CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-992

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use Pristiq safely and effectively. See full prescribing information for Pristiq.

Pristiq™ (desvenlafaxine) Extended-Release Tablets, oral
Initial U.S. Approval: 2008

WARNING: SUICIDALITY AND ANTIDEPRESSANT DRUGS
See full prescribing information for complete boxed warning.
Increased risk of suicidal thinking and behavior in children, adolescents and young adults taking antidepressants for major depressive disorder (MDD) and other psychiatric disorders. Pristiq is not approved for use in pediatric patients (5.1).

INDICATIONS AND USAGE

Pristiq, a selective serotonin and norepinephrine reuptake inhibitor (SNRI), is indicated for the treatment of major depressive disorder (MDD) (1).

DOSAGE AND ADMINISTRATION

- Recommended dose: 50 mg once daily with or without food (2.1).
- There was no evidence that doses greater than 50 mg/day confer any additional benefit (2.1).
- When discontinuing treatment, gradual dose reduction is recommended whenever possible (2.1 and 5.9).
- Tablets should be taken whole; do not divide, crush, chew, or dissolve (2.1).
- Renal Impairment: The recommended dose in patients with moderate renal impairment is 50 mg/day. The recommended dose in patients with severe renal impairment and end-stage renal disease (ESRD) is 50 mg every other day. The dose should not be escalated in patients with moderate or severe renal impairment or ESRD (2.2).
- Hepatic Impairment: dose escalation above 100 mg/day is not recommended (2.2).

DOSAGE FORMS AND STRENGTHS

Pristiq tablets are available as 50 and 100 mg tablets (3).

Each tablet contains 76 or 152 mg of desvenlafaxine succinate equivalent to 50 or 100 mg of desvenlafaxine, respectively (3).

CONTRAINDICATIONS

- Hypersensitivity to desvenlafaxine succinate, venlafaxine hydrochloride or any excipients in the Pristiq formulation (4.1).
- Do not use with an MAOI or within 14 days of stopping an MAOI. Allow 7 days after stopping Pristiq before starting an MAOI (4.2).

WARNINGS AND PRECAUTIONS

- **Clinical Worsening/Suicide Risk:** Monitor for clinical worsening and suicide risk (5.1).
- **Serotonin Syndrome:** Serotonin syndrome has been reported with SSRIs and SNRIs (5.2).
- **Elevated Blood Pressure**: Has occurred with Pristiq. Hypertension should be controlled before initiating treatment. Monitor blood pressure regularly during treatment (5.3).
- **Abnormal Bleeding:** Pristiq may increase the risk of bleeding events. Patients should be cautioned about the risk of bleeding associated with the concomitant use of Pristiq and NSAIDs, aspirin, or other drugs that affect coagulation (5. 4).
- **Narrow-angle Glaucoma:** Mydriasis has occurred with Pristiq. Patients with raised intraocular pressure or those at risk of angle-closure glaucoma should be monitored (5.5).
- **Activation of Mania/Hypomania:** Has occurred. Use cautiously in patients with Bipolar Disorder. Caution patients about the risk of activation of mania/hypomania (5.6).
- **Cardiovascular/Cerebrovascular Disease:** Use cautiously in patients with cardiovascular or cerebrovascular disease (5.7).
- **Cholesterol and Triglyceride Elevation:** Have occurred. Use cautiously in patients with lipid metabolism disorders. Consider monitoring serum cholesterol and triglyceride (5.8).
- **Discontinuation Symptoms:** Have occurred. Taper the dose when possible and monitor for discontinuation symptoms (5.9).
- **Renal Impairment:** Reduces the clearance of Pristiq. Dosage adjustment is necessary in severe and ESRD. In moderate renal impairment, the dose should not exceed 50 mg/day (5.10).
- **Seizure:** Can occur. Use cautiously in patients with seizure disorder (5.11).
- **Hyponatremia:** Can occur in association with SIADH (5.12).
- **Drugs Containing Desvenlafaxine or Venlafaxine:** Should not be used concomitantly with Pristiq (5.13).
- **Interstitial Lung Disease and Eosinophilic Pneumonia:** Can occur (5.14).

ADVERSE REACTIONS

Adverse reactions in patients in short-term fixed-dose studies (incidence ≥ 5% and 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 (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Wyeth Pharmaceuticals Inc. at 1-800-934-5556 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

USE IN SPECIFIC POPULATIONS

- Dosage adjustment is recommended in patients with severe renal impairment and end-stage renal disease. The dose should not be escalated in moderate to severe impairment or in ESRD (2.2, 8.6 and 12.6).
- For elderly patients, the possibility of reduced renal clearance of desvenlafaxine should be considered when determining dose (2.2).
- Only administer Pristiq to pregnant or breastfeeding women if the expected benefits outweigh the possible risks (8.1 and 8.3).

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: [m/year]

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FULL PRESCRIBING INFORMATION:

WARNING: SUICIDALITY AND ANTIDEPRESSANT DRUGS

Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of Major Depressive Disorder (MDD) and other psychiatric disorders. Anyone considering the use of Pristiq or any other antidepressant in a child, adolescent, or young adult must balance this risk with the clinical need. 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 in risk with antidepressants compared to placebo in adults aged 65 and older. Depression and certain other psychiatric disorders are themselves associated with increases in the risk of suicide. Patients of all ages who are started on antidepressant therapy should be monitored appropriately and observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. Pristiq is not approved for use in pediatric patients [*see Warnings and Precautions (5.1), Use in Specific Populations (8.4), and Patient Counseling Information (17.1)*].

1 INDICATIONS AND USAGE

Pristiq, a selective serotonin and norepinephrine reuptake inhibitor (SNRI), is indicated for the treatment of major depressive disorder (MDD) [*see Clinical Studies (14) and Dosage and Administration (2.1)*]. The efficacy of Pristiq has been established in four 8-week, placebo-controlled studies of outpatients who met DSM-IV criteria for major depressive disorder.

A major depressive episode (DSM-IV) implies a prominent and relatively persistent (nearly every day for at least 2 weeks) depressed or dysphoric mood that usually interferes with daily functioning, and includes at least 5 of the following 9 symptoms: depressed mood, loss of interest in usual activities, significant change in weight and/or appetite, insomnia or hypersomnia, psychomotor agitation or retardation, increased fatigue, feelings of guilt or worthlessness, slowed thinking or impaired concentration, or a suicide attempt or suicidal ideation.

2 DOSAGE AND ADMINISTRATION

2.1 Initial Treatment of Major Depressive Disorder

The recommended dose for Pristiq is 50 mg once daily, with or without food. In clinical studies, doses of 50-400 mg/day were shown to be effective, although no additional benefit was demonstrated at doses greater than 50 mg/day and adverse events and discontinuations were more frequent at higher doses.

When discontinuing therapy, gradual dose reduction is recommended whenever possible to minimize discontinuation symptoms [*see Dosage and Administration (2.4) and Warnings and Precautions (5.9)*].

