section 5.2 Pharmacokinetic Properties**].

### **Maintenance/Continuation/Extended Treatment**

It is generally agreed that acute episodes of major depressive disorder require several months or longer of sustained pharmacologic therapy. Longer-term efficacy of Desvenlafaxine succinate (Pristiq SR) (50-400 mg) was established in two maintenance trials [see **Section 5.4. Clinical Studies**]. Patients should be periodically reassessed to determine the need for continued treatment.

### **Discontinuing Desvenlafaxine succinate (Pristiq SR)**

Adverse reactions may occur upon discontinuation of Desvenlafaxine succinate (Pristiq SR) [see **Section 4.4. Special Warnings and Precautions for Use**]. Gradually reduce the dosage rather than stopping Desvenlafaxine succinate (Pristiq SR) abruptly when discontinuing therapy with Desvenlafaxine succinate (Pristiq SR). In some patients, discontinuation may need to occur over a period of several months.

### **Switching Patients from Other Antidepressants to Desvenlafaxine succinate (Pristiq SR)**

Discontinuation symptoms have been reported when switching patients from other antidepressants, including venlafaxine, to Desvenlafaxine succinate (Pristiq SR). Tapering of the initial antidepressant may be necessary to minimize discontinuation symptoms.

### **Switching Patients to or from a Monoamine Oxidase Inhibitor (MAOI) Intended to Treat Psychiatric Disorders**

At least 14 days should elapse between discontinuation of an MAOI intended to treat psychiatric disorders and initiation of therapy with Desvenlafaxine succinate (Pristiq SR). Conversely, at least 7 days should be allowed after stopping Desvenlafaxine succinate (Pristiq SR) before starting an MAOI intended to treat psychiatric disorders [see **Section 4.3 Contraindications**].

### **Use of Desvenlafaxine succinate (Pristiq SR) with other MAOIs such as Linezolid or Methylene Blue**

Do not start Desvenlafaxine succinate (Pristiq SR) in a patient who is being treated with linezolid or intravenous methylene blue because there is increased risk of serotonin syndrome. In a patient who requires more urgent treatment of a psychiatric condition, other interventions, including hospitalization, should be considered [see **Section 4.3 Contraindications**].

In some cases, a patient already receiving Desvenlafaxine succinate (Pristiq SR) therapy may require urgent treatment with linezolid or intravenous methylene blue. If acceptable alternatives to linezolid or intravenous methylene blue treatment are not available and the potential benefits of linezolid or intravenous methylene blue treatment are judged to outweigh the risks of serotonin syndrome in a particular patient, Desvenlafaxine succinate (Pristiq SR) should be stopped promptly, and linezolid or intravenous methylene blue can be administered. The patient should be monitored for symptoms of serotonin syndrome for 7 days or until 24 hours after the last dose of linezolid or intravenous methylene blue, whichever comes first. Therapy with Desvenlafaxine succinate (Pristiq SR) may be resumed 24 hours after the last dose of linezolid or intravenous methylene blue [see **Section 4.4 Special Warnings and Precautions for Use**].

The risk of administering methylene blue by non-intravenous routes (such as oral tablets or by local injection) or in intravenous doses much lower than 1 mg/kg with Desvenlafaxine succinate (Pristiq SR) is unclear. The clinician should, nevertheless, be aware of the possibility of emergent symptoms of serotonin syndrome with such use [see **Section 4.4 Special Warnings and Precautions for Use**].

## **4.3 Contraindications**

Hypersensitivity to desvenlafaxine succinate, venlafaxine hydrochloride or to any excipients such as hypromellose, microcrystalline cellulose, talc, magnesium stearate and film coating which

consists of polyvinyl alcohol, polyethylene glycol, titanium dioxide and iron oxides. Angioedema has been reported in patients treated with Desvenlafaxine succinate (Pristiq SR) [see **Section 4.8 Undesirable Effects**].

The use of MAOIs intended to treat psychiatric disorders with Desvenlafaxine succinate (Pristiq SR) or within 7 days of stopping treatment with Desvenlafaxine succinate (Pristiq SR) is contraindicated because of an increased risk of serotonin syndrome. The use of Desvenlafaxine succinate (Pristiq SR) within 14 days of stopping an MAOI intended to treat psychiatric disorders is also contraindicated [see **Sections 4.2 Dosage and Method of Administration** and **4.4 Special Warnings and Precautions for Use**].

Starting Desvenlafaxine succinate (Pristiq SR) in a patient who is being treated with MAOIs such as linezolid or intravenous methylene blue is also contraindicated because of an increased risk of serotonin syndrome [see **Sections 4.2 Dosage and Method of Administration** and **4.4 Special Warnings and Precautions for Use**].

#### **4.4 Special Warnings and Precautions for Use**

##### **Suicidal Thoughts and Behaviors in Pediatric and Young Adult Patients**

Patients with MDD, both adult and pediatric, may experience worsening of their depression and/or the emergence of suicidal ideation and behavior (suicidality) or unusual changes in behavior, whether or not they are taking antidepressant medications, and this risk may persist until significant remission occurs.

Suicide is a known risk of depression and certain other psychiatric disorders, and these disorders themselves are the strongest predictors of suicide. There has been a long-standing concern, however, that antidepressants may have a role in inducing worsening of depression and the emergence of suicidality in certain patients during the early phases of treatment. Pooled analyses of short-term placebo-controlled studies of antidepressant drugs (SSRIs and others) showed that these drugs increase the risk of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults (ages 18 to 24) with major depressive disorder (MDD) and other psychiatric disorders. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction with antidepressants compared to placebo in adults aged 65 and older.

The pooled analyses of placebo-controlled studies in children and adolescents with MDD, obsessive compulsive disorder (OCD), or other psychiatric disorders included a total of 24 short-term studies of 9 antidepressant drugs in over 4,400 patients. The pooled analyses of placebo-controlled studies in adults with MDD or other psychiatric disorders included a total of 295 short-term studies (median duration of 2 months) of 11 antidepressant drugs in over 77,000 patients. There was considerable variation in risk of suicidality among drugs, but a tendency toward an increase in the younger patients for almost all drugs studied. There were differences in absolute risk of suicidality across the different indications, with the highest incidence in MDD. The risk differences (drug vs. placebo), however, were relatively stable within age strata and across indications. These risk differences (drug-placebo difference in the number of cases of suicidality per 1,000 patients treated) are provided in Table 1.

**Table 1**

<b>Age Range</b>	<b>Drug-Placebo Difference in Number of Cases of Suicidality per 1,000 Patients Treated</b>
	Increases Compared to Placebo
<18	14 additional cases

18 to 24	5 additional cases
	Decreases Compared to Placebo
25 to 64	1 fewer case
≥65	6 fewer cases

No suicides occurred in any of the pediatric studies. There were suicides in the adult studies, but the number was not sufficient to reach any conclusion about drug effect on suicide.

It is unknown whether the suicidality risk extends to longer-term use, i.e., beyond several months. However, there is substantial evidence from placebo-controlled maintenance studies in adults with depression that the use of antidepressants can delay the recurrence of depression.

All patients being treated with antidepressants for any indication should be monitored appropriately and observed closely for clinical worsening, suicidality, and unusual changes in behavior, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases.

The following symptoms, anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, and mania, have been reported in adult and pediatric patients being treated with antidepressants for major depressive disorder as well as for other indications, both psychiatric and non-psychiatric. Although a causal link between the emergence of such symptoms and either the worsening of depression and/or the emergence of suicidal impulses has not been established, there is concern that such symptoms may represent precursors to emerging suicidality.

Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients whose depression is persistently worse, or who are experiencing emergent suicidality or symptoms that might be precursors to worsening depression or suicidality, especially if these symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms.

If the decision has been made to discontinue treatment, medication should be tapered, as rapidly as is feasible, but with recognition that abrupt discontinuation can be associated with certain symptoms [see **Sections 4.2 Dosage and Method of Administration, 4.4 Special Warnings and Precautions for Use**].

Families and caregivers of patients being treated with antidepressants for major depressive disorder or other indications, both psychiatric and non-psychiatric, should be alerted about the need to monitor patients for the emergence of agitation, irritability, unusual changes in behavior, and the other symptoms described above, as well as the emergence of suicidality, and to report such symptoms immediately to healthcare providers. Such monitoring should include daily observation by families and caregivers.

Prescriptions for Desvenlafaxine succinate (Pristiq SR) should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose.

