資料３－① デスベンラファキシン（desvenlafaxine）

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]

FULL PRESCRIBING INFORMATION: CONTENTS*

17.14 Pregnancy
17.15 Nursing
17.16 Residual Inert Matrix Tablet
17.17 FDA-Approved Medication Guide

***Sections or subsections omitted from the full prescribing information are not listed**

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