PACKAGE INSERT

PRISTIQ®

(desvenlafaxine)
Extended Release Tablets

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 MDD.

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.

Pediatrics (<18 years of age): PRISTIQ is not indicated for use in children under the age of 18. Two placebo-controlled studies in 587 pediatric patients 7 to 17 years of age with MDD did not demonstrate efficacy.

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 to 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. Based on clinical judgment, if dose increases are indicated for individual patients, they should occur gradually and at intervals of not less than 7 days. The maximum dose should not exceed 200 mg/day.

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 Selective Serotonin Reuptake Inhibitors (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.

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/day. The recommended starting dose in patients with severe renal impairment (24-hr CrCl <30 mL/min) or end-stage renal disease (ESRD) is 50 mg every other day. Because of individual variability in clearance in these patients, individualization of dosage may be desirable. Supplemental doses should not be given to patients after dialysis. The doses should not be escalated in patients with moderate or severe renal impairment, or ESRD [see *Warnings and Precautions (5.10), Use in Specific Populations (8.6)* and *Clinical Pharmacology (12.5)*].

Patients with hepatic impairment

The recommended dose in patients with hepatic impairment is 50 mg/day. Dose escalation above 100 mg/day is not recommended [see *Clinical Pharmacology (12.5)*].

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 (12.5)*].

2.3 Maintenance/Continuation/Extended Treatment

It is generally agreed that acute episodes of MDD require several months or longer of sustained pharmacologic therapy. However, the longer-term efficacy of PRISTIQ at a 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 rather than abrupt cessation is recommended. If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, then resuming the previously prescribed dose may be considered. Subsequently, the physician may continue decreasing the dose, but at a more gradual rate. In some patients, discontinuation may need to occur over periods of months or longer.

2.5 Switching Patients from Other Antidepressants to PRISTIQ

Discontinuation symptoms have been reported when switching patients from other antidepressants, including venlafaxine, to PRISTIQ. Tapering of the initial antidepressant may be necessary to minimize discontinuation symptoms.

2.6 Switching a Patient to or from a Monoamine Oxidase Inhibitor (MAOI) Intended to Treat Psychiatric Disorders

At least 14 days should elapse between discontinuation of a MAOI intended to treat psychiatric disorders and initiation of therapy with PRISTIQ. Conversely, at least 7 days should be allowed after stopping PRISTIQ before starting a MAOI intended to treat psychiatric disorders [see *Contraindications (4.2)*].

Use of PRISTIQ with reversible MAOIs such as Linezolid or Methylene Blue

Do not start PRISTIQ in a patient who is being treated with a reversible MAOI such as linezolid or in whom intravenous methylene blue has been administered because there is increased risk of serotonin syndrome. In a patient who requires more urgent treatment of a psychiatric condition, non-pharmacological interventions, including hospitalization, should be considered [see *Contraindications (4.2)*].

In some cases, a patient already receiving PRISTIQ therapy may require urgent treatment with linezolid or intravenous methylene blue. If acceptable alternatives to linezolid or intravenous methylene blue treatment are not available and the potential benefits of linezolid or intravenous methylene blue treatment are judged to outweigh the risks of serotonin syndrome in a particular patient, PRISTIQ should be stopped promptly, and linezolid or intravenous methylene blue can be administered. The patient should be monitored for symptoms of serotonin syndrome for two weeks or until 24 hours after the last dose of linezolid or intravenous methylene blue, whichever comes first. Therapy with PRISTIQ may be resumed 24 hours after the last dose of linezolid or intravenous methylene blue [see *Warnings and Precautions (5.2)*].

The risk of administering methylene blue by non-intravenous routes (such as oral tablets or by local injection) or in intravenous doses much lower than 1 mg/kg with PRISTIQ is unclear. The clinician should, nevertheless, be aware of the possibility of emergent symptoms of serotonin syndrome with such use [see *Warnings and Precautions (5.2)*].

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

Desvenlafaxine is an inhibitor of both norepinephrine and serotonin reuptake.

Desvenlafaxine succinate must not be used in combination with a monoamine oxidase inhibitor (MAOI), or within at least 14 days of discontinuing treatment with a MAOI. Based on the half-life of desvenlafaxine succinate, at least 7 days should be allowed after stopping desvenlafaxine succinate before starting a MAOI.