#### Screening Patients for Bipolar Disorder

A major depressive episode may be the initial presentation of bipolar disorder. It is generally believed (though not established in controlled studies) that treating such an episode with an antidepressant alone may increase the likelihood of precipitation of a mixed/manic episode in patients at risk for bipolar disorder. Whether any of the symptoms described above represent such a conversion is unknown. However, prior to initiating treatment with an antidepressant, patients

with depressive symptoms should be adequately screened to determine if they are at risk for bipolar disorder; such screening should include a detailed psychiatric history, including a family history of suicide, bipolar disorder, and depression. It should be noted that Desvenlafaxine succinate (Pristiq SR) is not approved for use in treating bipolar depression.

### **Serotonin Syndrome**

Serotonin-norepinephrine reuptake inhibitors (SNRIs) and selective-serotonin reuptake inhibitors (SSRIs), including Desvenlafaxine succinate (Pristiq SR), can precipitate serotonin syndrome, a potentially life-threatening condition. The risk is increased with concomitant use of other serotonergic drugs (including triptans, tricyclic antidepressants, fentanyl, lithium, tramadol, tryptophan, buspirone, amphetamines, and St. John's Wort) and with drugs that impair metabolism of serotonin, i.e., MAOIs [see **Sections 4.3 Contraindications** and **4.5 Interactions with Other Medicinal Products and Other Forms of Interaction**]. Serotonin syndrome can also occur when these drugs are used alone.

Serotonin syndrome signs and symptoms may include mental status changes (e.g., agitation, hallucinations, delirium, and coma), autonomic instability (e.g., tachycardia, labile blood pressure, dizziness, diaphoresis, flushing, hyperthermia), neuromuscular symptoms (e.g., tremor, rigidity, myoclonus, hyperreflexia, incoordination), seizures, and gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea).

The concomitant use of Desvenlafaxine succinate (Pristiq SR) with MAOIs is contraindicated. In addition, do not initiate Desvenlafaxine succinate (Pristiq SR) in a patient being treated with MAOIs such as linezolid or intravenous methylene blue. No reports involved the administration of methylene blue by other routes (such as oral tablets or local tissue injection). If it is necessary to initiate treatment with an MAOI such as linezolid or intravenous methylene blue in a patient taking Desvenlafaxine succinate (Pristiq SR), discontinue Desvenlafaxine succinate (Pristiq SR) before initiating treatment with the MAOI [see **Sections 4.3 Contraindications** and **4.5 Interactions with Other Medicinal Products and Other Forms of Interaction**].

Monitor all patients taking Desvenlafaxine succinate (Pristiq SR) for the emergence of serotonin syndrome. Discontinue treatment with Desvenlafaxine succinate (Pristiq SR) and any concomitant serotonergic agents immediately if the above symptoms occur, and initiate supportive symptomatic treatment. If concomitant use of Desvenlafaxine succinate (Pristiq SR) with other serotonergic drugs is clinically warranted, inform patients of the increased risk for serotonin syndrome and monitor for symptoms.

### **Elevated Blood Pressure**

Patients receiving Desvenlafaxine succinate (Pristiq SR) should have regular monitoring of blood pressure since increases in blood pressure were observed in clinical studies [see **Section 4.8 Undesirable Effects**]. Pre-existing hypertension should be controlled before initiating treatment with Desvenlafaxine succinate (Pristiq SR). Caution should be exercised in treating patients with pre-existing hypertension, cardiovascular, or cerebrovascular conditions that might be compromised by increases in blood pressure. Cases of elevated blood pressure requiring immediate treatment have been reported with Desvenlafaxine succinate (Pristiq SR).

Sustained blood pressure increases could have adverse consequences. For patients who experience a sustained increase in blood pressure while receiving Desvenlafaxine succinate (Pristiq SR), either dose reduction or discontinuation should be considered [see **Section 4.8 Undesirable Effects**].

### **Increased Risk of Bleeding**

Drugs that interfere with serotonin reuptake inhibition, including Desvenlafaxine succinate (Pristiq SR), may increase the risk of bleeding events. Concomitant use of aspirin, non-steroidal anti-inflammatory drugs, warfarin, and other anticoagulants may add to this 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 have ranged from ecchymosis, hematoma, epistaxis, and petechiae to life-threatening hemorrhages. Inform patients about the risk of bleeding associated with the concomitant use of Desvenlafaxine succinate (Pristiq SR) and antiplatelet agents or anticoagulants. For patients taking warfarin, carefully monitor coagulation indices when initiating, titrating, or discontinuing Desvenlafaxine succinate (Pristiq SR).

### **Angle Closure Glaucoma**

The pupillary dilation that occurs following use of many antidepressant drugs including Desvenlafaxine succinate (Pristiq SR) may trigger an angle closure attack in a patient with anatomically narrow angles who does not have a patent iridectomy. Avoid use of antidepressants, including Desvenlafaxine succinate (Pristiq SR), in patients with untreated anatomically narrow angles.

### **Activation of Mania/Hypomania**

During all MDD phase 2 and phase 3 studies, mania was reported for approximately 0.02% of patients treated with Desvenlafaxine succinate (Pristiq SR). 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 succinate (Pristiq SR) should be used cautiously in patients with a history or family history of mania or hypomania.

### **Discontinuation Syndrome**

Adverse reactions after discontinuation of serotonergic antidepressants, particularly after abrupt discontinuation, include: nausea, sweating, dysphoric mood, irritability, agitation, dizziness, sensory disturbances (e.g., paresthesia, such as electric shock sensations), tremor, anxiety, confusion, headache, lethargy, emotional lability, insomnia, hypomania, tinnitus, and seizures [see **Section 4.8 Undesirable Effects**].

There have been postmarketing reports of serious discontinuation symptoms with Desvenlafaxine succinate (Pristiq SR), which can be protracted and severe. Completed suicide, suicidal thoughts, and severe aggression (including hostility, rage, and homicidal ideation) have been observed in patients during reduction in Desvenlafaxine succinate (Pristiq SR) dosage, including during discontinuation. Other postmarketing reports describe visual changes (such as blurred vision or trouble focusing) and increased blood pressure after stopping or reducing the dose of Desvenlafaxine succinate (Pristiq SR).

Patients should be monitored when discontinuing treatment with Desvenlafaxine succinate (Pristiq SR). A gradual reduction in the dose, rather than abrupt cessation, is recommended. 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 healthcare provider may continue decreasing the dose, but at a more gradual rate. In some patients, discontinuation may need to occur over a period of several months [see **Section 4.2 Dosage and Method of Administration**].

## **Seizure**

Cases of seizure have been reported in pre-marketing clinical studies with Desvenlafaxine succinate (Pristiq SR). Desvenlafaxine succinate (Pristiq SR) has not been systematically evaluated in patients with a seizure disorder. Patients with a history of seizures were excluded from pre-marketing clinical studies. Desvenlafaxine succinate (Pristiq SR) should be prescribed with caution in patients with a seizure disorder.

## **Hyponatremia**

Hyponatremia may occur as a result of treatment with SSRIs and SNRIs, including Desvenlafaxine succinate (Pristiq SR). In many cases, this hyponatremia appears to be the result of the syndrome of inappropriate antidiuretic hormone secretion (SIADH). Cases with serum sodium lower than 110 mmol/L have been reported. Elderly patients may be at greater risk of developing hyponatremia with SSRIs and SNRIs. Also, patients taking diuretics or who are otherwise volume depleted can be at greater risk [see **Section 5.2 Pharmacokinetic Properties**]. Discontinuation of Desvenlafaxine succinate (Pristiq SR) should be considered in patients with symptomatic hyponatremia and appropriate medical intervention should be instituted.

Signs and symptoms of hyponatremia include headache, difficulty concentrating, memory impairment, confusion, weakness, and unsteadiness, which can lead to falls. Signs and symptoms associated with more severe and/or acute cases have included hallucination, syncope, seizure, coma, respiratory arrest, and death.

## **Interstitial Lung Disease and Eosinophilic Pneumonia**

Interstitial lung disease and eosinophilic pneumonia associated with venlafaxine (the parent drug of Desvenlafaxine succinate (Pristiq SR)) therapy have been rarely reported. The possibility of these adverse events should be considered in patients treated with Desvenlafaxine succinate (Pristiq SR) who present with progressive dyspnea, cough, or chest discomfort. Such patients should undergo a prompt medical evaluation, and discontinuation of Desvenlafaxine succinate (Pristiq SR) should be considered.

## **Sexual Dysfunction**

Use of SNRIs, including Desvenlafaxine succinate (Pristiq SR), may cause symptoms of sexual dysfunction [see **Section 4.8 Undesirable Effects**]. In male patients, SNRI use may result in ejaculatory delay or failure, decreased libido, and erectile dysfunction. In female patients, SNRI use may result in decreased libido and delayed or absent orgasm.

It is important for prescribers to inquire about sexual function prior to initiation of Desvenlafaxine succinate (Pristiq SR) and to inquire specifically about changes in sexual function during treatment, because sexual function may not be spontaneously reported. When evaluating changes in sexual function, obtaining a detailed history (including timing of symptom onset) is important because sexual symptoms may have other causes, including the underlying psychiatric disorder. Discuss potential management strategies to support patients in making informed decisions about treatment.

