Drug Safety Labeling Changes (SLC)

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PRISTIQ (NDA-021992)

(*DESVENLAFAXINE SUCCINATE*)

Safety Labeling Changes Approved By FDA Center for Drug Evaluation and Research (CDER)

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02/06/2018 (SUPPL-42)

Approved Drug Label (PDF) (http://www.accessdata.fda.gov/drugsatfda_docs/label/2018/021992s042lbl.pdf)

5 Warnings and Precautions

Additions and/or revisions underlined:

5.1 Suicidal Thoughts and Behaviors in Pediatric and Young Adult Patients

5.2 Serotonin Syndrome

Serotonin-norepinephrine reuptake inhibitors (SNRIs) and selective-serotonin reuptake inhibitors (SSRIs), including PRISTIQ, can precipitate serotonin syndrome, a potentially life-threatening condition. The risk is increased with concomitant use of other serotonergic drugs (including triptans, tricyclic antidepressants, fentanyl, lithium, tramadol, tryptophan, buspirone, amphetamines, and St. John's Wort) and with drugs that impair metabolism of serotonin, i.e., MAOIs Serotonin syndrome can also occur when these drugs are used alone.

Serotonin syndrome signs and symptoms may include mental status changes (e.g., agitation, hallucinations, delirium, and coma) …

… The concomitant use of PRISTIQ with MAOIs is contraindicated. In addition, do not initiate PRISTIQ in a patient being treated with MAOIs such as linezolid or intravenous methylene blue …

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

5.4 Increased Risk of Bleeding

Drugs that interfere with serotonin reuptake inhibition, including PRISTIQ, may increase the risk of bleeding events. Concomitant use of aspirin … Inform patients about the risk of bleeding associated with the concomitant use of PRISTIQ and antiplatelet agents or anticoagulants. For patients taking warfarin, carefully monitor coagulation indices when initiating, titrating, or discontinuing PRISTIQ.

5.5 Angle Closure Glaucoma

… in a patient with anatomically narrow angles who does not have a patent iridectomy. Avoid use of antidepressants, including PRISTIQ, in patients with untreated anatomically narrow angles.

5.7 Discontinuation Syndrome

Adverse reactions after discontinuation of serotonergic antidepressants, particularly after abrupt discontinuation, include: nausea, sweating, dysphoric mood, irritability, agitation, dizziness, sensory disturbances (e.g., paresthesia, such as electric shock sensations), tremor, anxiety, confusion, headache, lethargy, emotional lability, insomnia, hypomania, tinnitus, and seizures. A gradual reduction in dosage rather than abrupt cessation is recommended whenever possible.

6 Adverse Reactions

Additions and/or reactions underlined:

- Suicidal Thoughts and Behaviors in Pediatric and Young Adult Patients
- Increased Risk of Bleeding

7 Drug Interactions

Additions and/or reactions underlined:

7.1 Drugs Having Clinically Important Interactions with PRISTIQ

Table 8: Clinically Important Drug Interactions with PRISTIQ

Newly added table; please refer to label for complete information.

7.2 Drugs Having No Clinically Important Interactions with PRISTIQ

Based on pharmacokinetic studies, no dosage adjustment is required for drugs that are mainly metabolized by CYP3A4 (e.g., midazolam), or for drugs that are metabolized by both CYP2D6 and CYP3A4 (e.g., tamoxifen, aripiprazole), when administered concomitantly with PRISTIQ.

8 Use in Specific Populations

8.1 Pregnancy

PLLR conversion; additions and/or revisions underlined:

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to antidepressants during pregnancy. Healthcare providers are encouraged to register patients by calling the National Pregnancy Registry for Antidepressants at 1-844-405-6185.

Risk summary

There are no published studies on PRISTIQ in pregnant women; however published epidemiologic studies of pregnant women exposed to venlafaxine, the parent compound, have not reported a clear association with adverse developmental outcomes. There are risks associated with untreated depression in pregnancy and with exposure to SNRIs and SSRIs, including PRISTIQ, during pregnancy.

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

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

Clinical Considerations

Disease-associated maternal and/or embryo/fetal risk

A prospective longitudinal study of 201 women …

Maternal adverse reactions

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

Fetal/Neonatal adverse reactions

Exposure to SNRIs or SSRIs in late pregnancy may lead to an increased risk for neonatal complications requiring prolonged hospitalization, respiratory support, and tube feeding. Monitor neonates who were exposed to PRISTIQ in the third trimester of pregnancy for drug discontinuation syndrome.

Human Data

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

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

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

Neonates exposed to SNRIs or SSRIs, late in the third trimester …

Animal Data

… These doses were associated with a plasma exposure (AUC) 19 times (rats) and 0.5 times (rabbits) the AUC exposure at an adult human dose of 100 mg per day. However, fetal weights were decreased and skeletal ossification was delayed in rats in association with maternal toxicity at the highest dose, with an AUC exposure at the no-effect dose that is 4.5-times the AUC exposure at an adult human dose of 100 mg per day.

