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

7.3 Serotonergic Drugs

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

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

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

7.5 Ethanol

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

7.6 Potential for Other Drugs to Affect Desvenlafaxine

Inhibitors of CYP3A4 (ketoconazole)

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

Inhibitors of other CYP enzymes

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

7.7 Potential for Desvenlafaxine to Affect Other Drugs

Drugs metabolized by CYP2D6 (desipramine)

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

Clinical studies have shown that desvenlafaxine does not have a clinically relevant effect on CYP2D6 metabolism at the dose of 100 mg daily. When desvenlafaxine succinate was administered at a dose of 100 mg daily in conjunction with a single 50 mg dose of desipramine, a CYP2D6 substrate, the C_{max} and AUC of desipramine increased approximately 25% and 17%,

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

Drugs metabolized by CYP3A4 (midazolam)

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

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

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

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

7.8 P-glycoprotein Transporter

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

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

7.9 Electroconvulsive Therapy

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

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

Teratogenic effects – Pregnancy Category C

When desvenlafaxine succinate was administered orally to pregnant rats and rabbits during the period of organogenesis, there was no evidence of teratogenicity in rats at any doses tested, up to 10 times a human dose of 100 mg/day (on a mg/m^2 basis) in rats, and up to 15 times the a human dose of 100 mg/day (on a mg/m^2 basis) in rabbits. However, fetal weights were decreased in rats, with a no-effect dose 10 times a human dose of 100 mg/day (on a mg/m^2 basis).

When desvenlafaxine succinate was administered orally to pregnant rats throughout gestation and lactation, there was a decrease in pup weights and an increase in pup deaths during the first four days of lactation. The cause of these deaths is not known. The no-effect dose for rat pup

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

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

Non-teratogenic effects

Neonates exposed to SNRIs (Serotonin and Norepinephrine Reuptake Inhibitors), or SSRIs (Selective Serotonin Reuptake Inhibitors), late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding. Such complications can arise immediately upon delivery. Reported clinical findings have included respiratory distress, cyanosis, apnea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycemia, hypotonia, hypertonia, hyperreflexia, tremor, jitteriness, irritability, and constant crying. These features are consistent with either a direct toxic effect of SSRIs and SNRIs or, possibly, a drug discontinuation syndrome. It should be noted that, in some cases, the clinical picture is consistent with serotonin syndrome [*see Warnings and Precautions (5.2)*]. When treating a pregnant woman with Pristiq during the third trimester, the physician should carefully consider the potential risks and benefits of treatment [*see Dosage and Administration (2.2)*].

8.2 Labor and Delivery

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

8.3 Nursing Mothers

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

8.4 Pediatric Use

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

8.5 Geriatric Use

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

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

8.6 Renal Impairment

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

8.7 Hepatic Impairment

The mean $t_{1/2}$ changed from approximately 10 hours in healthy subjects and subjects with mild hepatic impairment to 13 and 14 hours in moderate and severe hepatic impairment, respectively. No adjustment in starting dosage is necessary for patients with hepatic impairment.

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

Desvenlafaxine is not a controlled substance.

9.2 Abuse and Dependence

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

10 OVERDOSAGE

10.1 Human Experience with Overdosage

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

Among the patients included in the MDD pre-marketing studies of Pristiq, there were four adults who ingested desvenlafaxine succinate (4000 mg [desvenlafaxine alone], 900, 1800 and 5200 mg [in combination with other drugs]); all patients recovered. In addition, one patient's 11-month-old child accidentally ingested 600 mg of desvenlafaxine succinate, was treated, and recovered. The adverse reactions reported within 5 days of an overdose > 600 mg that were possibly related to Pristiq included: headache, vomiting, agitation, dizziness, nausea, constipation, diarrhea, dry mouth, paresthesia, and tachycardia.

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

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

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

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

10.2 Management of Overdosage

Treatment should consist of those general measures employed in the management of overdosage with any SSRI/SNRI.

Ensure an adequate airway, oxygenation, and ventilation. Monitor cardiac rhythm and vital signs. General supportive and symptomatic measures are also recommended. Gastric lavage with a large-bore orogastric tube with appropriate airway protection, if needed, may be indicated if performed soon after ingestion or in symptomatic patients. Activated charcoal should be administered.

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

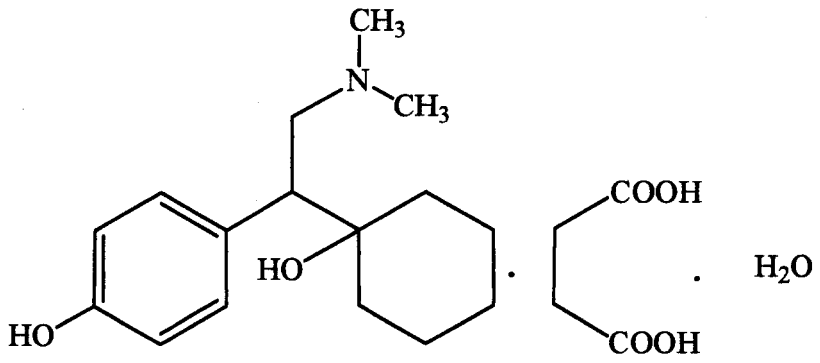
In managing an overdose, consider the possibility of multiple drug involvement. The physician should consider contacting a poison control center for additional information on the treatment of any overdose. Telephone numbers for certified poison control centers are listed in the Physicians Desk Reference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

11 DESCRIPTION

Pristiq is an extended-release tablet for oral administration that contains desvenlafaxine succinate, a structurally novel SNRI for the treatment of MDD. Desvenlafaxine (O-desmethylvenlafaxine) is the major active metabolite of the antidepressant venlafaxine, a

medication used to treat major depressive, generalized anxiety, social anxiety and panic disorders.