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

### **Drugs Having Clinically Important Interactions with Desvenlafaxine succinate (Pristiq SR)**



**Table 2: Clinically Important Drug Interactions with Desvenlafaxine succinate (Pristiq SR)**

Monoamine Oxidase Inhibitors (MAOI)	
<i>Clinical Impact</i>	The concomitant use of SSRIs and SNRIs including Desvenlafaxine succinate (Pristiq SR) with MAOIs increases the risk of serotonin syndrome.
<i>Intervention</i>	Concomitant use of Desvenlafaxine succinate (Pristiq SR) is contraindicated: <ul style="list-style-type: none"> <li>• With an MAOI intended to treat psychiatric disorders or within 7 days of stopping treatment with Desvenlafaxine succinate (Pristiq SR).</li> <li>• Within 14 days of stopping an MAOI intended to treat psychiatric disorders.</li> <li>• In a patient who is being treated with linezolid or intravenous methylene blue.</li> </ul> [see <b>Sections 4.2 Dosage and Administration, 4.3 Contraindications and 4.4 Special Warnings and Precautions for Use</b> ]
<i>Examples</i>	selegiline, tranylcypromine, isocarboxazid, phenelzine, linezolid, methylene blue
Other Serotonergic Drugs	
<i>Clinical Impact</i>	Concomitant use of Desvenlafaxine succinate (Pristiq SR) with other serotonergic drugs increases the risk of serotonin syndrome.
<i>Intervention</i>	Monitor for symptoms of serotonin syndrome when Desvenlafaxine succinate (Pristiq SR) is used concomitantly with other drugs that may affect the serotonergic neurotransmitter systems. If serotonin syndrome occurs, consider discontinuation of Desvenlafaxine succinate (Pristiq SR) and/or concomitant serotonergic drugs [see <b>Section 4.4 Special Warnings and Precautions for Use</b> ].
<i>Examples</i>	other SNRIs, SSRIs, triptans, tricyclic antidepressants, fentanyl, lithium, tramadol, buspirone, amphetamines, tryptophan, and St. John's Wort
Drugs that Interfere with Hemostasis	
<i>Clinical Impact</i>	Concomitant use of Desvenlafaxine succinate (Pristiq SR) with an antiplatelet or anticoagulant drug may potentiate the risk of bleeding. This may be due to the effect of Desvenlafaxine succinate (Pristiq SR) on the release of serotonin by platelets.
<i>Intervention</i>	Closely monitor for bleeding for patients receiving an antiplatelet or anticoagulant drug when Desvenlafaxine succinate (Pristiq SR) is initiated or discontinued [see <b>Section 4.4 Special Warnings and Precautions for Use</b> ].
<i>Examples</i>	NSAIDs, aspirin, and warfarin
Drugs that are Primarily Metabolized by CYP2D6	
<i>Clinical Impact</i>	Concomitant use of Desvenlafaxine succinate (Pristiq SR) increases C <sub>max</sub> and AUC of a drug primarily metabolized by CYP2D6 which may increase the risk of toxicity of the CYP2D6 substrate drug [see <b>Section 5.2 Pharmacokinetic Properties</b> ].
<i>Intervention</i>	Original dose should be taken when co-administered with Desvenlafaxine succinate (Pristiq SR) 100 mg or lower. Reduce the dose of these drugs by up to one-half if co-administered with 400 mg of Desvenlafaxine succinate (Pristiq SR).
<i>Examples</i>	desipramine, atomoxetine, dextromethorphan, metoprolol, nebivolol, perphenazine, tolterodine

## **Drugs Having No Clinically Important Interactions with Desvenlafaxine succinate (Pristiq SR)**

Based on pharmacokinetic studies, no dosage adjustment is required for drugs that are mainly metabolized by CYP3A4 (e.g., midazolam), or for drugs that are metabolized by both CYP2D6 and CYP3A4 (e.g., tamoxifen, aripiprazole), when administered concomitantly with Desvenlafaxine succinate (Pristiq SR) [see **Section 5.2 Pharmacokinetic Properties**].

### **Alcohol**

A clinical study has shown that Desvenlafaxine succinate (Pristiq SR) 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 succinate (Pristiq SR).

### **Drug-Laboratory Test Interactions**

False-positive urine immunoassay screening tests for phencyclidine (PCP) and amphetamine have been reported in patients taking desvenlafaxine. This is due to lack of specificity of the screening tests. False-positive test results may be expected for several days following discontinuation of desvenlafaxine therapy. Confirmatory tests, such as gas chromatography/mass spectrometry, will distinguish desvenlafaxine from PCP and amphetamine.

## **4.6 Fertility, Pregnancy and Lactation**

### **Fertility**

No information available

### **Pregnancy**

#### *Risk Summary*

There are no published studies on Desvenlafaxine succinate (Pristiq SR) in pregnant women; however published epidemiologic studies of pregnant women exposed to venlafaxine, the parent compound, have not reported a clear association with adverse developmental outcomes (see **Sub-section Data**). There are risks associated with untreated depression in pregnancy and with exposure to SNRIs and SSRIs, including Desvenlafaxine Succinate (Pristiq SR), during pregnancy (see **Sub-section Clinical Considerations**).

In reproductive developmental studies in rats and rabbits treated with desvenlafaxine succinate, there was no evidence of teratogenicity at a plasma exposure (AUC) that is up to 19-times (rats) and 0.5-times (rabbits) the exposure at an adult human dose of 100 mg per day. However, fetotoxicity and pup deaths were observed in rats at 4.5-times the AUC exposure observed with an adult human dose of 100 mg per day.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

#### *Clinical Considerations*

## **Disease-Associated Maternal and/or Embryo/Fetal Risk**

A prospective longitudinal study of 201 women with a history of major depression who were euthymic at the beginning of pregnancy, showed that women who discontinued antidepressant medication during pregnancy were more likely to experience a relapse of major depression than women who continued antidepressant medication.

## **Maternal Adverse Reactions**

Exposure to SNRIs in mid to late pregnancy may increase the risk for preeclampsia, and exposure to SNRIs near delivery may increase the risk for postpartum hemorrhage.

## **Fetal/Neonatal Adverse Reactions**

Exposure to SNRIs or SSRIs in late pregnancy may lead to an increased risk for neonatal complications requiring prolonged hospitalization, respiratory support, and tube feeding. Monitor neonates who were exposed to Desvenlafaxine succinate (Pristiq SR) in the third trimester of pregnancy for drug discontinuation syndrome (see **Sub-section Data**).

### *Data*

#### **Human Data**

Published epidemiological studies of pregnant women exposed to the parent compound venlafaxine have not reported a clear association with major birth defects or miscarriage. Methodological limitations of these observational studies include possible exposure and outcome misclassification, lack of adequate controls, adjustment for confounders, and confirmatory studies; therefore, these studies cannot establish or exclude any drug-associated risk during pregnancy.

Retrospective cohort studies based on claims data have shown an association between venlafaxine use and preeclampsia, compared to depressed women who did not take an antidepressant during pregnancy. One study that assessed venlafaxine exposure in the second trimester or first half of the third trimester and preeclampsia showed an increased risk compared to unexposed depressed women [adjusted (adj) RR 1.57, 95% CI 1.29-1.91]. Preeclampsia was observed at venlafaxine doses equal to or greater than 75 mg/day and a duration of treatment >30 days. Another study that assessed venlafaxine exposure in gestational weeks 10-20 and preeclampsia showed an increased risk at doses equal to or greater than 150 mg/day. Available data are limited by possible outcome misclassification and possible confounding due to depression severity and other confounders.

Retrospective cohort studies based on claims data have suggested an association between venlafaxine use near the time of delivery or through delivery and postpartum hemorrhage. One study showed an increased risk for postpartum hemorrhage when venlafaxine exposure occurred through delivery, compared to unexposed depressed women [adj RR 2.24 (95% CI 1.69-2.97)]. There was no increased risk in women who were exposed to venlafaxine earlier in pregnancy. Limitations of this study include possible confounding due to depression severity and other confounders. Another study showed an increased risk for postpartum hemorrhage when SNRI exposure occurred for at least 15 days in the last month of pregnancy or through delivery, compared to unexposed women (adj RR 1.64-1.76). The results of this study may be confounded by the effects of depression.

Neonates exposed to SNRIs or SSRIs 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 SNRIs or, possibly, a drug discontinuation syndrome. It should be noted that, in some cases, the clinical picture is consistent with serotonin syndrome [see **Section 4.4 Special Warnings and Precautions for Use**].

