Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Pediatric Postmarketing Pharmacovigilance Review

Date:	October 25, 2021
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Product Name:	Pristiq (desvenlafaxine succinate)
Pediatric Labeling Approval Date:	February 6, 2018
Application Type/Number:	NDA 021992
Applicant:	PF Prism CV
OSE RCM #:	2021-1201

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EXECUTIVE SUMMARY

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for desvenlafaxine in pediatric patients through age 17 years. The Division of Pharmacovigilance (DPV) conducted this review in accordance with the Food and Drug Administration Amendments Act (FDAAA) Best Pharmaceuticals for Children Act (BPCA) and the Pediatric Research Equity Act (PREA). This review focuses on U.S. serious, unlabeled adverse events associated with desvenlafaxine in pediatric patients.

The FDA approved desvenlafaxine succinate (Pristiq) on February 29, 2008. Desvenlafaxine is indicated for treatment of adults with major depressive disorder (MDD). On February 6, 2018, the desvenlafaxine product labeling was updated to include the results of the pediatric studies that failed to demonstrate efficacy over placebo in pediatric patients. Desvenlafaxine is not approved for use in pediatric patients.

We reviewed 90 FAERS U.S. serious reports with desvenlafaxine in the pediatric population (ages 0 - < 18 years) from February 29, 2008 through May 31, 2021. We identified no new safety signals, and no increased severity or frequency of any labeled adverse events, and no deaths directly associated with desvenlafaxine.

DPV did not identify any new pediatric safety concerns for desvenlafaxine at this time. DPV recommends no regulatory action at this time and will continue to monitor all adverse events associated with the use of desvenlafaxine.

1 INTRODUCTION

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for desvenlafaxine in pediatric patients through age 17 years. The Division of Pharmacovigilance (DPV) conducted this review in accordance with the Food and Drug Administration Amendments Act (FDAAA) Best Pharmaceuticals for Children Act (BPCA) and the Pediatric Research Equity Act (PREA). This review focuses on U.S. serious, unlabeled adverse events associated with desvenlafaxine in pediatric patients.

1.1 PEDIATRIC REGULATORY HISTORY

The FDA approved desvenlafaxine succinate extended-release tablets (Pristiq) on February 29, 2008, for treatment of major depressive disorder (MDD) in adults. Desvenlafaxine is available as 25 mg, 50 mg, and 100 mg extended-release tablets. Desvenlafaxine is not approved for use in pediatric patients. Under PREA, two studies were conducted to assess the safety and effectiveness of desvenlafaxine in children (ages 7 to 11 years) and adolescents (ages 12 to 17 years). A written request was issued on February 10, 2009, including these two studies. Two 8-week, randomized, double-blind, placebo-controlled, parallel groups conducted in 587 patients (7 to 17 years of age) for the treatment of MDD each failed to demonstrate efficacy over placebo in pediatric patients at week 8. Efficacy was defined by a change in Children's Depression Rating Scale-Revised (CDRS-R) total scores.[1] On February 6, 2018, the desvenlafaxine product labeling was updated to include the results of the pediatric studies that failed to demonstrate efficacy over placebo in pediatric patients.[2]

DPV has not previously presented an evaluation of postmarketing adverse event reports for desvenlafaxine in pediatric patients to the Pediatric Advisory Committee (PAC).

1.2 RELEVANT LABELED SAFETY INFORMATION

The Boxed Warnings, Contraindications, Warnings and Precautions, and Adverse Reactions (from the Highlights of Prescribing Information), and Pediatric Use sections of the desvenlafaxine product labeling are reproduced below.[2]

WARNING: SUICIDAL THOUGHTS AND BEHAVIORS

See full prescribing information for complete boxed warning.