Starting PRISTIQ in a patient who is being treated with a reversible MAOI such as linezolid or in whom intravenous methylene blue has been administered is also contraindicated because of an increased risk of serotonin syndrome [see *Dosage and Administration (2.6)* and *Warnings and Precautions (5.2)*].

5 WARNINGS AND PRECAUTIONS

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

Desvenlafaxine succinate is an SNRI, a class of medicines that may be used to treat depression. All patients treated with desvenlafaxine should be monitored appropriately and observed closely for clinical worsening and suicidality. Patients, their families, and their caregivers should be encouraged to be alert to the emergence of anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, mania, other unusual changes in behavior, worsening of depression, and suicidal ideation, especially when initiating therapy or during any change in dose or dosage regimen. The risk of suicide attempt must be considered, especially in depressed patients and the smallest quantity of drug, consistent with good patient management should be provided to reduce the risk of overdose.

Suicide is a known risk of depression and certain other psychiatric disorders, and these disorders themselves are 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 trials of antidepressant medicines (SSRIs

and others) showed that these medicines increase the risk of suicidality in children, adolescents, and young adults (ages 18-24) with major depression and other psychiatric disorders. Short-term trials did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction in the risk of suicidality with antidepressants compared to placebo in adults aged 65 years and older.

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

Table 1

Age Range	Drug-placebo Difference in Number of Cases of Suicidality per 1,000 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 MDD as well as for other indications, both psychiatric and non-psychiatric. Although a causal link between the emergence of such symptoms and either the worsening of

depression and/or the emergence of suicidal impulses has not been established, there is concern that such symptoms may represent precursors to emerging suicidality.

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

If the decision has been made to discontinue treatment, medication should be tapered, as rapidly as is feasible, but with recognition that abrupt discontinuation can be associated with certain symptoms [see *Warnings and Precautions (5.9)* and *Dosage and Administration (2.4)* for a description of the risks of discontinuation of PRISTIQ].

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

As with other serotonergic agents, the development of a potentially life-threatening serotonin syndrome or Neuroleptic Malignant Syndrome (NMS)-like reactions may occur with PRISTIQ, particularly with concomitant use of other serotonergic drugs (including SSRIs, SNRIs, triptans, tricyclic antidepressants, fentanyl, lithium, tramadol, tryptophan, buspirone, amphetamines, and St. John's Wort), with drugs that impair metabolism of serotonin (e.g. MAOIs, including reversible MAOIs such as linezolid and intravenous methylene blue), or with antipsychotics or other dopamine antagonists.

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

most severe form, can resemble NMS, which includes hyperthermia, muscle rigidity, autonomic instability with possible rapid fluctuation of vital signs, and mental status changes. Patients should be monitored for the emergence of serotonin syndrome or NMS-like signs and symptoms.

The concomitant use of PRISTIQ with MAOIs intended to treat psychiatric disorders is contraindicated. PRISTIQ should also not be started in a patient who is being treated with MAOIs such as linezolid or intravenous methylene blue. All reports with methylene blue that provided information on the route of administration involved intravenous administration in the dose range of 1 mg/kg to 8 mg/kg. No reports involved the administration of methylene blue by other routes (such as oral tablets or local tissue injection) or at lower doses. There may be circumstances when it is necessary to initiate treatment with a MAOI such as linezolid or intravenous methylene blue in a patient taking PRISTIQ. PRISTIQ should be discontinued before initiating treatment with the MAOI [see *Contraindications (4.2)* and *Dosage and Administration (2.6)*].

If concomitant treatment with PRISTIQ and other serotonergic drugs, including triptans, tricyclic antidepressants, fentanyl, lithium, tramadol, buspirone, amphetamines, tryptophan and St. John's Wort, that may affect the serotonergic and/or dopaminergic neurotransmitter systems is clinically warranted, careful observation of the patient is advised, and the patient should be made aware of a potential increased risk for serotonin syndrome, particularly during treatment initiation and dose increases.

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

Treatment with PRISTIQ and any concomitant serotonergic or antidopaminergic agents, including antipsychotics, should be discontinued immediately if the above events occur and supportive symptomatic treatment should be initiated.