### **Animal Data**

When desvenlafaxine succinate was administered orally to pregnant rats and rabbits during the period of organogenesis at doses up to 300 mg/kg/day and 75 mg/kg/day, respectively, no teratogenic effects were observed. These doses were associated with a plasma exposure (AUC) 19 times (rats) and 0.5 times (rabbits) the AUC exposure at an adult human dose of 100 mg per day. However, fetal weights were decreased and skeletal ossification was delayed in rats in association with maternal toxicity at the highest dose, with an AUC exposure at the no-effect dose that is 4.5-times the AUC exposure at an adult human dose of 100 mg per day.

When desvenlafaxine succinate was administered orally to pregnant rats throughout gestation and lactation, there was a decrease in pup weights and an increase in pup deaths during the first four days of lactation at the highest dose of 300 mg/kg/day. The cause of these deaths is not known. The AUC exposure at the no-effect dose for rat pup mortality was 4.5-times the AUC exposure at an adult human dose of 100 mg per day. Post-weaning growth and reproductive performance of the progeny were not affected by maternal treatment with desvenlafaxine succinate at exposures 19 times the AUC exposure at an adult human dose of 100 mg per day.

### **Lactation**

#### *Risk Summary*

Available limited data from published literature show low levels of desvenlafaxine in human milk, and have not shown adverse reactions in breastfed infants [see Sub-section Data]. There are no data on the effects of desvenlafaxine on milk production.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Desvenlafaxine succinate (Pristiq SR) and any potential adverse effects on the breastfed child from Desvenlafaxine succinate (Pristiq SR) or from the underlying maternal condition.

#### *Data*

A lactation study was conducted in 10 breastfeeding women (at a mean of 4.3 months post-partum) who were being treated with a 50-150 mg daily dose of desvenlafaxine for postpartum depression. Sampling was performed at steady state (up to 8 samples) over a 24 hour dosing period, and included foremilk and hindmilk. The mean relative infant dose was calculated to be 6.8% (range of 5.5-8.1%). No adverse reactions were seen in the infants.

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

Not applicable

### **4.8 Undesirable Effects**

The following adverse reactions are discussed in greater detail in other sections of the label.

- Hypersensitivity [see **Section 4.3 Contraindications**]
- Suicidal Thoughts and Behaviors in Pediatric and Young Adult Patients [see **Section 4.4 Special Warnings and Precautions for Use**]
- Serotonin Syndrome [see **Section 4.4 Special Warnings and Precautions for Use**]
- Elevated Blood Pressure [see **Section 4.4 Special Warnings and Precautions for Use**]
- Increased Risk of Bleeding [see **Section 4.4 Special Warnings and Precautions for Use**]
- Angle Closure Glaucoma [see **Section 4.4 Special Warnings and Precautions for Use**]
- Activation of Mania/Hypomania [see **Section 4.4 Special Warnings and Precautions for Use**]
- Discontinuation Syndrome [see **Section 4.4 Special Warnings and Precautions for Use**]
- Seizure [see **Section 4.4 Special Warnings and Precautions for Use**]
- Hyponatremia [see **Section 4.4 Special Warnings and Precautions for Use**]
- Interstitial Lung Disease and Eosinophilic Pneumonia [see **Section 4.4 Special Warnings and Precautions for Use**]
- Sexual Dysfunction [see **Section 4.4 Special Warnings and Precautions for Use**]

### **Clinical Studies Experience**

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in clinical practice.

#### **Patient Exposure**

Desvenlafaxine succinate (Pristiq SR) was evaluated for safety in 8,394 patients diagnosed with major depressive disorder who participated in multiple-dose pre-marketing studies, representing 2,784 patient-years of exposure. Of the total 8,394 patients exposed to at least one dose of Desvenlafaxine succinate (Pristiq SR); 2,116 were exposed to Desvenlafaxine succinate (Pristiq SR) for 6 months, representing 1,658 patient-years of exposure, and 421 were exposed for one year, representing 416 patient-years of exposure.

#### **Adverse Reactions Reported as Reasons for Discontinuation of Treatment**

In the pre-marketing pooled 8-week placebo-controlled studies in patients with MDD, 1,834 patients were exposed to Desvenlafaxine succinate (Pristiq SR) (50 to 400 mg). Of the 1,834 patients, 12% discontinued treatment due to an adverse reaction, compared with 3% of the 1,116 placebo-treated patients. At the recommended dose of 50 mg, the discontinuation rate due to an adverse reaction for Desvenlafaxine succinate (Pristiq SR) (4.1%) was similar to the rate for placebo (3.8%). For the 100 mg dose of Desvenlafaxine succinate (Pristiq SR) the discontinuation rate due to an adverse reaction was 8.7%.

The most common adverse reactions leading to discontinuation in at least 2% and at a rate greater than placebo of the Desvenlafaxine succinate (Pristiq SR) treated patients in the short-term studies, up to 8 weeks, were: nausea (4%); dizziness, headache and vomiting (2% each). In a longer-term study, up to 9 months, the most common was vomiting (2%).

### Common Adverse Reactions in Placebo-Controlled MDD Studies

The most commonly observed adverse reactions in Desvenlafaxine succinate (Pristiq SR) treated MDD patients in pre-marketing pooled 8-week, placebo-controlled, fixed-dose studies (incidence  $\geq 5\%$  and at least twice the rate of placebo in the 50 or 100 mg dose groups) were: nausea, dizziness, insomnia, hyperhidrosis, constipation, somnolence, decreased appetite, anxiety, and specific male sexual function disorders.

Table 3 shows the incidence of common adverse reactions that occurred in  $\geq 2\%$  of Desvenlafaxine succinate (Pristiq SR) treated MDD patients and twice the rate of placebo at any dose in the pre-marketing pooled 8-week, placebo-controlled, fixed dose clinical studies.

**Table 3: Common Adverse Reactions ( $\geq 2\%$  in any Fixed-Dose Group and Twice the Rate of Placebo) in Pre-marketing Pooled MDD 8-Week Placebo-Controlled Studies**

System Organ Class Preferred Term	Percentage of Patients Reporting Reaction				
	Placebo (n=636)	Desvenlafaxine succinate (Pristiq SR)			
		50 mg (n=317)	100 mg (n=424)	200 mg (n=307)	400 mg (n=317)
<b>Cardiac disorders</b>					
Blood pressure increased	1	1	1	2	2
<b>Gastrointestinal disorders</b>					
Nausea	10	22	26	36	41
Dry mouth	9	11	17	21	25
Constipation	4	9	9	10	14
Vomiting	3	3	4	6	9
<b>General disorders and administration site conditions</b>					
Fatigue	4	7	7	10	11
Chills	1	1	<1	3	4
Feeling jittery	1	1	2	3	3
<b>Metabolism and nutrition disorders</b>					
Decreased appetite	2	5	8	10	10
<b>Nervous system disorders</b>					
Dizziness	5	13	10	15	16
Somnolence	4	4	9	12	12
Tremor	2	2	3	9	9
Disturbance in attention	<1	<1	1	2	1
<b>Psychiatric disorders</b>					
Insomnia	6	9	12	14	15
Anxiety	2	3	5	4	4
Nervousness	1	<1	1	2	2
Abnormal dreams	1	2	3	2	4
<b>Renal and urinary disorders</b>					
Urinary hesitation	0	<1	1	2	2
<b>Respiratory, thoracic and mediastinal disorders</b>					
Yawning	<1	1	1	4	3
<b>Skin and subcutaneous tissue disorders</b>					
Hyperhidrosis	4	10	11	18	21
<b>Special Senses</b>					
Vision blurred	1	3	4	4	4
Mydriasis	<1	2	2	6	6
Vertigo	1	2	1	5	3

**Table 3: Common Adverse Reactions ( $\geq 2\%$  in any Fixed-Dose Group and Twice the Rate of Placebo) in Pre-marketing Pooled MDD 8-Week Placebo-Controlled Studies**

System Organ Class Preferred Term	Percentage of Patients Reporting Reaction				
	Placebo (n=636)	Desvenlafaxine succinate (Pristiq SR)			
		50 mg (n=317)	100 mg (n=424)	200 mg (n=307)	400 mg (n=317)
Tinnitus	1	2	1	1	2
Dysgeusia	1	1	1	1	2
<b>Vascular disorders</b>					
Hot flush	<1	1	1	2	2

Sexual Function Adverse Reactions

Table 4 shows the incidence of sexual function adverse reactions that occurred in  $\geq 2\%$  of Desvenlafaxine succinate (Pristiq SR) treated MDD patients in any fixed-dose group (pre-marketing pooled 8-week, placebo-controlled, fixed-dose, clinical studies) [see **Section 4.4 Special Warnings and Precautions for Use**].