Pristiq should be taken at approximately the same time each day. Tablets must be swallowed whole with fluid and not divided, crushed, chewed, or dissolved.

2.2 Special Populations

Pregnant women during the third trimester

Neonates exposed to SNRIs or SSRIs late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding [*see Use in Specific Populations (8.1)*]. When treating pregnant women with Pristiq during the third trimester, the physician should carefully consider the potential risks and benefits of treatment. The physician may consider tapering Pristiq in the third trimester.

Patients with renal impairment

No dosage adjustment is necessary in patients with mild renal impairment (24-hr CrCl = 50-80 mL/min).

The recommended dose in patients with moderate renal impairment (24-hr CrCl = 30-50 mL/min) is 50 mg per day. The recommended 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. Supplemental doses should not be given to patients after dialysis [*see Use in Specific Populations (8.6) and Clinical Pharmacology (12.6)*].

Patients with hepatic impairment

No adjustment of the starting dosage is necessary for patients with hepatic impairment. However, dose escalation above 100 mg/day is not recommended *[see Clinical Pharmacology (12.6)]*.

Elderly patients

No dosage adjustment is required solely on the basis of age; however, the possibility of reduced renal clearance of Pristiq should be considered when determining the dose [*see Use in Specific Populations (8.5) and Clinical Pharmacology (12.6)*].

2.3 Maintenance/continuation/extended Treatment

It is generally agreed that acute episodes of major depressive disorder require several months or longer of sustained pharmacologic therapy. However, the longer-term efficacy of Pristiq at the dose of 50 mg/day that was effective in short-term, controlled studies has not been studied. Patients should be periodically reassessed to determine the need for continued treatment.

2.4 Discontinuing Pristiq

Symptoms associated with discontinuation of Pristiq, other SNRIs and SSRIs have been reported [*see Warnings and Precautions (5.9)*]. Patients should be monitored for these symptoms

when discontinuing treatment. A gradual reduction in the dose (by giving 50 mg of Pristiq less frequently) 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.

2.5 Switching Patients To or From a Monoamine Oxidase Inhibitor (MAOI)

At least 14 days must elapse between discontinuation of an MAOI and initiation of therapy with Pristiq. In addition, at least 7 days must be allowed after stopping Pristiq before starting an MAOI [*see Contraindications (4.2)*].

3 DOSAGE FORMS AND STRENGTHS

Pristiq™ (desvenlafaxine) Extended-Release Tablets are available as 50 and 100 mg tablets.

50 mg, light pink, square pyramid tablet debossed with "W" over "50" on the flat side

100 mg, reddish-orange, square pyramid tablet debossed with "W" over "100" on the flat side

4 CONTRAINDICATIONS

4.1 Hypersensitivity

Hypersensitivity to desvenlafaxine succinate, venlafaxine hydrochloride or to any excipients in the Pristiq formulation.

4.2 Monoamine Oxidase Inhibitors

Pristiq must not be used concomitantly in patients taking monoamine oxidase inhibitors (MAOIs) or in patients who have taken MAOIs within the preceding 14 days due to the risk of serious, sometimes fatal, drug interactions with SNRI or SSRI treatment or with other serotonergic drugs. These interactions have been associated with symptoms that include tremor, myoclonus, diaphoresis, nausea, vomiting, flushing, dizziness, hyperthermia with features resembling neuroleptic malignant syndrome, seizures, rigidity, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes that include extreme agitation progressing to delirium and coma. Based on the half-life of desvenlafaxine, at least 7 days should be allowed after stopping Pristiq before starting an MAOI [*see Dosage and Administration (2.5)*].

5 WARNINGS AND PRECAUTIONS

5.1 Clinical Worsening and Suicide Risk

Patients with major depressive disorder (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 18-24) 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 1000 patients treated) are provided in Table 1.

Table 1

Age Range	Drug-Placebo Difference in Number of Cases of Suicidality per 1000 Patients Treated
	Increases Compared to Placebo
<18	14 additional cases
18-24	5 additional cases
	Decreases Compared to Placebo
25-64	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 nonpsychiatric. 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 Warnings and Precautions (5.9) and Dosage and Administration (2.3)*] for a description of the risks of discontinuation of Pristiq.

Families and caregivers of patients being treated with antidepressants for major depressive disorder or other indications, both psychiatric and nonpsychiatric, 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 health care providers. Such monitoring should include daily observation by families and caregivers. Prescriptions for Pristiq 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 Pristiq is not approved for use in treating bipolar depression.

5.2 Serotonin Syndrome

The development of a potentially life-threatening serotonin syndrome may occur with Pristiq treatment, particularly with concomitant use of other serotonergic drugs (including SSRIs, SNRIs and triptans) and with drugs that impair metabolism of serotonin (including MAOIs).

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).

The concomitant use of Pristiq and MAOIs is contraindicated [*see Contraindications (4.2)*].

If concomitant treatment with Pristiq and an SSRI, another 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 Pristiq with serotonin precursors (such as tryptophan supplements) is not recommended.

5.3 Elevated Blood Pressure

Patients receiving Pristiq should have regular monitoring of blood pressure since sustained increases in blood pressure were observed in clinical studies. Pre-existing hypertension should be controlled before initiating treatment with Pristiq. Caution should be exercised in treating patients with pre-existing hypertension or other underlying conditions that might be compromised by increases in blood pressure. Cases of elevated blood pressure requiring immediate treatment have been reported with Pristiq.

Sustained hypertension

Sustained blood pressure increases could have adverse consequences. For patients who experience a sustained increase in blood pressure while receiving Pristiq, either dose reduction or discontinuation should be considered [*see Adverse Reactions (6.1)*]. Treatment with Pristiq at all doses from 50 mg/day to 400 mg/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 2). Analyses of patients in Pristiq controlled studies who met criteria for sustained hypertension revealed a consistent increase in the proportion of subjects who developed sustained hypertension. This was seen at all doses with a suggestion of a higher rate at 400 mg/day.

Table 2: Proportion of Patients with Sustained Elevation of Supine Diastolic Blood Pressure

Treatment Group	Proportion of Patients with Sustained Hypertension
Placebo	0.5%
Pristiq 50 mg/day	1.3%
Pristiq 100 mg/day	0.7%
Pristiq 200 mg/day	1.1%
Pristiq 400 mg/day	2.3%

5.4 Abnormal Bleeding

SSRIs and SNRIs, including Pristiq, may increase the risk of bleeding events. Concomitant use of aspirin, , nonsteroidal 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. Patients should be cautioned about the risk of bleeding associated with the concomitant use of Pristiq and NSAIDs, aspirin, or other drugs that affect coagulation or bleeding.

5.5 Narrow-angle Glaucoma

Mydriasis has been reported in association with Pristiq; therefore, patients with raised intraocular pressure or those at risk of acute narrow-angle glaucoma (angle-closure glaucoma) should be monitored.

5.6 Activation of Mania/Hypomania

During all MDD and VMS (vasomotor symptoms) phase 2 and phase 3 studies, mania was reported for approximately 0.1% of patients treated with Pristiq. 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, Pristiq should be used cautiously in patients with a history or family history of mania or hypomania.