5.3 Elevated Blood Pressure

Patients receiving PRISTIQ should have regular monitoring of blood pressure since increases in blood pressure were observed in clinical studies, particularly with higher doses. Pre-existing hypertension should be controlled before initiating treatment with PRISTIQ. Caution should be exercised in treating patients with 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) ≥90 mm Hg and ≥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 patients 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

Selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs), including PRISTIQ, may increase the risk of bleeding events. Concomitant use of aspirin, non-steroidal anti-inflammatory drugs (NSAIDs), 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

In clinical trials, mania was reported for 0.03% 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 Disorders

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 MDD. 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 and SSRIs, there have been post-marketing 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, seizures, visual impairment and hypertension. While these events are generally self-limiting, there have been reports of serious discontinuation symptoms, and sometimes these effects can be protracted and severe. In addition, suicide/suicidal thoughts and aggression have been observed in patients during changes in desvenlafaxine dosing regimen, including during discontinuation.

Patients should be monitored 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 [see *Dosage and Administration (2.4)* and *Adverse Reactions (6.1)*]. In some patients, discontinuation may need to occur over periods of months or longer.

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 (12.5)*]. 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 Seizures

Cases of seizure have been reported in clinical trials with PRISTIQ. PRISTIQ has not been systematically evaluated in patients with a seizure disorder. Patients with a history of seizures were excluded from clinical trials. 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 (SIADH) secretion. 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 (12.5)*]. 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 Venlafaxine and/or Desvenlafaxine

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

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.

5.15 Sexual Dysfunction

Serotonin-norepinephrine reuptake inhibitors (SNRIs) may cause symptoms of sexual dysfunction [see *Adverse Reactions (6.1)*]. There have been reports of long-lasting sexual dysfunction where the symptoms have continued despite discontinuation of SNRIs.

5.16 Effects on Ability to Drive and Use Machines

Interference with Cognitive and Motor Performance

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

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)*]
- Seizures [see *Warnings and Precautions (5.11)*]

6.1 Clinical Trials 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 leading to discontinuation of therapy

Combined across 8-week placebo-controlled pre-marketing studies for MDD, 12% of the 1,834 patients who received PRISTIQ (50-400 mg) discontinued treatment due to an adverse event, compared with 3% of the 1,116 placebo-treated patients in those studies. At the recommended dose of 50 mg, the discontinuation rate due to an adverse event 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 event was 8.7%.

The most common adverse reactions leading to discontinuation in at least 2% of the PRISTIQ treated patients in the short-term trials, up to 12 weeks, were: nausea (2%); in the long-term studies, up to 11 months, no events lead to discontinuation in at least 2% of the patients and at a rate greater than placebo in the double-blind phase.

Patient exposure

The safety of desvenlafaxine was established in a total of 8,453 patients who were exposed to at least one dose of desvenlafaxine ranging from 10 to 400 mg/day in MDD clinical trials or from post-marketing experience. Long-term safety was evaluated in 2,140 patients who were exposed to PRISTIQ for at least 6 months and with 421 patients exposed for 1 year. In general, the adverse reactions were most frequent in the first week of treatment. 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.

Adverse drug reactions (ADRs) by System Organ Class (SOC) and CIOMS frequency category listed in order of decreasing medical seriousness within each frequency category and SOC.

Adverse Events Table – MDD Studies						
System Organ Class	**Very Common ≥1/10**	**Common ≥1/100 to <1/10**	**Uncommon ≥1/1,000 to <1/100**	**Rare ≥1/10,000 to <1/1,000**	**Very Rare <1/10,000**	**Frequency Not Known (cannot be estimated from available data)**
Immune System Disorders			Hypersensitivity			
Metabolism and Nutrition Disorders		Decreased appetite		Hyponatraemia		
Psychiatric Disorders	Insomnia	Withdrawal syndrome, anxiety, nervousness, abnormal dreams, irritability, libido decreased, anorgasmia	Depersonalisation, orgasm abnormal	Mania, hypomania, hallucination		
Nervous System Disorders	Headache, dizziness, somnolence	Tremor, paraesthesia, disturbance in attention, dysgeusia	Syncope, dyskinesia	Serotonin syndrome[*†], convulsion, dystonia[‡]		
Eye Disorders		Vision blurred, mydriasis				
Ear and Labyrinth Disorders		Vertigo, tinnitus				
Cardiac Disorders		Tachycardia, palpitations		Stress cardiomyopathy (takotsubo cardiomyopathy)[*†]		
Vascular Disorders		Blood pressure increased, hot flush	Orthostatic hypotension, peripheral coldness			