**Table 4: Sexual Function Adverse Reactions ( $\geq 2\%$  in Men or Women in any Desvenlafaxine succinate (Pristiq SR) Group) During the On-Therapy Period**

	Desvenlafaxine succinate (Pristiq SR)				
	Placebo (n=239)	50 mg (n=108)	100 mg (n=157)	200 mg (n=131)	400 mg (n=154)
<b>Men only</b>					
Anorgasmia	0	0	3	5	8
Libido decreased	1	4	5	6	3
Orgasm abnormal	0	0	1	2	3
Ejaculation delayed	<1	1	5	7	6
Erectile dysfunction	1	3	6	8	11
Ejaculation disorder	0	0	1	2	5
Ejaculation failure	0	1	0	2	2
Sexual dysfunction	0	1	0	0	2
<b>Women only</b>					
Anorgasmia	0	1	1	0	3

Other Adverse Reactions Observed in Premarketing and Post-marketing Clinical Studies

Other infrequent adverse reactions, not described elsewhere in the label, occurring at an incidence of  $< 2\%$  in MDD patients treated with Desvenlafaxine succinate (Pristiq SR) were:

**Cardiac disorders** – Tachycardia.

**General disorders and administration site conditions** – Asthenia.

**Investigations** – Weight increased, liver function test abnormal, blood prolactin increased.

**Musculoskeletal and connective tissue disorders** – Musculoskeletal stiffness.

**Nervous system disorders** – Syncope, convulsion, dystonia.

**Psychiatric disorders** – Depersonalization, bruxism.

**Renal and urinary disorders** – Urinary retention.

**Skin and subcutaneous tissue disorders** – Rash, alopecia, photosensitivity reaction, angioedema.

In clinical studies, there were uncommon reports of ischemic cardiac adverse reactions, 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 succinate (Pristiq SR) treatment as compared to placebo.

### **Laboratory, ECG and Vital Sign Changes Observed in MDD Clinical Studies**

The following changes were observed in pre-marketing placebo-controlled, short-term MDD studies with Desvenlafaxine succinate (Pristiq SR).

#### ***Lipids***

Elevations in fasting serum total cholesterol, LDL (low density lipoproteins) cholesterol, and triglycerides occurred in the controlled studies. Some of these abnormalities were considered potentially clinically significant.

The percentage of patients who exceeded a predetermined threshold value is shown in Table 5.

**Table 5: Incidence (%) of Patients With Lipid Abnormalities of Potential Clinical Significance\***

	Placebo	Desvenlafaxine succinate (Pristiq SR)			
		50 mg	100 mg	200 mg	400 mg
Total Cholesterol *(Increase of $\geq 50$ mg/dl and an absolute value of $\geq 261$ mg/dl)	2	3	4	4	10
LDL Cholesterol *(Increase $\geq 50$ mg/dl and an absolute value of $\geq 190$ mg/dl)	0	1	0	1	2
Triglycerides, fasting *(Fasting: $\geq 327$ mg/dl)	3	2	1	4	6

#### ***Proteinuria***

Proteinuria, greater than or equal to trace, was observed in the pre-marketing fixed-dose controlled studies (see Table 6). This proteinuria was not associated with increases in BUN or creatinine and was generally transient.

**Table 6: Incidence (%) of Patients with Proteinuria in the Fixed-dose Clinical Studies**

	Placebo	Desvenlafaxine succinate (Pristiq SR)			
		50 mg	100 mg	200 mg	400 mg
Proteinuria	4	6	8	5	7

#### ***Vital Sign Changes***



Table 7 summarizes the changes that were observed in placebo-controlled, short-term, pre-marketing studies with Desvenlafaxine succinate (Pristiq SR) in patients with MDD (doses 50 to 400 mg).

**Table 7: Mean Changes in Vital Signs at Final on Therapy for All Short-term, Fixed-dose Controlled Studies**

	Placebo	Desvenlafaxine succinate (Pristiq SR)			
		50 mg	100 mg	200 mg	400 mg
<b>Blood pressure</b>					
Supine systolic bp (mm Hg)	-1.4	1.2	2.0	2.5	2.1
Supine diastolic bp (mm Hg)	-0.6	0.7	0.8	1.8	2.3
<b>Pulse rate</b>					
Supine pulse (bpm)	-0.3	1.3	1.3	0.9	4.1
<b>Weight (kg)</b>	0.0	-0.4	-0.6	-0.9	-1.1

Treatment with Desvenlafaxine succinate (Pristiq SR) at all doses from 50 mg per day to 400 mg per day in controlled studies was associated with sustained hypertension, defined as treatment-emergent supine diastolic blood pressure (SDBP)  $\geq 90$  mm Hg and  $\geq 10$  mm Hg above baseline for 3 consecutive on-therapy visits (see Table 8). Analyses of patients in Desvenlafaxine succinate (Pristiq SR) pre-marketing short-term controlled studies who met criteria for sustained hypertension revealed a consistent increase in the proportion of patients who developed sustained hypertension. This was seen at all doses with a suggestion of a higher rate at 400 mg per day.

**Table 8: Proportion of Patients with Sustained Elevation of Supine Diastolic Blood Pressure**

Treatment Group	Proportion of Patients with Sustained Hypertension
Placebo	0.5%
Desvenlafaxine succinate (Pristiq SR) 50 mg per day	1.3%
Desvenlafaxine succinate (Pristiq SR) 100 mg per day	0.7%
Desvenlafaxine succinate (Pristiq SR) 200 mg per day	1.1%
Desvenlafaxine succinate (Pristiq SR) 400 mg per day	2.3%

### ***Orthostatic Hypotension***

In the pre-marketing short-term, placebo-controlled clinical studies with doses of 50 to 400 mg, systolic orthostatic hypotension (decrease  $\geq 30$  mm Hg from supine to standing position) occurred more frequently in patients  $\geq 65$  years of age receiving Desvenlafaxine succinate (Pristiq SR) (8%, 7/87) versus placebo (2.5%, 1/40), compared to patients  $< 65$  years of age receiving Desvenlafaxine succinate (Pristiq SR) (0.9%, 18/1,937) versus placebo (0.7%, 8/1,218).

### **Post-marketing Experience**

The following adverse reaction has been identified during post-approval use of Desvenlafaxine succinate (Pristiq SR). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure:

- Skin and subcutaneous tissue disorders*** – Stevens-Johnson syndrome
- Gastrointestinal disorders*** – Pancreatitis acute

**Cardiovascular system** – Takotsubo cardiomyopathy

## 4.9 Overdose and Treatment

### Human Experience with Overdosage

There is limited clinical trial experience with desvenlafaxine succinate overdosage in humans. However, Desvenlafaxine succinate (Pristiq SR) is the major active metabolite of venlafaxine. Overdose experience reported with venlafaxine (the parent drug of Desvenlafaxine succinate (Pristiq SR)) is presented below.

In post-marketing experience, overdose with venlafaxine (the parent drug of Desvenlafaxine succinate (Pristiq SR)) has occurred predominantly in combination with alcohol and/or other drugs. The most commonly reported events in overdosage include tachycardia, changes in level of consciousness (ranging from somnolence to coma), mydriasis, seizures, and vomiting. Electrocardiogram changes (e.g., prolongation of QT interval, bundle branch block, QRS prolongation), sinus and ventricular tachycardia, bradycardia, hypotension, rhabdomyolysis, vertigo, liver necrosis, serotonin syndrome, and death have been reported.

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

### Management of Overdosage

No specific antidotes for Desvenlafaxine succinate (Pristiq SR) are known. In managing overdosage, consider the possibility of multiple drug involvement.

## 4.10 Abuse and Dependence

### Controlled Substance

Desvenlafaxine succinate (Pristiq SR) is not a controlled substance.

## 5.0 PHARMACOLOGICAL PROPERTIES

### Mechanism of Action

The exact mechanism of the antidepressant action of desvenlafaxine is unknown, but is thought to be related to the potentiation of serotonin and norepinephrine in the central nervous system, through inhibition of their reuptake. Non-clinical studies have shown that desvenlafaxine is a potent and selective SNRI.

## 5.1 Pharmacodynamic Properties

Desvenlafaxine lacked significant affinity for numerous receptors, including muscarinic-cholinergic, H1-histaminergic, or  $\alpha$ 1-adrenergic receptors *in vitro*. Desvenlafaxine also lacked monoamine oxidase (MAO) inhibitory activity.

### ECG changes

Electrocardiograms were obtained from 1,492 desvenlafaxine treated patients with major depressive disorder and 984 placebo-treated patients in clinical studies lasting up to 8 weeks. No clinically relevant differences were observed between desvenlafaxine treated and placebo-treated patients for QT, QTc, PR, and QRS intervals. In a thorough QTc study with prospectively determined criteria, desvenlafaxine did not cause QT prolongation. No difference was observed between placebo and desvenlafaxine treatments for the QRS interval.