5.7 Cardiovascular/Cerebrovascular Disease

Caution is advised in administering Pristiq to patients with cardiovascular, cerebrovascular, or lipid metabolism disorders [*see Adverse Reactions (6.1)*]. Increases in blood pressure and small increases in heart rate were observed in clinical studies with Pristiq. Pristiq 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 studies.

5.8 Serum Cholesterol and Triglyceride Elevation

Dose-related elevations in fasting serum total cholesterol, LDL (low density lipoprotein) cholesterol, and triglycerides were observed in the controlled studies. Measurement of serum lipids should be considered during treatment with Pristiq [*see Adverse Reactions (6.1)*].

5.9 Discontinuation of Treatment with Pristiq

Discontinuation symptoms have been systematically and prospectively evaluated in patients treated with Pristiq during clinical studies in Major Depressive Disorder. Abrupt discontinuation or dose reduction has been associated with the appearance of new symptoms that include dizziness, nausea, headache, irritability, insomnia, diarrhea, anxiety, fatigue, abnormal dreams, and hyperhidrosis. In general, discontinuation events occurred more frequently with longer duration of therapy.

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., paresthesia, 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.

Patients should be monitored for these symptoms when discontinuing treatment with Pristiq. 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 Dosage and Administration (2.4) and Adverse Reactions (6.1)*].

5.10 Renal Impairment

In patients with moderate or severe renal impairment or end-stage renal disease (ESRD) the clearance of Pristiq was decreased, thus prolonging the elimination half-life of the drug. As a result, there were potentially clinically significant increases in exposures to Pristiq [*see Clinical Pharmacology (12.6)*]. Dosage adjustment (50 mg every other day) is necessary in patients with severe renal impairment or ESRD. The doses should not be escalated in patients with moderate or severe renal impairment or ESRD [*see Dosage and Administration (2.2)*].

5.11 Seizure

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

5.12 Hyponatremia

Hyponatremia may occur as a result of treatment with SSRIs and SNRIs, including Pristiq. 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 Use in Specific Populations (8.5) and Clinical Pharmacology (12.6)*]. Discontinuation of Pristiq 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.

5.13 Co-administration of Drugs Containing Desvenlafaxine and Venlafaxine

Desvenlafaxine is the major active metabolite of venlafaxine. Products containing desvenlafaxine and products containing venlafaxine should not be used concomitantly with Pristiq.

5.14 Interstitial Lung Disease and Eosinophilic Pneumonia

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

6 ADVERSE REACTIONS

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

- Hypersensitivity [*see Contraindications (4.1)*]
- Effects on blood pressure [*see Warnings and Precautions (5.3)*]
- Abnormal bleeding [*see Warnings and Precautions (5.4)*]
- Mydriasis [*see Warnings and Precautions (5.5)*]
- Hypomania and mania [*see Warnings and Precautions (5.6)*]
- Serum cholesterol and triglyceride elevation [*see Warnings and Precautions (5.8)*]
- Seizure [*see Warnings and Precautions (5.11)*]

6.1 Clinical Studies Experience

The most commonly observed adverse reactions in Pristiq-treated MDD patients in short-term fixed-dose studies (incidence ≥ 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.

Adverse reactions reported as reasons for discontinuation of treatment

Combined across 8-week placebo-controlled pre-marketing studies for major depressive disorder, 12% of the 1,834 patients who received Pristiq (50-400 mg) discontinued treatment due to an adverse experience, compared with 3% of the 636 placebo-treated patients in those studies. At the recommended dose of 50 mg, the discontinuation rate due to an adverse experience for Pristiq (4.1%) was similar to the rate for placebo (3.8%). For the 100 mg dose of Pristiq the discontinuation rate due to an adverse experience was 8.7%.

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

Patient exposure

Pristiq was evaluated for safety in 3,292 patients diagnosed with major depressive disorder who participated in multiple-dose pre-marketing studies, representing 1,289 patient-years of exposure. Among these 3,292 Pristiq-treated patients, 1,834 patients were exposed to Pristiq in 8-week, placebo-controlled studies at doses ranging from 50 to 400 mg/day. Out of the 1,834

patients, 687 Pristiq-treated patients continued into a 10-month open-label study. Of the total 3,292 patients exposed to at least one dose of Pristiq, 1,070 were exposed to Pristiq for 6 months, representing 842 patient-years of exposure, and 274 were exposed for one year, representing 241 patient-years of exposure.

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

Common adverse reactions in placebo-controlled MDD studies

Table 3 shows the incidence of common adverse reactions that occurred in ≥ 2% of Pristiq-treated MDD patients at any dose in the 8-week, placebo-controlled, fixed dose, pre-marketing clinical studies. In general, the adverse reactions were most frequent in the first week of treatment.

Table 3: Common Adverse Reactions: Percentage of Patients (≥ 2% in any Fixed-Dose Group) in MDD 8-Week Placebo-Controlled Studies[a]

	Percentage of Patients Reporting Reaction				
		Pristiq			
System Organ Class **Preferred Term**	**Placebo**	**50 mg**	**100 mg**	**200 mg**	**400 mg**
Cardiac disorders					
Palpitations	2	1	3	2	3
Tachycardia	1	1	<1	1	2
Blood pressure increased	1	1	1	2	2
Gastrointestinal disorders					
Nausea	10	22	26	36	41
Dry mouth	9	11	17	21	25
Diarrhea	9	11	9	7	5
Constipation	4	9	9	10	14
Vomiting	3	3	4	6	9
General disorders and administration site conditions					
Fatigue	4	7	7	10	11
Chills	1	1	<1	3	4
Feeling jittery	1	1	2	3	3
Asthenia	1	1	2	1	1
Metabolism and nutrition disorders					
Decreased appetite	2	5	8	10	10
Weight decreased	1	2	1	1	2
Nervous system disorders					
Dizziness	5	13	10	15	16

Table 3: Common Adverse Reactions: Percentage of Patients (≥ 2% in any Fixed-Dose Group) in MDD 8-Week Placebo-Controlled Studies[a]

System Organ Class Preferred Term	Percentage of Patients Reporting Reaction				
		Pristiq			
	Placebo	50 mg	100 mg	200 mg	400 mg
Somnolence	4	4	9	12	12
Headache	23	20	22	29	25
Tremor	2	2	3	9	9
Paraesthesia	1	2	2	1	3
Disturbance in attention	<1	<1	1	2	1
Psychiatric disorders					
Insomnia	6	9	12	14	15
Anxiety	2	3	5	4	4
Nervousness	1	<1	1	2	2
Irritability	1	2	2	2	2
Abnormal dreams	1	2	3	2	4
Renal and urinary disorders					
Urinary hesitation	0	<1	1	2	2
Respiratory, thoracic and mediastinal disorders					
Yawning	<1	1	1	4	3
Skin and subcutaneous tissue disorders					
Hyperhidrosis	4	10	11	18	21
Rash	<1	1	1	2	<1
Special Senses					
Vision blurred	1	3	4	4	4
Mydriasis	<1	2	2	6	6
Tinnitus	1	2	1	1	2
Dysguesia	1	1	1	1	2
Vascular disorders					
Hot flush	<1	1	1	2	2

a: Percentage based on the number of patients (placebo, n = 636; Pristiq 50 mg, n = 317; Pristiq 100 mg, n = 424; Pristiq 200 mg, n = 307; Pristiq 400 mg, n = 317).