Adverse Events Table – MDD Studies						
System Organ Class	**Very Common ≥1/10**	**Common ≥1/100 to <1/10**	**Uncommon ≥1/1,000 to <1/100**	**Rare ≥1/10,000 to <1/1,000**	**Very Rare <1/10,000**	**Frequency Not Known (cannot be estimated from available data)**
Respiratory, Thoracic, and Mediastinal Disorders		Yawning	Epistaxis			
Gastrointestinal Disorders	Nausea, dry mouth	Diarrhoea, vomiting, constipation		Pancreatitis acute		
Skin and Subcutaneous Tissue Disorders	Hyperhidrosis	Rash	Alopecia	Stevens-Johnson syndrome[*†], angioedema, photosensitivity reaction		
Musculoske-letal and Connective Tissue Disorders		Musculoskeletal stiffness				
Renal and Urinary Disorders			Urinary retention, urinary hesitation, proteinuria			
Reproductive System and Breast Disorders		Erectile dysfunction[§], ejaculation delayed[§]	Ejaculation disorder[§], ejaculation failure[§], sexual dysfunction			
General Disorders and Administration Site Conditions		Fatigue, asthenia, chills, feeling jittery				
Investigations		Liver function test abnormal, weight increased, weight decreased	Blood cholesterol increased, blood triglycerides increased, blood prolactin increased			

Adverse Events Table – MDD Studies						
System Organ Class	**Very Common ≥1/10**	**Common ≥1/100 to <1/10**	**Uncommon ≥1/1,000 to <1/100**	**Rare ≥1/10,000 to <1/1,000**	**Very Rare <1/10,000**	**Frequency Not Known (cannot be estimated from available data)**

[*] ADR identified post-marketing
[†] ADR Frequency estimated using "The Rule of 3"
‡ Dystonia has been identified in MDD subjects and is not in the combined MDD and VMS ADR table or the VMS-only ADR table, where the event is represented as extrapyramidal disorder.
[§] Frequency is calculated based on men only
ADR = Adverse drug reaction; MDD = Major depressive disorder; VMS = vasomotor symptoms.

Sexual function adverse reactions

Table 3 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 3: Sexual Function Disorders: Adverse Reactions (≥2% in Men[a] or Women[b] in any PRISTIQ Group) During the On-Therapy Period

		PRISTIQ			
System Organ Class Preferred Term	**Placebo**	**50 mg**	**100 mg**	**200 mg**	**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 clinical studies

Other infrequent adverse reactions, not described elsewhere in section 6.1, occurring at an incidence of <2% in MDD patients treated with PRISTIQ were:

Psychiatric disorders – Bruxism

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 symptoms

Adverse events reported in association with abrupt discontinuation, dose reduction or tapering of treatment in MDD clinical studies at a rate of ≥2% include: dizziness, withdrawal syndrome, 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.

Serum Lipids

Dose-related elevations in fasting serum total cholesterol, LDL (low density lipoproteins) cholesterol, and triglycerides were observed in controlled trials. Measurement of serum lipids should be considered during treatment with desvenlafaxine [see *Warnings and Precautions (5.8)*].

The percentage of patients who exceeded a predetermined threshold value is shown in Table 4.

Table 4: 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 5). This proteinuria was not associated with increases in BUN or creatinine and was generally transient.

Table 5: 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 MDD 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 6 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 6: 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.

Orthostatic hypotension

In the short-term, placebo-controlled clinical studies with doses of 50-400 mg, systolic orthostatic hypotension (decrease ≥30 mm Hg from supine to standing position) occurred more frequently in patients ≥65 years of age receiving PRISTIQ (8.0%, 7/87) versus placebo (2.5%, 1/40), compared to patients <65 years of age receiving PRISTIQ (0.9%, 18/1,937) versus placebo (0.7%, 8/1,218).

6.2 Adverse Reactions Identified During Post-approval Use

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

Skin and subcutaneous tissue disorders – Stevens-Johnson syndrome, toxic epidermal necrosis, and/or erythema multiforme.

6.3 Adverse Reactions Reported with Other SNRIs

Although gastrointestinal bleeding is not considered adverse reaction for PRISTIQ, it is an adverse reaction for other SNRIs and may also occur with PRISTIQ.

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)

[see *Dosage and Administration (2.6), Contraindications (4.2),* and *Warnings and Precautions (5.2)*].