Desvenlafaxine is designated *RS*-4-[2-dimethylamino-1-(1-hydroxycyclohexyl)ethyl]phenol and has the empirical formula of $C_{16}H_{25}NO_2$ (free base) and $C_{16}H_{25}NO_2 \cdot C_4H_6O_4 \cdot H_2O$ (succinate monohydrate). Desvenlafaxine succinate monohydrate has a molecular weight of 399.48. The structural formula is shown below.



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

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

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

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

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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

12.2 Pharmacodynamics

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

12.3 Pharmacokinetics

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

12.4 Absorption and Distribution

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

A food-effect study involving administration of Pristiq to healthy subjects under fasting and fed conditions (high-fat meal) indicated that the C_{max} was increased about 16% in the fed state, while the AUCs were similar. This difference is not clinically significant; therefore, Pristiq can be taken without regard to meals [*see Dosage and Administration (2.1)*].

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

12.5 Metabolism and Elimination

Desvenlafaxine is primarily metabolized by conjugation (mediated by UGT isoforms) and, to a minor extent, through oxidative metabolism. CYP3A4 is the cytochrome P450 isozyme mediating the oxidative metabolism (N-demethylation) of desvenlafaxine. The CYP2D6 metabolic pathway is not involved, and after administration of 100 mg, the pharmacokinetics of desvenlafaxine was similar in subjects with CYP2D6 poor and extensive metabolizer phenotype. Approximately 45% of desvenlafaxine is excreted unchanged in urine at 72 hours after oral administration. Approximately 19% of the administered dose is excreted as the glucuronide metabolite and < 5% as the oxidative metabolite (N,O-didesmethylvenlafaxine) in urine.

12.6 Special Populations

Age

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

Gender

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

Race

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

Hepatic insufficiency

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

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

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

The mean $t_{1/2}$ changed from approximately 10 hours in healthy subjects and subjects with mild hepatic impairment to 13 and 14 hours in moderate and severe hepatic impairment, respectively. No adjustment in starting dosage is necessary for patients with hepatic impairment.

Renal insufficiency

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

The mean terminal half-life ($t_{1/2}$) was prolonged from 11.1 hours in the control subjects to approximately 13.5, 15.5, 17.6, and 22.8 hours in mild, moderate, severe renal impairment and ESRD subjects, respectively. Less than 5% of the drug in the body was cleared during a standard 4-hour hemodialysis procedure.

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

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

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

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

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

Mutagenesis

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

Impairment of fertility

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

14 CLINICAL STUDIES

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

Pristiq showed superiority over placebo as measured by improvement in the 17-item Hamilton Rating Scale for Depression ($HAM\text{-}D_{17}$) total score in four studies and overall improvement, as measured by the Clinical Global Impressions Scale - Improvement (CGI-I), in three of the four studies. In studies directly comparing 50 mg/day and 100 mg/day there was no suggestion of a greater effect with the higher dose *[see Dosage and Administration (2.1)]*. Overall, while adverse events and discontinuations were more frequent at higher doses, no severe toxicity was observed.

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

16 HOW SUPPLIED/STORAGE AND HANDLING

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

17 PATIENT COUNSELING INFORMATION

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

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

17.1 Suicide Risk

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

17.2 Concomitant Medication

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

17.3 Serotonin Syndrome

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

17.4 Elevated Blood Pressure

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

17.5 Abnormal Bleeding

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

17.6 Narrow-angle Glaucoma

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

17.7 Activation of Mania/Hypomania

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

17.8 Cardiovascular/Cerebrovascular Disease

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

17.9 Serum Cholesterol and Triglyceride Elevation

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

17.10 Discontinuation

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

17.11 Interference with Cognitive and Motor Performance

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

17.12 Alcohol

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

17.13 Allergic Reactions

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

17.14 Pregnancy

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

17.15 Nursing

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

17.16 Residual Inert Matrix Tablet

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

17.17 FDA-Approved Medication Guide

MEDICATION GUIDE

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

(desvenlafaxine)

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

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

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

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

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

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

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

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

What else do I need to know about antidepressant medicines?

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

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

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

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

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

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

Important Information about Pristiq

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

What is Pristiq?

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

Who should not take Pristiq?

Do not take Pristiq if you:

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

What should I tell my healthcare provider before taking Pristiq?

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

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

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

Serotonin syndrome

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

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

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

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

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

How should I take Pristiq?

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

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

What should I avoid while taking Pristiq?

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

What are the possible side effects of Pristiq?

Pristiq can cause serious side effects including:

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

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

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

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

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

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

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

Common side effects with Pristiq include:

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

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

How should I store Pristiq?

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

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

General Information about the safe and effective use of Pristiq

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

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

What are the ingredients in Pristiq?

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

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

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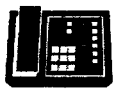
Contact Information
Please visit our web site at www.pristiq.com, or call our toll-free number 1-888-Pristiq to receive more information.

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



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