## **5.2 Pharmacokinetic Properties**

The single-dose pharmacokinetics of desvenlafaxine are linear and dose-proportional in a dose range of 50 to 600 mg (1 to 12 times the recommended approved dosage) per day. With once-daily dosing, steady-state plasma concentrations are achieved within approximately 4 to 5 days. At steady-state, multiple-dose accumulation of desvenlafaxine is linear and predictable from the single-dose pharmacokinetic profile.

### **Absorption**

The absolute oral bioavailability of Desvenlafaxine succinate (Pristiq SR) after oral administration is about 80%.

### Effect of Food

Ingestion of a high-fat meal, (800 to 1000 calories) increased desvenlafaxine  $C_{max}$  about 16% and had no effect on AUC.

### **Distribution**

Steady state volume of distribution of desvenlafaxine is 3.4 L/kg. Plasma protein binding of desvenlafaxine is 30% and is independent of drug concentration.

### **Elimination**

#### Metabolism

Desvenlafaxine is primarily metabolized by conjugation (mediated by UGT isoforms) and, to a minor extent through oxidative metabolism. CYP3A4 mediates the oxidative metabolism (N-demethylation) of desvenlafaxine. The CYP2D6 metabolic pathway is not involved. The pharmacokinetics of desvenlafaxine was similar in subjects with CYP2D6 poor and extensive metabolizer phenotype.

#### Excretion

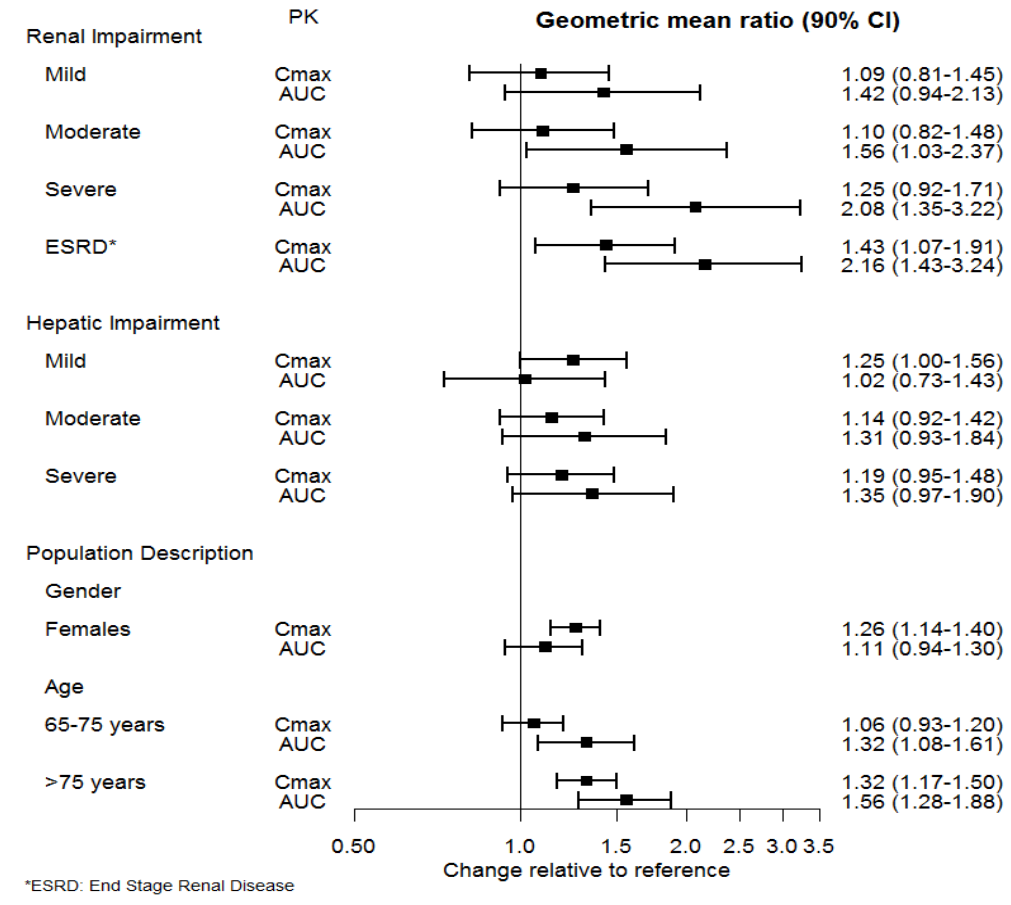
Approximately 45% of desvenlafaxine is excreted unchanged in urine at 72 hours after oral administration. Approximately 19% of the administered dose is excreted as the glucuronide metabolite and <5% as the oxidative metabolite (N,O-didesmethylvenlafaxine) in urine.

### **Specific Populations**

No clinically significant differences in the exposures of desvenlafaxine were observed based on ethnicity (White, Black, Hispanic).

The effect of intrinsic patient factors on the pharmacokinetics of desvenlafaxine is presented in Figure 1.

**Figure 1: Impact of Intrinsic Factors (Renal, Hepatic Impairment and Population Description) on Desvenlafaxine Pharmacokinetics**



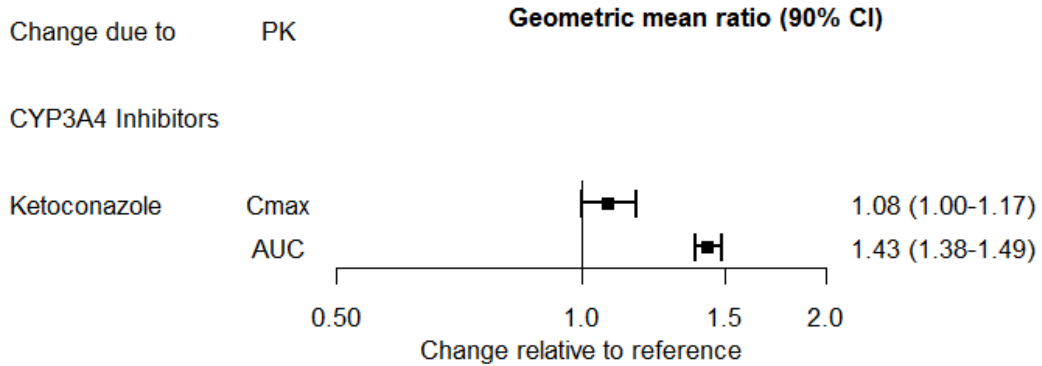
## **Drug Interaction Studies**

### *Clinical Studies*

#### **Other Drugs on Desvenlafaxine Succinate (Pristiq SR)**

The effect of ketoconazole on the exposures of desvenlafaxine is summarized in Figure 2.

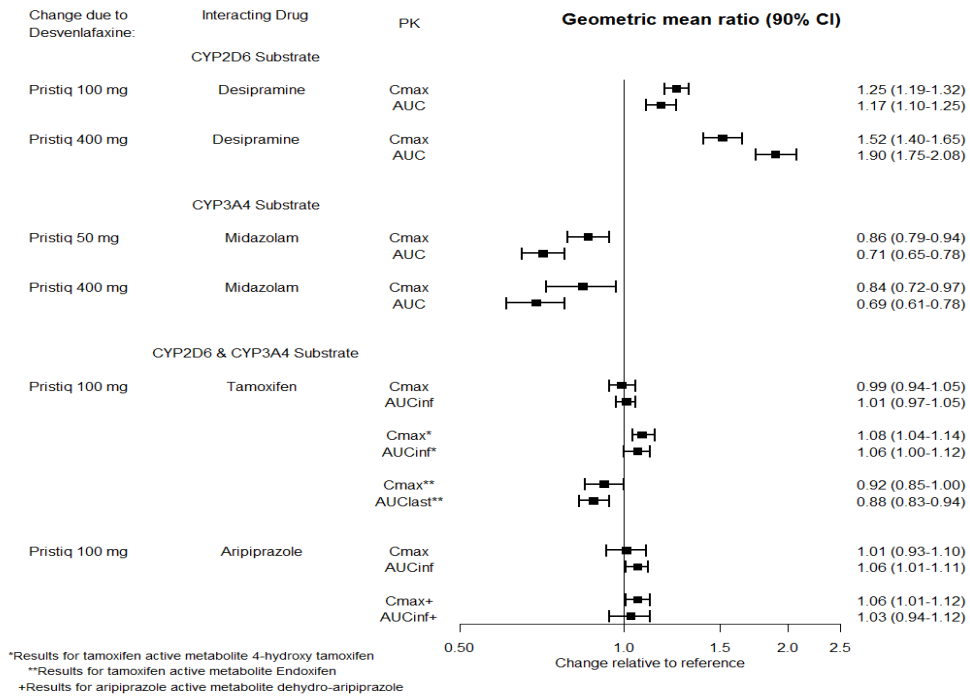
**Figure 2: Effect of Other Drugs on Desvenlafaxine Pharmacokinetics**



**Desvenlafaxine Succinate (Pristiq SR) on Other Drugs**

The effects of Desvenlafaxine succinate (Pristiq SR) on the exposures of other drugs are summarized in Figure 3.