Sexual function adverse reactions

Table 4 shows the incidence of sexual function adverse reactions that occurred in ≥ 2% of Pristiq-treated MDD patients in any fixed-dose group (8-week, placebo-controlled, fixed and flexible-dose, pre-marketing clinical studies).

Table 4: Sexual Function Disorders: Adverse Reactions (≥ 2% in Men[a] or Women[b] in any Pristiq Group) During the On-Therapy Period

System Organ Class Preferred Term	Placebo	Pristiq 50 mg	Pristiq 100 mg	Pristiq 200 mg	Pristiq 400 mg
Men only					
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
Women only					
Anorgasmia	0	1	1	0	3

a: Percentage based on the number of men (placebo, n = 239; Pristiq 50 mg, n = 108; Pristiq 100 mg, n = 157; Pristiq 200 mg, n = 131; Pristiq 400 mg, n = 154).
b: Percentage based on the number of women (placebo, n = 397; Pristiq 50 mg, n = 209; Pristiq 100 mg, n = 267; Pristiq 200 mg, n = 176; Pristiq 400 mg, n = 163).

Other adverse reactions observed in pre-marketing clinical studies

Other infrequent adverse reactions, not described elsewhere, occurring at an incidence of < 2% in MDD patients treated with Pristiq were:

Immune system disorders – Hypersensitivity.

Investigations – Liver function test abnormal, blood prolactin increased.

Nervous system disorders – Convulsion, syncope, extrapyramidal disorder.

Psychiatric disorders – Depersonalization, hypomania.

Respiratory, thoracic and mediastinal disorders – Epistaxis.

Vascular disorders – Orthostatic hypotension.

In clinical studies, 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 Pristiq treatment as compared to placebo [*see Warnings and Precautions (5.7)*].

Discontinuation events

Adverse events reported in association with abrupt discontinuation, dose reduction or tapering of treatment in MDD clinical studies at a rate of ≥ 5% include: dizziness, nausea, headache, irritability, insomnia, diarrhea, anxiety, abnormal dreams, fatigue, and hyperhidrosis. In general, discontinuation events occurred more frequently with longer duration of therapy [*see Dosage and Administration (2.4) and Warnings and Precautions (5.9)*].

Laboratory, ECG and vital sign changes observed in MDD clinical studies

The following changes were observed in placebo-controlled, short term, pre-marketing MDD studies with Pristiq.

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 [*see Warnings and Precautions (5.8)*].

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*

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

Proteinuria

Proteinuria, greater than or equal to trace, was observed in the 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

		Pristiq			
	Placebo	**50 mg**	**100 mg**	**200 mg**	**400 mg**
Proteinuria	4	6	8	5	7

ECG changes

Electrocardiograms were obtained from 1,492 Pristiq-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 Pristiq-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.

Vital sign changes

Table 7 summarizes the changes that were observed in placebo-controlled, short-term, pre-marketing studies with Pristiq 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

		Pristiq			
	Placebo	**50 mg**	**100 mg**	**200 mg**	**400 mg**
Blood pressure					
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
Pulse rate					
Supine pulse (bpm)	-0.3	1.3	1.3	0.9	4.1
Weight (kg)	0.0	-0.4	-0.6	-0.9	-1.1

At the final on-therapy assessment in the 6-month, double-blind, placebo-controlled phase of a long-term study in patients who had responded to Pristiq during the initial 12-week, open-label phase, there was no statistical difference in mean weight change between Pristiq- and placebo-treated patients.

7 DRUG INTERACTIONS

7.1 Central Nervous System (CNS)-Active Agents

The risk of using Pristiq in combination with other CNS-active drugs has not been systematically evaluated. Consequently, caution is advised when Pristiq is taken in combination with other CNS-active drugs [*see Warnings and Precautions (5.13)*].

7.2 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 Pristiq (SNRIs or SSRIs), or who have recently had SNRI or SSRI therapy discontinued prior to initiation of an MAOI [*see Contraindications (4.2)*].

7.3 Serotonergic Drugs

Based on the mechanism of action of Pristiq and the potential for serotonin syndrome, caution is advised when Pristiq is co-administered with other drugs that may affect the serotonergic neurotransmitter systems [*see Warnings and Precautions (5.2)*].

7.4 Drugs that Interfere with Hemostasis (e.g., NSAIDs, Aspirin, and Warfarin)

Serotonin release by platelets plays an important role in hemostasis. Epidemiological studies of case-control and cohort design that have demonstrated an association between use of psychotropic drugs that interfere with serotonin reuptake and the occurrence of upper gastrointestinal bleeding. These studies have also shown that concurrent use of an NSAID or aspirin may potentiate this risk of bleeding. Altered anticoagulant effects, including increased bleeding, have been reported when SSRIs and SNRIs are coadministered with warfarin. Patients receiving warfarin therapy should be carefully monitored when Pristiq is initiated or discontinued.

7.5 Ethanol

A clinical study 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 Pristiq.

7.6 Potential for Other Drugs to Affect Desvenlafaxine

Inhibitors of CYP3A4 (ketoconazole)

CYP3A4 is a minor pathway for the metabolism of Pristiq. In a clinical study, ketoconazole (200 mg BID) increased the area under the concentration vs. time curve AUC of Pristiq (400 mg single dose) by about 43% and C_{max} by about 8%. Concomitant use of Pristiq with potent inhibitors of CYP3A4 may result in higher concentrations of Pristiq.

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 Pristiq.

7.7 Potential for Desvenlafaxine to Affect Other Drugs

Drugs metabolized by CYP2D6 (desipramine)

In vitro studies showed minimal inhibitory effect of desvenlafaxine on CYP2D6.

Clinical studies have shown that desvenlafaxine does not have a clinically relevant effect on CYP2D6 metabolism at the 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 C_{max} and AUC of desipramine increased approximately 25% and 17%,

respectively. When 400 mg (8 times the recommended 50 mg dose) was administered, the C_{max} and AUC of desipramine increased approximately 50% and 90%, respectively. Concomitant use of desvenlafaxine with a drug metabolized by CYP2D6 can result in higher concentrations of that drug.

Drugs metabolized by CYP3A4 (midazolam)

In vitro, desvenlafaxine does not inhibit or induce the CYP3A4 isozyme.

In a clinical study, Pristiq 400 mg daily (8 times the recommended 50 mg dose) was co-administered with a single 4 mg dose of midazolam (a CYP3A4 substrate). The AUC and C_{max} of midazolam decreased by approximately 31% and 16%, respectively. Concomitant use of Pristiq with a drug metabolized by CYP3A4 can result in lower exposures to that drug.