7.3 Serotonergic Drugs

[see *Dosage and Administration (2.6), Contraindications (4.2),* and *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 co-administered 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 minimally involved in desvenlafaxine elimination. In a clinical trial, ketoconazole (200 mg BID) increased the area under the concentration vs. time curve (AUC) of PRISTIQ (400 mg single dose) by about 43%, a weak interaction, and C_{max} by about 8%. Concomitant use of PRISTIQ with potent inhibitors of CYP3A4 may result in higher exposure to 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 trials 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. When desvenlafaxine succinate was administered at a dose of 100 mg daily in conjunction with a single 60 mg dose of codeine, a CYP2D6 substrate metabolized to morphine, the AUC of codeine was unchanged, the AUC of morphine decreased approximately 8%. Concomitant use of desvenlafaxine with a drug metabolized by CYP2D6 may result in increased concentrations of that drug and decreased concentrations of its CYP2D6 metabolites.

Drugs metabolized by CYP3A4 (midazolam)

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

In a clinical trial, 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. In a second study, PRISTIQ 50 mg daily was co-administered with a single 4 mg dose of midazolam. The AUC and C_{max} of midazolam decreased by approximately 29% and 14%, respectively. Concomitant use of PRISTIQ with a drug metabolized by CYP3A4 may result in lower exposure to that drug.

Drugs metabolized by a combination of both CYP2D6 and CYP3A4 (tamoxifen and aripiprazole).

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

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

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

Drugs metabolized by CYP1A2, 2A6, 2C8, 2C9 and 2C19

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

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 for MDD.

7.10 Drug-Laboratory Test Interactions

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

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

Major depressive disorder

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 30 times on a mg/kg basis and up to 5 times the maximum recommended human dose (MRHD) of 200 mg/day (on a mg/m^2 basis) in rats. In rabbits, there was no evidence of teratogenicity at doses up to 23 times (on a mg/kg basis) the MRHD of 200 mg/day, or 7 times the MRHD (on a mg/m^2 basis). However, fetal weights were decreased in rats with a no-effect dose 30 times the MRHD (on a mg/kg basis) and 5 times the MRHD (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 30 times on a mg/kg basis and 5 times the MRHD of 200 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 90 times the MRHD (on a mg/kg basis) and 15 times the MRHD (on a mg/m^2 basis).

There are no adequate and well-controlled studies of PRISTIQ in pregnant women. Studies have demonstrated that desvenlafaxine crosses the human placenta. Therefore, PRISTIQ should be used during pregnancy only if the potential benefits justify the potential risks. If desvenlafaxine is used until, or shortly before birth, discontinuation effects in the newborn should be considered.

Data from the Quebec Pregnancy Cohort reported that, following exposure to SNRIs (including desvenlafaxine) during the second half of pregnancy, persistent pulmonary hypertension of the newborn (PPHN) was identified in 0.2% of all neonates; no statistical significance in the increased risk of PPHN in response to second/third trimester exposure could be established.

In a prospective, observational study, the median (interquartile range [IQR]) gestational age was higher in infants born to control mothers than those born to mothers treated with antidepressants (40 [39-40 weeks] vs. 39 [38-40 weeks]; $p<0.05$). Neonates born to control mothers also had a longer median (IQR) length at birth (51 [49-51.6] cm vs. 49 [47-51] cm; $p<0.05$) than infants born to mothers in the cases group. The infants also displayed mild behavioral anomalies, categorized as less optimal functioning for habituation and motor and autonomic clusters (using the Brazelton Neonatal Behavioral Assessment Scale [BNBAS]); however these events were self-limiting and usually resolved in 1 to 2 weeks.

In another study, 6 of the 7 neonates with *in utero* exposure to venlafaxine at near term had acceptable Apgar scores at birth; however an improvement in Apgar scores at 5 minutes was observed in all 7 neonates. No cases of intrauterine growth retardation were recorded. The adverse events observed in 5 neonates at birth, included respiratory distress, tachypnea, irritability, tremors, excessive suckling, rigidity, increased tonus, vomiting, hyper-reflexia, disorganized movements of limbs, initial decreased reactivity, agitation, poor sleep and liquid/abundant stool. In 4 of the 5 neonates, the events resolved spontaneously without the need for any pharmacological treatment, while one neonate required resuscitation and continuous positive airway pressure (C-PAP) for 48 hours. Although respiratory distress

was attributed to the plasma concentration of venlafaxine or desvenlafaxine at birth, the occurrence of the other adverse events correlated with the declining levels of venlafaxine, suggests that these events could potentially signal withdrawal symptoms in the neonate following a decline in levels of venlafaxine after exposure to significantly high levels of the drug *in utero*.