**Figure 3: Effects of Desvenlafaxine Succinate (Pristiq SR) on Pharmacokinetics of Other Drugs**



**In Vitro Studies**

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.

Desvenlafaxine does not inhibit CYP1A2, 2A6, 2C8, 2C9, 2C19, CYP2D6, or CYP3A4 isozymes. Desvenlafaxine does not induce CYP3A4 either.

Desvenlafaxine is not a substrate or an inhibitor for the P-glycoprotein (P-gp) transporter.

### ***Pediatric Use***

The safety and effectiveness of Desvenlafaxine succinate (Pristiq SR) have not been established in pediatric patients for the treatment of MDD.

Efficacy was not demonstrated in two adequate and well controlled, 8-week, randomized, double-blind, placebo-controlled, parallel group studies conducted in 587 patients (7 to 17 years of age) for the treatment of MDD.

Antidepressants, such as Desvenlafaxine succinate (Pristiq SR), increase the risk of suicidal thoughts and behaviors in pediatric patients [see the **Boxed Warning** and **Section 4.4. Special warnings and Precautions for Use**].

Desvenlafaxine succinate (Pristiq SR) was associated with a decrease in body weight in placebo-controlled trials in pediatric patients with MDD. The incidence of weight loss ( $\geq 3.5\%$  of baseline weight) was 22%, 14%, and 7% for patients treated with low dose Desvenlafaxine succinate (Pristiq SR), high dose Desvenlafaxine succinate (Pristiq SR), and placebo, respectively.

The risks associated with longer term Desvenlafaxine succinate (Pristiq SR) use were assessed in 6-month, open-label extension studies in pediatric patients (7 to 17 years of age) with MDD. Pediatric patients (7 to 17 years of age) had mean changes in weight that approximated expected changes, based on data from age- and sex-matched peers.

In clinical trials, when compared to adult patients receiving the same dose of Desvenlafaxine succinate (Pristiq SR), exposure to desvenlafaxine was similar in adolescent patients 12 to 17 years of age, and was about 30% higher in pediatric patients 7 to 11 years of age.

### ***Juvenile Animal Studies***

In a juvenile animal study, male and female rats were treated with desvenlafaxine (75, 225 and 675 mg/kg/day) starting on postnatal day (PND) 22 through 112. Behavioral deficits (longer time immobile in a motor activity test, longer time swimming in a straight channel test, and lack of habituation in an acoustic startle test) were observed in males and females but were reversed after a recovery period. A No Adverse Effect Level (NOAEL) was not identified for these deficits. The Low Adverse Effect Level (LOAEL) was 75 mg/kg/day which was associated with plasma exposure (AUC) twice the levels measured with a pediatric dose of 100 mg/day.

In a second juvenile animal study, male and female rats were administered desvenlafaxine (75, 225 or 675 mg/kg/day) for 8-9 weeks starting on PND 22 and were mated with naïve counterparts. Delays in sexual maturation and decreased fertility, number of implantation sites and total live embryos were observed in treated females at all doses. The LOAEL for these findings is 75 mg/kg/day which was associated with an AUC twice the levels measured with a pediatric dose of 100 mg/day. These findings were reversed at the end of a 4-week recovery period. The relevance of these findings to humans is not known.

### ***Geriatric Use***

Of the 4,158 patients in pre-marketing clinical studies with Desvenlafaxine succinate (Pristiq SR), 6% 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 studies, 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 succinate (Pristiq SR) [see **Section 4.8. Undesirable Effects**]. For elderly patients, possible reduced renal clearance of Desvenlafaxine succinate (Pristiq SR) should be considered when determining dose [see **Sections 4.2 Dosage and Method of Administration**].

SSRIs and SNRIs, including Desvenlafaxine succinate (Pristiq SR), have been associated with cases of clinically significant hyponatremia in elderly patients, who may be at greater risk for this adverse event [see **Section 4.4. Special Warnings and Precautions for Use**].

## **5.3 Preclinical Safety Data**

### **Carcinogenesis, Mutagenesis, Impairment of Fertility**

#### **Carcinogenesis**

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

Mice received desvenlafaxine at dosages up to 500/300 mg/kg/day (dosage lowered after 45 weeks of dosing). The AUC exposure at 300 mg/kg/day dose is estimated at 10 times the AUC exposure at an adult human dose of 100 mg per day.

Rats received desvenlafaxine at dosages up to 300 mg/kg/day (males) or 500 mg/kg/day (females). The AUC exposure at the highest dose is estimated at 11 (males) or 26 (females) times the AUC exposure at an adult human dose of 100 mg per day.

#### **Mutagenesis**

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**

When desvenlafaxine succinate was administered orally to male and female rats, fertility was reduced at the high dose of 300 mg/kg/day, which is 10 (males) and 19 (females) times the AUC exposure at an adult human dose of 100 mg per day. There was no effect on fertility at 100 mg/kg/day, which is 3 (males) or 5 (females) times the AUC exposure at an adult human dose of 100 mg per day. These studies did not address reversibility of the effect on fertility. The relevance of these findings to humans is not known.

## 5.4 Clinical Studies

### Major Depressive Disorder

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

Desvenlafaxine succinate (Pristiq SR) 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 studies and overall improvement, as measured by the Clinical Global Impressions Scale - Improvement (CGI-I), in three of the four studies. In studies directly comparing 50 mg per day and 100 mg per day there was no suggestion of a greater effect with the higher dose and adverse reactions and discontinuations were more frequent at higher doses [see **Section 4.2 Dosage and Method of Administration**].

**Table 9: Primary Efficacy (HAM-D<sub>17</sub>) Results for Short-term Studies**

Study No.	Primary Endpoint: HAM-D <sub>17</sub>	Placebo	Desvenlafaxine succinate (Pristiq SR)			
			50 mg/day	100 mg/day	200 mg/day	400 mg/day
1	Baseline Score (SD <sup>a</sup> )	23.1 (2.5)		23.2 (2.5)	22.9 (2.4)	23.0 (2.2)
	Difference from Placebo (95% CI <sup>c</sup> )			-2.9 <sup>b</sup> (-5.1, -0.8)	-2.0	-3.1 <sup>b</sup> (-5.2, -0.9)
2	Baseline Score (SD <sup>a</sup> )	25.3 (3.3)			24.8 (2.9)	25.2 (3.2)
	Difference from Placebo (95% CI <sup>c</sup> )				-3.3 <sup>b</sup> (-5.3, -1.2)	-2.8 <sup>b</sup> (-4.8, -0.7)
3	Baseline Score (SD <sup>a</sup> )	23.0 (2.6)	23.4 (2.6)	23.4 (2.6)		
	Difference from Placebo (95% CI <sup>c</sup> )		-1.9 <sup>b</sup> (-3.5, -0.3)	-1.5		
4	Baseline Score (SD <sup>a</sup> )	24.3 (2.6)	24.3 (2.4)	24.4 (2.7)		
	Difference from Placebo (95% CI <sup>c</sup> )		-2.5 <sup>b</sup> (-4.1, -0.9)	-3.0 <sup>b</sup> (-4.7, -1.4)		

<sup>a</sup> Standard deviation;

<sup>b</sup> Adjusted p-value <0.05;

<sup>c</sup> Difference between least squares means at final evaluation, calculated as drug response minus placebo response; unadjusted 95% confidence intervals