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.

7.8 P-glycoprotein Transporter

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

The pharmacokinetics of Pristiq are unlikely to be affected by drugs that inhibit the P-glycoprotein transporter, and desvenlafaxine is not likely to affect the pharmacokinetics of drugs that are substrates of the P-glycoprotein transporter.

7.9 Electroconvulsive Therapy

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

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

Teratogenic effects – Pregnancy Category C

When desvenlafaxine succinate 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 10 times a human dose of 100 mg/day (on a mg/m^2 basis) in rats, and up to 15 times the a human dose of 100 mg/day (on a mg/m^2 basis) in rabbits. However, fetal weights were decreased in rats, with a no-effect dose 10 times a human dose of 100 mg/day (on a mg/m^2 basis).

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. The cause of these deaths is not known. The no-effect dose for rat pup

mortality was 10 times a human dose of 100 mg/day (on a mg/m^2 basis). Post-weaning growth and reproductive performance of the progeny were not affected by maternal treatment with desvenlafaxine at a dose 29 times a human dose of 100 mg/day (on a mg/m^2 basis).

There are no adequate and well-controlled studies of Pristiq in pregnant women. Therefore, Pristiq should be used during pregnancy only if the potential benefits justify the potential risks.

Non-teratogenic effects

Neonates exposed to SNRIs (Serotonin and Norepinephrine Reuptake Inhibitors), or SSRIs (Selective Serotonin Reuptake Inhibitors), 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 Warnings and Precautions (5.2)*]. When treating a pregnant woman with Pristiq during the third trimester, the physician should carefully consider the potential risks and benefits of treatment [*see Dosage and Administration (2.2)*].

8.2 Labor and Delivery

The effect of Pristiq on labor and delivery in humans is unknown. Pristiq should be used during labor and delivery only if the potential benefits justify the potential risks.

8.3 Nursing Mothers

Desvenlafaxine (O-desmethylvenlafaxine) is excreted in human milk. Because of the potential for serious adverse reactions in nursing infants from Pristiq, 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 Pristiq to breastfeeding women if the expected benefits outweigh any possible risk.

8.4 Pediatric Use

Safety and effectiveness in the pediatric population have not been established [*see Box Warning* and *Warnings and Precautions (5.1)*]. Anyone considering the use of Pristiq in a child or adolescent must balance the potential risks with the clinical need.

8.5 Geriatric Use

Of the 3,292 patients in clinical studies with Pristiq, 5% were 65 years of age or older. No overall differences in safety or efficacy were observed between these patients and younger patients, but greater sensitivity of some older individuals cannot be ruled out. For elderly patients, possible reduced renal clearance of desvenlafaxine should be considered when determining dose [*see Dosage and Administration (2.2) and Clinical Pharmacology (12.6)*]. If Pristiq is poorly tolerated, every other day dosing can be considered.

SSRIs and SNRIs, including Pristiq, have been associated with cases of clinically significant hyponatremia in elderly patients, who may be at greater risk for this adverse event (see PRECAUTIONS, Hyponatremia).

8.6 Renal Impairment

In subjects with renal impairment the clearance of Pristiq was decreased. In subjects with severe renal impairment (24-hr CrCl < 30 mL/min) and end-stage renal disease, elimination half-lives were significantly prolonged, increasing exposures to Pristiq; therefore, dosage adjustment is recommended in these patients [*see Dosage and Administration (2.2) and Clinical Pharmacology (12.6)*].

8.7 Hepatic Impairment

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. No adjustment in starting dosage is necessary for patients with hepatic impairment.

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

Desvenlafaxine is not a controlled substance.

9.2 Abuse and Dependence

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

10 OVERDOSAGE

10.1 Human Experience with Overdosage

There is limited clinical experience with desvenlafaxine succinate overdosage in humans. In pre-marketing clinical studies, no cases of fatal acute overdose of desvenlafaxine were reported.

Among the patients included in the MDD pre-marketing studies of Pristiq, there were four adults who ingested 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. The adverse reactions reported within 5 days of an overdose > 600 mg that were possibly related to Pristiq included: headache, vomiting, agitation, dizziness, nausea, constipation, diarrhea, dry mouth, paresthesia, and tachycardia.

Desvenlafaxine (Pristiq) is the major active metabolite of venlafaxine. Overdose experience reported with venlafaxine (the parent drug of Pristiq) is presented below; the identical information can be found in the *Overdosage* section of the venlafaxine package insert.

In postmarketing experience, overdose with venlafaxine (the parent drug of Pristiq) 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.

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

10.2 Management of Overdosage

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.

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. No specific antidotes for desvenlafaxine are known.

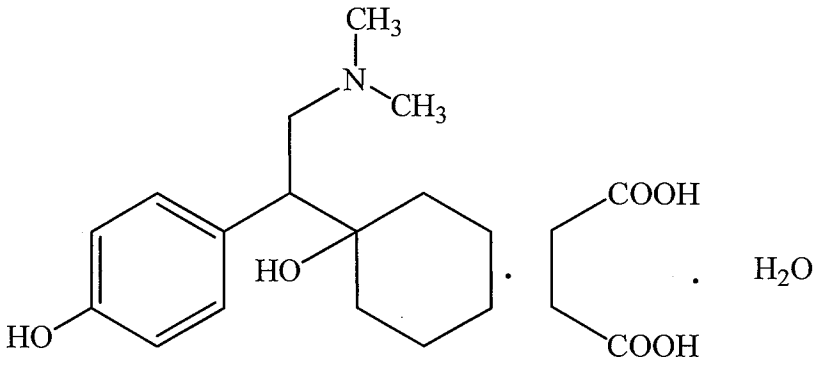
In managing an overdose, consider the possibility of multiple drug involvement. The physician should consider contacting a poison control center for additional information on the treatment of any overdose. Telephone numbers for certified poison control centers are listed in the Physicians Desk Reference (PDR®).

11 DESCRIPTION

Pristiq 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, generalized anxiety, social anxiety and panic disorders.

Desvenlafaxine is designated *RS*-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.

Pristiq is formulated as an extended-release tablet for once-a-day oral administration.

Each tablet contains 76 or 152 mg of desvenlafaxine succinate equivalent to 50 or 100 mg of desvenlafaxine, respectively.

Inactive ingredients consist of hypromellose, microcrystalline cellulose, talc, magnesium stearate and film coating, which consists of sodium carboxymethylcellulose, maltodextrin, dextrose, titanium dioxide, stearic acid and iron oxide(s).

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Non-clinical studies have shown that desvenlafaxine succinate is a potent and selective serotonin and norepinephrine reuptake inhibitor (SNRI). The clinical efficacy of desvenlafaxine succinate is thought to be related to the potentiation of these neurotransmitters in the central nervous system.