… The cause of these deaths is not known. The AUC exposure at the no-effect dose for rat pup mortality was 4.5-times the AUC exposure at an adult human dose of 100 mg per day. Post-weaning growth and reproductive performance of the progeny were not affected by maternal treatment with desvenlafaxine succinate at exposures 19 times the AUC exposure at an adult human dose of 100 mg per day.

8.2 Lactation

PLLR conversion; additions and/or revisions underlined:

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

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

Data

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

8.4 Pediatric Use

Additions and/or revisions underlined:

The safety and effectiveness of PRISTIQ have not been established in pediatric patients for the treatment of MDD.

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

Antidepressants, such as PRISTIQ, increase the risk of suicidal thoughts and behaviors in pediatric patients.

PRISTIQ was associated with a decrease in body weight in placebo-controlled trials in pediatric patients with MDD. The incidence of weight loss (greater than or equal to 3.5% of baseline weight) was 22%, 14%, and 7% for patients treated with low dose PRISTIQ, high dose PRISTIQ, and placebo, respectively.

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

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

Juvenile Animal Studies

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

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

8.6 Renal Impairment

Additions and/or revisions underlined:

Adjust the maximum recommended dosage in patients with moderate or severe renal impairment (CLcr 15 to 50 mL/min, C-G), or end-stage renal disease (CLcr less than 15 mL/min, C-G).

8.7 Hepatic Impairment

Additions and/or revisions underlined:

Adjust the maximum recommended dosage in patients with moderate to severe hepatic impairment (Child-Pugh score 7 to 15).

17 PCI/PI/MG (Patient Counseling Information/Patient Information/Medication Guide)

MEDICATION GUIDE

This has been revised; please refer to label for complete information.

PATIENT COUNSELING INFORMATION

Additions and/or revisions underlined:

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Suicidal Thoughts and Behaviors

Advise patients and caregivers to look for the emergence of suicidality, especially early during treatment and when the dose is adjusted up or down, and instruct them to report such symptoms to the healthcare provider.

Increased Risk of Bleeding

Inform patients about the concomitant use of PRISTIQ with NSAIDs, aspirin, other antiplatelet drugs, warfarin, or other coagulants because the combined use of has been associated with an increased risk of bleeding. Advise patients to inform their health care providers if they are taking or planning to take any prescription or over-the-counter medications that increase the risk of bleeding.

Discontinuation

Advise patients not to abruptly stop taking PRISTIQ without talking first with their healthcare professional.

12/19/2017 (SUPPL-46)

Approved Drug Label (PDF) (http://www.accessdata.fda.gov/drugsatfda_docs/label/2017/021992s046lbl.pdf)

6 Adverse Reactions

6.2 Postmarketing Experience

(Additions and/or revisions are underlined)

Cardiovascular system – Takotsubo cardiomyopathy

01/04/2017 (SUPPL-44)

Approved Drug Label (PDF) (http://www.accessdata.fda.gov/drugsatfda_docs/label/2017/021992s044lbl.pdf)

5 Warnings and Precautions

5.2 Serotonin Syndrome

(additions underlined)

The development of a potentially life-threatening serotonin syndrome has been reported with SNRIs and SSRIs, including PRISTIQ, alone but particularly with concomitant use of other serotonergic drugs (including triptans, tricyclic antidepressants, fentanyl, lithium, tramadol, tryptophan, buspirone, amphetamines, and St. John's Wort), and with drugs that impair metabolism of serotonin (in particular, MAOIs, both those intended to treat psychiatric disorders and also others, such as linezolid and intravenous methylene blue).

…

If concomitant use of PRISTIQ with other serotonergic drugs, including triptans, tricyclic antidepressants, fentanyl, lithium, tramadol, buspirone, amphetamines, tryptophan, and St. John's Wort is clinically warranted, patients should be made aware of a potential increased risk for serotonin syndrome, particularly during treatment initiation and dose increases.

17 PCI/PI/MG (Patient Counseling Information/Patient Information/Medication Guide)

17 PATIENT COUNSELING INFORMATION

(addition underlined)

Serotonin Syndrome

Caution patients about the risk of serotonin syndrome, particularly with the concomitant use of PRISTIQ with other serotonergic agents (including triptans, tricyclic antidepressants, fentanyl, lithium, tramadol, amphetamines, tryptophan, buspirone, and St. John's Wort supplements).

MEDICATION GUIDE

Serotonin syndrome

(addition underlined)

Rare, but potentially life-threatening conditions 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, heart and blood vessels, and digestive system work. **Especially tell your healthcare provider if you take the following:**

- amphetamine