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

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

Non-teratogenic effects

Neonates exposed to SNRIs 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)*].

Epidemiological data have suggested that the use of SSRIs in pregnancy, particularly in late pregnancy, may increase the risk of persistent pulmonary hypertension in the newborn (PPHN). Although no studies have investigated an association of PPHN to SNRI treatment, this potential risk cannot be ruled out with desvenlafaxine taking into account the related mechanism of action (inhibition of the re-uptake of serotonin).

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. No adverse events occurred in either the lactating mothers or the nursing infants, however, the effect in infants have not been established. PRISTIQ should only be taken by breastfeeding women if the expected benefits outweigh the possible risks.

8.4 Pediatric Use

Two placebo-controlled studies in 587 pediatric patients 7 to 17 years of age with MDD did not demonstrate efficacy. Anyone considering the use of PRISTIQ in a child or adolescent must balance the potential risks with the clinical need.

In general, the adverse reaction profile of PRISTIQ (in placebo-controlled clinical studies) in children and adolescents (aged 7 to 17) was similar to that seen for adults.

The most frequently reported events from the placebo-controlled studies were: Headache (17.3%), Nausea (8.6%), Abdominal pain upper (8.5%), Nasopharyngitis (5.3%), Dizziness (4.6%), Upper respiratory tract infection (4.2%), Decreased appetite (4.2%), Vomiting (3.9%), Fatigue (3.2%), and Insomnia (3.2%). Of these, events with an incidence in the PRISTIQ groups >2 times that of the placebo group were: Fatigue (4.2% vs. 1.7%), and Insomnia (4.2% vs. 1.7%).

When compared to adverse event rates in adults, the following events occurred more frequently in pediatric patients *(incidence of ≥3% in pediatric patients and <3% in adults)*: Abdominal pain upper, Weight increased, Gastroenteritis viral, Dysmenorrhoea, Accidental overdose, Cough, Irritability, Oropharyngeal pain, and Sinusitis.

As with adults, increased blood pressure, abnormal bleeding, mania/hypomania, discontinuation syndrome, seizure, suicide attempt, suicidal behavior, self-injurious behavior and suicidal ideation were observed in pediatric clinical studies (see section 5.1).

8.5 Geriatric Use

Of the 7,785 patients in MDD clinical studies with PRISTIQ, approximately 5% were 65 years of age or older. No overall differences in safety or efficacy were observed between these patients and younger patients; however, in the short-term, placebo-controlled studies, there was a higher incidence of systolic orthostatic hypotension in patients ≥65 years of age compared to patients <65 years of age treated with PRISTIQ [see *Adverse Reactions (6)*]. For elderly patients, possible reduced renal clearance of desvenlafaxine should be considered when determining dose [see *Dosage and Administration (2.2)* and *Clinical Pharmacology (12.5)*]. 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 *Warnings and Precautions (5.12)*].

Greater sensitivity of some older individuals cannot be ruled out.

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 (12.5)*].

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. The recommended dose in patients with hepatic impairment is 50 mg/day.

Dose escalation above 100 mg/day is not recommended [see *Clinical Pharmacology (12.5)*].

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

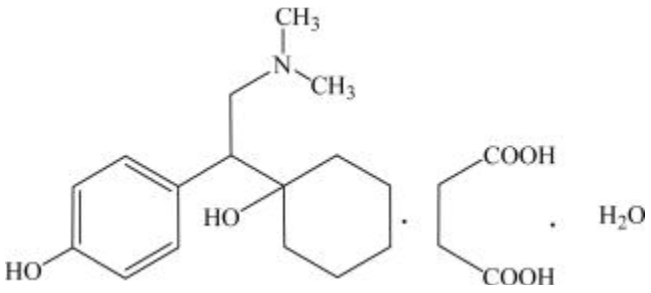
Induction of emesis is not recommended. Because of the moderate volume of distribution of this drug, forced diuresis, dialysis, hemoperfusion, and exchange transfusion are unlikely to be of benefit. No specific antidotes for desvenlafaxine are known.