12.2 Pharmacodynamics

Desvenlafaxine lacked significant affinity for numerous receptors, including muscarinic-cholinergic, H1-histaminergic, or α_1-adrenergic receptors *in vitro*. Pristiq also lacked monoamine oxidase (MAO) inhibitory activity.

12.3 Pharmacokinetics

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.

12.4 Absorption and Distribution

The absolute oral bioavailability of Pristiq after oral administration is about 80%. Mean time to peak plasma concentrations (T_{max}) is about 7.5 hours after oral administration.

A food-effect study involving administration of Pristiq 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, Pristiq can be taken without regard to meals [*see Dosage and Administration (2.1)*].

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

12.5 Metabolism and Elimination

Desvenlafaxine is primarily metabolized by conjugation (mediated by UGT isoforms) and, to a minor extent, through oxidative metabolism. CYP3A4 is the cytochrome P450 isozyme mediating the oxidative metabolism (N-demethylation) of desvenlafaxine. The CYP2D6 metabolic pathway is not involved, and after administration of 100 mg, the pharmacokinetics of desvenlafaxine was similar in subjects with CYP2D6 poor and extensive metabolizer phenotype. 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.

12.6 Special Populations

Age

In a study of healthy subjects administered doses of up to 300 mg, there was an approximate 32% increase in C_{max} and a 55% increase in AUC in subjects older than 75 years of age (n = 17), compared with subjects 18 to 45 years of age (n = 16). Subjects 65 to 75 years of age (n = 15) had no change in C_{max}, but an approximately 32% increase in AUC, compared to subjects 18 to 45 years of age [*see Dosage and Administration (2.2)*].

Gender

In a study of healthy subjects administered doses up to of 300 mg, women had an approximately 25% higher C_{max} and an approximately 10% higher AUC than age-matched men. No adjustment of dosage on the basis of gender is needed.

Race

Pharmacokinetic analysis showed that race (White, n = 466; Black, n = 97; Hispanic, n = 39; Other, n = 33) had no apparent effect on the pharmacokinetics of Pristiq. No adjustment of dosage on the basis of race is needed.

Hepatic insufficiency

The disposition of desvenlafaxine succinate after administration of 100 mg was 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 to 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 similar 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. No adjustment in starting dosage is necessary for patients with hepatic impairment.

Renal insufficiency

The disposition of desvenlafaxine after administration of 100 mg was studied in subjects with mild (n = 9), moderate (n = 8), severe (n = 7) and end-stage renal disease (ESRD) (n = 9) requiring dialysis and in healthy, age-matched control subjects (n = 8). Elimination was significantly correlated with creatinine clearance. Increases in AUCs of about 42% in mild renal impairment (24-hr CrCl = 50-80 mL/min), about 56% in moderate renal impairment (24-hr CrCl = 30-50 mL/min), about 108% in severe renal impairment (24-hr CrCl $\leq$ 30 mL/min), and about 116% in ESRD subjects were observed, compared with healthy, age-matched control subjects.

The mean terminal half-life ($t_{1/2}$) was prolonged from 11.1 hours in the control subjects to approximately 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.

Dosage adjustment (every other day dosing) is recommended in patients with significant impairment of renal function [*see Dosage and Administration (2.2) and Use in Specific Populations (8.6)*].

13 NONCLINICAL TOXICOLOGY

13.1 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 succinate at dosages up to 500/300 mg/kg/day (dosage lowered after 45 weeks of dosing). The 300 mg/kg/day dose is 15 times a human dose of 100 mg/day on a mg/m^2 basis.

Rats received desvenlafaxine succinate at dosages up to 300 mg/kg/day (males) or 500 mg/kg/day (females). The highest dose is 29 (males) or 48 (females) times a human dose of 100 mg/day on a mg/m^2 basis.

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

Reduced fertility was observed in a study in which both male and female rats received desvenlafaxine succinate. This effect was noted at oral doses approximately 10 times a human dose of 100 mg/day on a mg/m^2 basis. There was no effect on fertility at oral doses approximately 3 times a human dose of 100 mg/day on a mg/m^2 basis.

14 CLINICAL STUDIES

The efficacy of Pristiq as a treatment for depression was established in four 8-week, randomized, double-blind, placebo-controlled, fixed-dose studies (at doses of 50 mg/day to 400 mg/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 Pristiq once daily, or placebo (n = 118). In a second study, patients received either 200 mg (n = 121) or 400 mg (n = 124) of Pristiq 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 Pristiq once daily, or placebo (n = 150 and n = 161).

Pristiq showed superiority over placebo as measured by improvement in the 17-item Hamilton Rating Scale for Depression ($HAM\text{-}D_{17}$) 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/day and 100 mg/day there was no suggestion of a greater effect with the higher dose *[see Dosage and Administration (2.1)]*. Overall, while adverse events and discontinuations were more frequent at higher doses, no severe toxicity was observed.

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.

16 HOW SUPPLIED/STORAGE AND HANDLING

Pristiq™ (desvenlafaxine) Extended-Release Tablets are available as follows:

50 mg, light pink, square pyramid tablet debossed with "W" (over) "50" on the flat side

NDC 0008-1211-14, bottle of 14 tablets.

NDC 0008-1211-30, bottle of 30 tablets.

NDC 0008-1211-01, bottle of 90 tablets.

NDC 0008-1211-50, 10 blisters of 10 (HUD).

100 mg, reddish-orange, square pyramid tablet debossed with "W" (over) "100" on the flat side

NDC 0008-1222-14, bottle of 14 tablets.

NDC 0008-1222-30, bottle of 30 tablets.

NDC 0008-1222-01, bottle of 90 tablets.

NDC 0008-1222-50, 10 blisters of 10 (HUD).

Store at 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature].

Each tablet contains 76 or 152 mg of desvenlafaxine succinate equivalent to 50 or 100 mg of desvenlafaxine, respectively.

The appearance of these tablets is a trademark of Wyeth Pharmaceuticals.

U.S. Patent No. 6,673,838.

17 PATIENT COUNSELING INFORMATION

Advise patients, their families, and their caregivers about the benefits and risks associated with treatment with Pristiq and counsel them in its appropriate use.

Advise patients, their families, and their caregivers to read the Medication Guide and assist them in understanding its contents. The complete text of the Medication Guide is reprinted at the end of this document [*see Patient Counseling Information (17.17)*].

17.1 Suicide Risk

Advise patients, their families and caregivers to look for the emergence of suicidality, especially early during treatment and when the dose is adjusted up or down [*see Box Warning and Warnings and Precautions (5.1)*].

17.2 Concomitant Medication

Advise patients taking Pristiq not to use concomitantly other products containing desvenlafaxine or venlafaxine. Healthcare professionals should instruct patients not to take Pristiq with an MAOI or within 14 days of stopping an MAOI and to allow 7 days after stopping Pristiq before starting an MAOI [*see Contraindications (4.2)*].

17.3 Serotonin Syndrome

Caution patients about the risk of serotonin syndrome, particularly with the concomitant use of Pristiq and triptans, tramadol, tryptophan supplements or other serotonergic agents [*see Warnings and Precautions (5.2) and Drug Interactions (7.3)*].