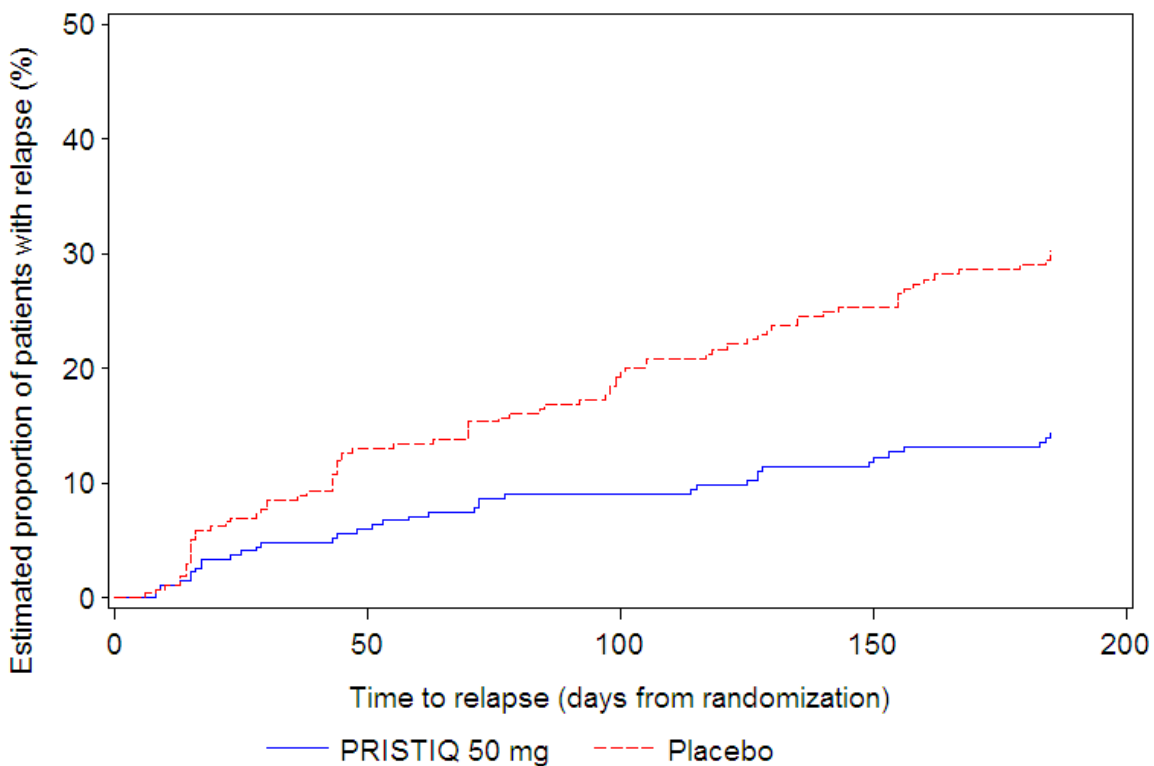
Analyses of the relationships between treatment outcome and age and treatment outcome and gender did not suggest any differential responsiveness on the basis of these patient characteristics. There was insufficient information to determine the effect of race on outcome in these studies.

In a longer-term trial (Study 5), adult outpatients meeting DSM-IV criteria for major depressive disorder, who responded to 8 weeks of open-label acute treatment with 50 mg per day Desvenlafaxine and subsequently remained stable for 12 weeks on Desvenlafaxine, were assigned



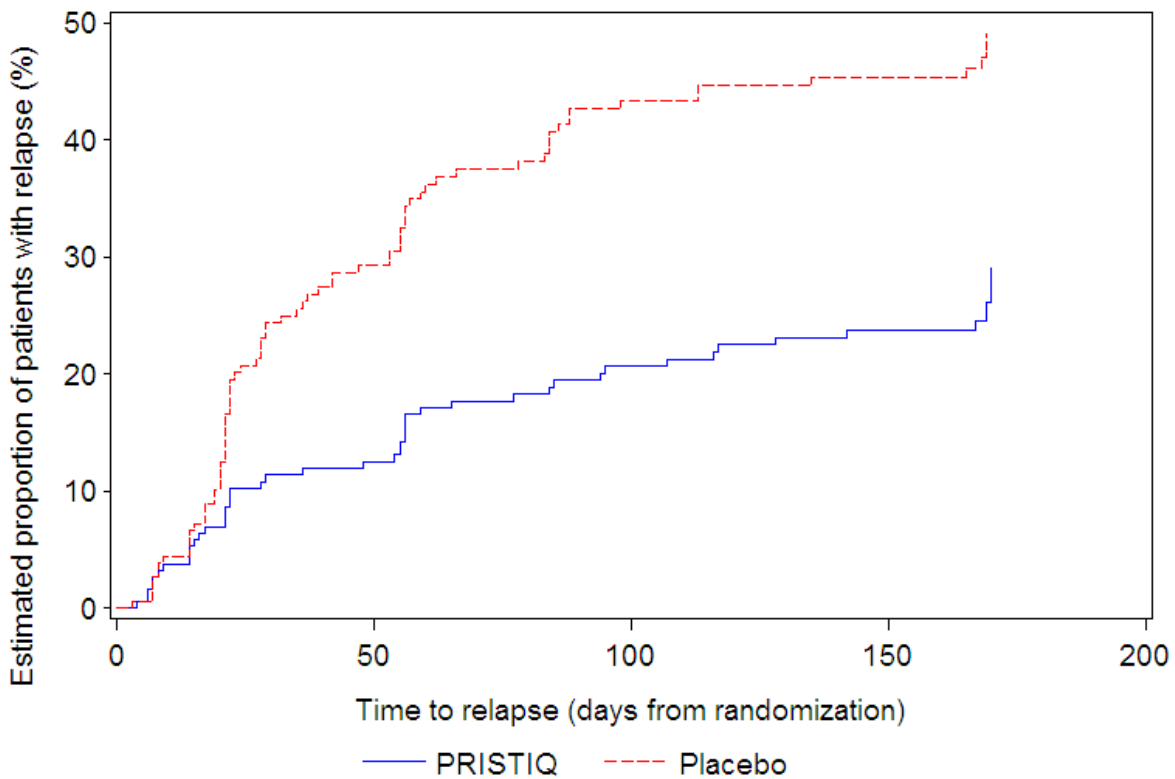
randomly in a double-blind manner to remain on active treatment or switch to placebo for up to 26 weeks of observation for relapse. Response during the open-label phase was defined as a HAM-D<sub>17</sub> total score of  $\leq 11$  and CGI-I  $\leq 2$  at the day 56 evaluation; stability was defined as HAM-D<sub>17</sub> total score of  $\leq 11$  and CGI-I  $\leq 2$  at week 20 and not having a HAM-D<sub>17</sub> total score of  $\geq 16$  or a CGI-I score  $\geq 4$  at any office visit. Relapse during the double-blind phase was defined as follows: (1) a HAM-D<sub>17</sub> total score of  $\geq 16$  at any office visit, (2) discontinuation for unsatisfactory efficacy response, (3) hospitalized for depression, (4) suicide attempt, or (5) suicide. Patients receiving continued Desvenlafaxine treatment experienced statistically significantly longer time to relapse compared with placebo. At 26 weeks, the Kaplan-Meier estimated proportion of relapse was 14% with Desvenlafaxine treatment versus 30% with placebo.

**Figure 4: Estimated Proportion of Relapses vs. Number of Days since Randomization (Study 5)**



In another longer-term trial (Study 6), 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 per day) they had received during acute treatment or to placebo for up to 26 weeks of observation for relapse. Response during the open-label phase was defined as a HAM-D<sub>17</sub> total score of  $\leq 11$  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  $\geq 16$  at any office visit, (2) a CGI-I score of  $\geq 6$  (versus day 84) at any office visit, or (3) discontinuation from the trial due to unsatisfactory response. Patients receiving continued Desvenlafaxine treatment experienced statistically significantly longer time to relapse over the subsequent 26 weeks compared with those receiving placebo. At 26 weeks, the Kaplan-Meier estimated proportion of relapse was 29% with Desvenlafaxine treatment versus 49% with placebo.

**Figure 5: Estimated Proportion of Relapses vs. Number of Days since Randomization (Study 6)**



In a postmarketing study, the efficacy of Desvenlafaxine succinate (Pristiq SR) at a dose lower than 50 mg per day was evaluated in an 8-week, multicenter, randomized, double-blind, placebo-controlled, fixed-dose study in adult outpatients with Major Depressive Disorder. The treatment arms were 25 mg (n=232), 50 mg (n=236), and placebo (n=231). The 50 mg dose was superior to placebo, as measured by the mean change from baseline on the HAMD-17. The 25 mg dose was not superior to placebo.

## 6.0 PHARMACEUTICAL PARTICULARS

### 6.1 Shelf-Life

See outer package for the expiry date of the product.

### 6.2 Storage Condition

Store at temperatures not exceeding 30°C.

### 6.3 Availability

Light pink, square (pyramid, one-sided), film-coated tablet, debossed "W" over "50" on the flat side. Available in Alu/Clear PVDC blister pack x 14 tablets (Boxes of 28's).

## 6.4 Other Information

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

Patients receiving Desvenlafaxine succinate (Pristiq SR) 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.

## 7.0 FDA REGISTRATION NUMBER

50 mg Extended Release Tablet: DR-XY36221

## 8.0 DATE OF FIRST AUTHORIZATION/RENEWAL OF AUTHORIZATION

50 mg Extended Release Tablet: 27 June 2011

Keep out of reach of children.

**For suspected adverse drug reaction, report to FDA: [www.fda.gov.ph](http://www.fda.gov.ph)**

**Seek medical attention immediately at the first sign of any adverse drug reaction.**

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

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