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 once-a-day 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 succinate monohydrate and has the empirical formula of $C_{16}H_{25}NO_2$ (free base) and $C_{16}H_{25}NO_2 \bullet C_4H_6O_4 \bullet H_2O$ (succinate salt 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 75.87 or 151.77 mg of desvenlafaxine succinate equivalent to 50 or 100 mg of desvenlafaxine, respectively.

Inactive ingredients for the 50 mg tablet consist of hypromellose, microcrystalline cellulose, talc, magnesium stearate and film coating, which consists of polyvinyl alcohol, polyethylene glycol, talc, titanium dioxide, and iron oxides.

Inactive ingredients for the 100 mg tablet consist of hypromellose, microcrystalline cellulose, talc, magnesium stearate and film coating, which consists of polyvinyl alcohol, polyethylene glycol, talc, titanium dioxide, iron oxide and FD&C yellow # 6.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Non-clinical studies have shown that desvenlafaxine succinate is a 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.

Desvenlafaxine lacked significant affinity for numerous receptors, including muscarinic-cholinergic, H_1-histaminergic, or α_1-adrenergic receptors *in vitro*. Pharmacologic activity at these receptors has been hypothesized to be associated with the various anticholinergic, sedative, and cardiovascular effects seen with other psychotropic drugs. In the same comprehensive binding profile assay, desvenlafaxine also lacked significant affinity for various ion channels, including calcium, chloride, potassium and sodium ion channels and also lacked monoamine oxidase (MAO) inhibitory activity. Desvenlafaxine lacked significant activity in the *in vitro* cardiac potassium channel (hERG) assay.

In preclinical rodent models, desvenlafaxine demonstrated activity predictive of antidepressant, anxiolytic and thermoregulatory actions, and pain inhibitory properties.

12.2 Pharmacokinetics

The single-dose pharmacokinetics of desvenlafaxine are linear and dose-proportional in a dose range of 50 to 600 mg/day. The mean terminal half-life, $t_{1/2}$, is approximately 11 hours. With once-daily dosing, steady-state plasma concentrations are achieved within approximately 4-5 days. At steady-state, multiple-dose accumulation of desvenlafaxine is linear and predictable from the single-dose pharmacokinetic profile.

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

12.3 Absorption and Distribution

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

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 non-vascular compartments.

12.4 Metabolism and Elimination

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

12.5 Special Populations

Age

In a trial of healthy subjects administered doses of up to 300 mg, there was an age-dependent decrease in desvenlafaxine clearance, resulting in a 32% increase in C_{max} and

a 55% increase in AUC values in subjects older than 75 years of age (n = 17), as 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)*].

Pediatric

The PRISTIQ pediatric development program investigated the acute treatment of MDD in pediatric patients (ages 7 to 17) and consisted of 6 studies: 2 Phase 2 studies (Study 3151A6-2000-US hereafter referred to as B2061012, and its 26-week open label extension (OLE) Study 3151A6-2001-US hereafter referred to as B2061013), and 4 Phase 3 studies (8 week Studies B2061014 and B2061032 hereafter referred to as the placebo-controlled studies, and their respective 26 week OLE Studies B2061031 and B2061030). A total of 761 subjects were evaluated across the clinical development program, of which 684 unique patients received DVS SR in at least one of the 6 studies.

The results of the two placebo-controlled studies showed no statistically significant difference between placebo and PRISTIQ for the pre-defined primary endpoint [change from baseline to Week 8 in the Children's Depression Rating Scale – Revised (CDRS-R)]. There was no relationship between desvenlafaxine exposure and change from baseline to Week 8 CDRS-R total score.

Gender

In a study of healthy subjects administered doses of up to 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 pharmacokinetics 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 in healthy subjects (n = 12).

Average AUC was increased by approximately 31% and 35% in patients with moderate and severe hepatic impairment, respectively, as compared to healthy subjects. Average AUC values were 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. The recommended dose in patients with hepatic impairment is 50 mg/day. Dose escalation above 100 mg/day is not recommended [see *Use in Specific Populations (8.7)*].