17.4 Elevated Blood Pressure

Advise patients that they should have regular monitoring of blood pressure when taking Pristiq [*see Warnings and Precautions (5.3)*].

17.5 Abnormal Bleeding

Patients should be cautioned about the concomitant use of desvenlafaxine and NSAIDs, aspirin, warfarin, or other drugs that affect coagulation since combined use of psychotropic drugs that interfere with serotonin reuptake and these agents has been associated with an increased risk of bleeding. [*see Warnings and Precautions (5.4)*].

17.6 Narrow-angle Glaucoma

Advise patients with raised intraocular pressure or those at risk of acute narrow-angle glaucoma (angle-closure glaucoma) that mydriasis has been reported and they should be monitored [*see Warnings and Precautions (5.5)*].

17.7 Activation of Mania/Hypomania

Advise patients, their families and caregivers to observe for signs of activation of mania/hypomania [*see Warnings and Precautions (5.6)*].

17.8 Cardiovascular/Cerebrovascular Disease

Caution is advised in administering Pristiq to patients with cardiovascular, cerebrovascular, or lipid metabolism disorders [*see Adverse Reactions (6.1) and Warnings and Precautions (5.7)*].

17.9 Serum Cholesterol and Triglyceride Elevation

Advise patients that elevations in total cholesterol, LDL and triglycerides may occur and that measurement of serum lipids may be considered [*see Warnings and Precautions (5.8)*].

17.10 Discontinuation

Advise patients not to stop taking Pristiq without talking first with their healthcare professional. Patients should be aware that discontinuation effects may occur when stopping Pristiq [*see Warnings and Precautions (5.9) and Adverse Reactions (6.1)*].

17.11 Interference with Cognitive and Motor Performance

Caution patients about operating hazardous machinery, including automobiles, until they are reasonably certain that Pristiq therapy does not adversely affect their ability to engage in such activities.

17.12 Alcohol

Advise patients to avoid alcohol while taking Pristiq [*see Drug Interactions (7.5)*].

17.13 Allergic Reactions

Advise patients to notify their physician if they develop allergic phenomena such as rash, hives, swelling, or difficulty breathing.

17.14 Pregnancy

Advise patients to notify their physician if they become pregnant or intend to become pregnant during therapy [*see Use in Specific Populations (8.1)*].

17.15 Nursing

Advise patients to notify their physician if they are breastfeeding an infant [*see Use in Specific Populations (8.3)*].

17.16 Residual Inert Matrix Tablet

Patients receiving Pristiq 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.

17.17 FDA-Approved Medication Guide

MEDICATION GUIDE

Pristiq™ (pris-**TEEK**) Extended-Release Tablets

(desvenlafaxine)

Antidepressant Medicines, Depression and Other Serious Mental Illnesses, and Suicidal Thoughts or Actions

Read the Medication Guide that comes with you or your family member's antidepressant medicine. This Medication Guide is only about the risk of suicidal thoughts and actions with antidepressant medicines. **Talk to your, or your family member's, healthcare provider about:**

- all risks and benefits of treatment with antidepressant medicines
- all treatment choices for depression or other serious mental illness

What is the most important information I should know about antidepressant medicines, depression and other serious mental illnesses, and suicidal thoughts or actions?

1. **Antidepressant medicines may increase suicidal thoughts or actions in some children, teenagers, and young adults within the first few months of treatment.**
2. **Depression and other serious mental illnesses are the most important causes of suicidal thoughts and actions. Some people may have a particularly high risk of having suicidal thoughts or actions.** These include people who have (or have a family history of) bipolar illness (also called manic-depressive illness) or suicidal thoughts or actions.
3. **How can I watch for and try to prevent suicidal thoughts and actions in myself or a family member?**

- Pay close attention to any changes, especially sudden changes, in mood, behaviors, thoughts, or feelings. This is very important when an antidepressant medicine is started or when the dose is changed.
- Call the healthcare provider right away to report new or sudden changes in mood, behavior, thoughts, or feelings.
- Keep all follow-up visits with the healthcare provider as scheduled. Call the healthcare provider between visits as needed, especially if you have concerns about symptoms.

Call a healthcare provider right away if you or your family member has any of the following symptoms, especially if they are new, worse, or worry you:

• thoughts about suicide or dying	• trouble sleeping (insomnia)
• attempts to commit suicide	• new or worse irritability
• new or worse depression	• acting aggressive, being angry, or violent
• new or worse anxiety	• acting on dangerous impulses
• feeling very agitated or restless	• an extreme increase in activity and talking (mania)
• panic attacks	• other unusual changes in behavior or mood

What else do I need to know about antidepressant medicines?

- Never stop an antidepressant medicine without first talking to a healthcare provider. Stopping an antidepressant medicine suddenly can cause other symptoms.

• **Antidepressants are medicines used to treat depression and other illnesses.** It is important to discuss all the risks of treating depression and also the risks of not treating it. Patients and their families or other caregivers should discuss all treatment choices with the healthcare provider, not just the use of antidepressants.

• **Antidepressant medicines have other side effects.** Talk to the healthcare provider about the side effects of the medicine prescribed for you or your family member.

• **Antidepressant medicines can interact with other medicines.** Know all of the medicines that you or your family member takes. Keep a list of all medicines to show the healthcare provider. Do not start new medicines without first checking with your healthcare provider.

• **Not all antidepressant medicines prescribed for children are FDA approved for use in children.** Talk to your child's healthcare provider for more information.

This Medication Guide has been approved by the U.S. Food and Drug Administration for all antidepressants.

Important Information about Pristiq

Read the patient information that comes with Pristiq before you take Pristiq and each time you refill your prescription. There may be new information. If you have questions, ask your healthcare provider. This information does not take the place of talking with your healthcare provider about your medical condition or treatment.

What is Pristiq?

- Pristiq is a prescription medicine used to treat depression. Pristiq belongs to a class of medicines known as SNRIs (or serotonin-norepinephrine reuptake inhibitors).
- Pristiq has not been studied orapproved for use in children and adolescents.

Who should not take Pristiq?

Do not take Pristiq if you:

- are allergic to desvenlafaxine, venlafaxine or any of the ingredients in Pristiq. See the end of this Medication Guide for a complete list of ingredients in Pristiq.
- currently take or have taken within the last 14 days, any medicine known as an MAOI. Taking an MAOI with certain other medicines, including Pristiq, can cause serious or even life-threatening side effects. Also, you must wait at least 7 days after you stop taking Pristiq before you take any MAOI.

What should I tell my healthcare provider before taking Pristiq?

Tell your healthcare provider about all your medical conditions, including if you:

- have high blood pressure.
- have heart problems.
- have high cholesterol or high triglycerides.
- have a history of a stroke.