Renal insufficiency

The pharmacokinetics of desvenlafaxine succinate 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. Total body clearance was reduced by 29% in mild, 39% in moderate, 51% in severe renal impairment and 58% in ESRD compared to healthy subjects. This reduced clearance resulted in increases in AUCs of 42% in mild 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 ≤ 30 mL/min), and 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 healthy subjects to 13.5, 15.5, 17.6, and 22.8 hours in mild, moderate, severe renal impairment and ESRD subjects, respectively. Less than 5% of the drug in the body was cleared during a standard 4-hour hemodialysis procedure.

Therefore, supplemental doses should not be given to patients after dialysis.

The recommended dose in patients with moderate renal impairment is 50 mg per day. Dosage adjustment (50 mg every other day) is recommended in patients with severe renal impairment or ESRD. Doses should not be escalated in patients with moderate or severe renal impairment, or ESRD [see *Dosage and Administration (2.2)* and *Use in Specific Populations (8.6)*].

13 NON-CLINICAL 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 90 times, on a mg/kg basis, the maximum recommended human dose (MRHD) of 200 mg/day, and 7 times the MRHD, on a mg/m^2 basis.

Rats received desvenlafaxine succinate at dosages up to 300 mg/kg/day (males) or 500 mg/kg/day (females). The highest dose was 90 (males) or 150 (females) times, on a mg/kg basis, the MRHD of 200 mg/day, and 15 (males) or 24 (females) times the MRHD of 200 mg/day, on a mg/m^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 30 times, on a mg/kg basis, and 5 times the maximum human dose (MRHD) of 200 mg/day on a mg/m^2 basis. There was no effect on fertility at oral doses approximately 9 times the MRHD on a mg/kg basis, and 1.5 times the MRHD on a mg/m^2 basis. The human relevance of this finding is unknown.

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) and two relapse prevention trials in adult outpatients who met the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) criteria for MDD. In the first trial, 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 trial, patients received either 200 mg (n = 121) or 400 mg (n = 124) of PRISTIQ once daily, or placebo (n = 124). In two additional trials, patients received 50 mg (n = 150 and n = 164) or 100 mg (n = 147 and n = 158) of 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-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. There was no clear evidence that doses greater than 50 mg/day conferred any additional benefit [see *Dosage and Administration (2.1)*].

In a long-term trial, adult outpatients meeting DSM-IV criteria for MDD, who responded to 8 weeks of open-label acute treatment with 50 mg/day desvenlafaxine and subsequently remained stable for 12 weeks on desvenlafaxine, were assigned randomly in a double-blind manner to remain on active treatment or switch to placebo for up to 26 weeks of observation for relapse. Response during the open phase was defined as a HAM-D$_{17}$ total score of ≤11 and CGI-I ≤2 at the day 56 evaluation; stability was defined as not having a HAM-D$_{17}$ total score of ≥16 at any office visit. Relapse during the double-blind phase was defined as follows: (1) a HAM-D$_{17}$ total score of ≥16 at any office visit, (2) discontinuation for unsatisfactory efficacy response, (3) hospitalized for depression, (4) suicide attempt, or (5) suicide. Patients receiving continued desvenlafaxine treatment experienced statistically significantly longer time to relapse compared with placebo. At 26 weeks, the Kaplan-Meier estimated probability of relapse was 14% with desvenlafaxine treatment versus 30% with placebo.

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

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

15 HOW SUPPLIED

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. Cartons containing 7 or 28 tablets.

100 mg, reddish-orange, square pyramid tablet debossed with “W” (over) “100” on the flat side. Cartons containing 7 or 28 tablets.

Not all presentations may be marketed.

16 STORAGE

Store below 30°C.

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.

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 or Neuroleptic Malignant Syndrome (NMS)-like Reactions

Caution patients about the risk of serotonin syndrome, or Neuroleptic Malignant Syndrome (NMS)-like reactions, particularly with the concomitant use of PRISTIQ with other serotonergic agents (including triptans, tricyclic antidepressants, fentanyl, lithium, tramadol, buspirone, and St. John's Wort) [see *Warnings and Precautions (5.2)*].

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 PRISTIQ 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 Switching Patients from Other Antidepressants to PRISTIQ

Discontinuation symptoms have been reported when switching patients from other antidepressants, including venlafaxine, to PRISTIQ. Tapering of the initial antidepressant may be necessary to minimize discontinuation symptoms.

17.12 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.

17.13 Alcohol

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

17.14 Allergic Reactions

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

17.15 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)*].

17.16 Nursing

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

17.17 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.

18 PRODUCT OWNER

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