- have glaucoma.
- have kidney problems.
- have liver problems.
- have or had bleeding problems.
- have or had seizures or convulsions.
- have mania or bipolar disorder.
- have low sodium levels in your blood.
- are pregnant or plan to become pregnant. It is not known if Pristiq will harm your unborn baby.
- are breastfeeding. Pristiq can pass into your breast milk and may harm your baby. Talk with your healthcare provider about the best way to feed your baby if you take Pristiq.

Serotonin syndrome

A rare but potentially life-threatening condition called serotonin syndrome can happen when medicines such as Pristiq are taken with certain other medicines. Serotonin syndrome can cause serious changes in how your brain, muscles and digestive system work. **Especially tell your healthcare provider if you take the following:**

- medicines to treat migraine headaches known as triptans
- medicines used to treat mood disorders, including tricyclics, lithium, selective serotonin reuptake inhibitors (SSRIs), or serotonin norepinephrine reuptake inhibitors (SNRIs)
- silbutramine
- tramadol
- St. John's Wort
- MAOIs (including linezolid, an antibiotic)
- tryptophan supplements

Ask your healthcare provider if you are not sure if you are taking any of these medicines.

Before you take Pristiq with any of these medicines, talk to your healthcare provider about serotonin syndrome. See "What are the possible side effects of Pristiq?"

Pristiq contains the medicine desvenlafaxine. Do not take Pristiq with other medicines containing venlafaxine or desvenlafaxine.

How should I take Pristiq?

- Take Pristiq exactly as your healthcare provider has told you.
- Take Pristiq at about the same time each day.
- Pristiq may be taken either with or without food.
- Swallow Pristiq tablets whole with fluid. Do not crush, cut, chew, or dissolve Pristiq tablets because the tablets are time released.
- When you take Pristiq, you may see something in your stool that looks like a tablet. This is the empty shell from the tablet after the medicine has been absorbed by your body.

- It is common for antidepressant medicines such as Pristiq to take several weeks before you start to feel better. Do not stop taking Pristiq if you do not feel results right away.
- Do not stop taking or change the dose of Pristiq without talking with your healthcare provider, even if you feel better.
- Talk with your healthcare provider about how long you should use Pristiq. Take Pristiq for as long as your healthcare provider tells you to.
- If you miss a dose of Pristiq, take it as soon as you remember. If it is almost time for your next dose, skip the missed dose. Do not try to "make up" for the missed dose by taking two doses at the same time.
- Do not take more Pristiq than prescribed by your healthcare provider. If you take more Pristiq than the amount prescribed, contact your healthcare provider right away.
- In case of an overdose of Pristiq, call your healthcare provider or poison control center, or go to the emergency room right away.

What should I avoid while taking Pristiq?

- Do not drive a car or operate machinery until you know how Pristiq affects you.
- Avoid drinking alcohol while taking Pristiq.

What are the possible side effects of Pristiq?

Pristiq can cause serious side effects including:

- **See the beginning of this Medication Guide - Antidepressant Medicines, Depression and other Serious Mental Illnesses, and Suicidal Thoughts or Actions.**
- **Serotonin syndrome. See "What should I tell my healthcare provider before taking Pristiq?"**

  Get medical help right away if you think that you have serotonin syndrome. Signs and symptoms of serotonin syndrome may include one or more of the following:

  - restlessness
  - hallucinations (seeing and hearing things that are not real)
  - loss of coordination
  - fast heart beat
  - increased body temperature
  - increase in blood pressure
  - diarrhea
  - coma
  - nausea
  - vomiting

- **Pristiq may also cause other serious side effects including:**
- **New or worsened high blood pressure (hypertension)** Your healthcare provider should monitor your blood pressure before and while you are taking Pristiq. If you have high blood pressure, it should be controlled before you start taking Pristiq.
- **Abnormal bleeding or bruising** Pristiq and other SNRIs/ SSRIs may cause you to have an increased chance of bleeding. Taking aspirin, NSAIDs (non-steroidal anti-

inflammatory drugs), or blood thinners may add to this risk. Tell your healthcare provider right away about any unusual bleeding or bruising.

- **Glaucoma (increased eye pressure)**
- **Increased cholesterol and triglyceride levels in your blood**
- **Symptoms when stopping Pristiq (discontinuation symptoms)** Side effects may occur when stopping Pristiq (discontinuation symptoms), especially when therapy is stopped suddenly. Your healthcare provider may want to decrease your dose slowly to help avoid side effects. Some of these side effects may include:
  - dizziness
  - nausea
  - headache
  - irritability
  - sleeping problems (insomnia)
  - anxiety
  - abnormal dreams
  - tiredness
  - sweating
  - diarrhea
- **Seizures (convulsions)**
- **Low sodium levels in your blood** (Symptoms of this may include: headache, difficulty concentrating, memory changes, confusion, weakness and unsteadiness on your feet. In severe or more sudden cases, symptoms can include: hallucinations (seeing or hearing things that are not real), fainting, seizures and coma. If not treated, severe low sodium levels could be fatal.)

Contact your healthcare provider if you think you have any of these side effects.

Common side effects with Pristiq include:

- nausea
- headache
- dry mouth
- sweating
- dizziness
- insomnia
- constipation
- loss of appetite
- sleepiness
- tiredness
- diarrhea
- vomiting
- anxiety
- tremor
- dilated pupils
- decreased sex drive
- delayed orgasm and ejaculation

These are not all the possible side effects of Pristiq. Tell your healthcare provider about any side effect that bothers you or does not go away. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088. For more information on these and other side effects associated with Pristiq, talk to your healthcare provider visit our web site at www.pristiq.com or call our toll-free number 1-888-Pristiq.

How should I store Pristiq?

- Store Pristiq at 68° to 77°F (20° to 25°C)

- Do not use Pristiq after the expiration date (EXP), which is on the container. The expiration date refers to the last day of that month.
- Keep Pristiq and all medicines out of the reach of children.

General Information about the safe and effective use of Pristiq

Medicines are sometimes used for conditions that are not mentioned in Medication Guides. Do not use Pristiq for a condition for which it was not prescribed. Do not give Pristiq to other people, even if they have the same symptoms that you have. It may harm them.

This Medication Guide summarizes the most important information about Pristiq. If you would like more information, talk with your healthcare provider. You can ask you pharmacist or healthcare provider for information about Pristiq that is written for healthcare professionals. For more information, go to www.pristiq.com or call 1-888-Pristiq (774-7847).

What are the ingredients in Pristiq?

Active ingredient: desvenlafaxine
Inactive ingredients: hypromellose, microcrystalline cellulose, talc, magnesium stearate, a film coating which consists of sodium carboxymethylcellulose, maltodextrin, dextrose, titanium dioxide, stearic acid and iron oxide(s).

This Medication Guide has been approved by the U.S. Food and Drug Administration.

Issued February 2008

Contact Information
Please visit our web site at www.pristiq.com, or call our toll-free number 1-888-Pristiq to receive more information.

This product's label may have been updated. For current package insert and further product information, please visit www.wyeth.com or call our medical communications department toll-free at 1-800-934-5556.

Wyeth®

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Rev 02/08