- **Increased the risk of suicidal thoughts and behaviors in children, adolescents and young adults taking antidepressants (5.1).**
- **Closely monitor for clinical worsening and emergence of suicidal thoughts and behaviors (5.1).**
- **PRISTIQ is not approved for use in pediatric patients (8.4).**

CONTRAINDICATIONS

- Hypersensitivity to desvenlafaxine succinate, venlafaxine hydrochloride or any excipients in the PRISTIQ formulation (4).
- *Serotonin Syndrome and MAOIs*: Do not use MAOIs intended to treat psychiatric disorders with PRISTIQ or within 7 days of stopping treatment with PRISTIQ. Do not use PRISTIQ within 14 days of stopping an MAOI intended to treat psychiatric disorders. In addition, do not start PRISTIQ in a patient who is being treated with linezolid or intravenous methylene blue (4).

WARNINGS AND PRECAUTIONS

- *Serotonin Syndrome:* Increased risk when co-adminstered with other serotonergic agents (e.g., SSRI, SNRI, triptans), but also when taken alone. If it occurs, discontinue PRISTIQ and initiate supportive treatment (5.2).
- *Elevated Blood Pressure:* Control hypertension before initiating treatment. Monitor blood pressure regularly during treatment (5.3).
- *Increased Risk of Bleeding:* Concomitant use of aspirin, NSAIDs, other antiplatelet drugs, warfarin, and other anticoagulants may increase this risk (5.4).
- *Angle Closure Glaucoma:* Avoid use of antidepressants, including PRISTIQ, in patients with untreated anatomically narrow angles treated. (5.5)
- *Activation of Mania/Hypomania:* Use cautiously in patients with Bipolar Disorder. Caution patients about risk of activation of mania/hypomania (5.6).
- *Discontinuation Syndrome:* Taper dose when possible and monitor for discontinuation symptoms (5.7).
- *Seizure:* Can occur. Use cautiously in patients with seizure disorder (5.8).
- *Hyponatremia:* Can occur in association with SIADH (5.9).
- *Interstitial Lung Disease and Eosinophilic Pneumonia:* Can occur (5.10).

ADVERSE REACTIONS

Most common adverse reactions (incidence ≥5% and twice the rate of placebo in the 50 or 100 mg dose groups) were: nausea, dizziness, insomnia, hyperhidrosis, constipation, somnolence, decreased appetite, anxiety, and specific male sexual function disorders (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Wyeth Pharmaceuticals Inc., a subsidiary of Pfizer Inc., at 1-800-438-1985 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*

8.4 Pediatric Use

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 *[see the Boxed Warning and Warnings and Precautions (5.1)]*.

PRISTIQ was associated with a decrease in body weight in placebo-controlled trials in pediatric patients with MDD. The incidence of weight loss (≥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.

2 METHODS AND MATERIALS

2.1 FAERS SEARCH STRATEGY

DPV searched the FAERS database with the strategy described in Table 1.

Table 1. FAERS Search Strategy*	
Date of search	June 8, 2021
Time period of search	February 29, 2008† - May 31, 2021
Search type	FBIS Quick Query, Product-Manufacturer Reporting Summary
Product terms	Product active ingredient: desvenlafaxine, desvenlafaxine succinate, desvenlafaxine fumarate monohydrate
MedDRA search terms (Version 24.0)	All PTs

* See **Appendix A** for a description of the FAERS database.
†Initial approval date for desvenlafaxine
Abbreviations: FBIS = FDA Business Intelligence System, MedDRA=Medical Dictionary for Regulatory Activities, PT=Preferred Term

3 RESULTS

3.1 FAERS

3.1.1 Total Number of FAERS Reports by Age

Table 2 presents the number of adult and pediatric FAERS reports from February 29, 2008 through May 31, 2021, with desvenlafaxine.

Table 2. Total Adult and Pediatric FAERS Reports* Received by FDA From February 29, 2008 Through May 31, 2021 With Desvenlafaxine			
	All reports (U.S.)	**Serious† (U.S.)**	**Death (U.S.)**
Adults (≥ 18 years)	10,758 (9,525)	4,297 (3,094)	406 (278)
Pediatrics (0 - <18 years)	192‡ (141)	141‡ (90)	5‡ (5)

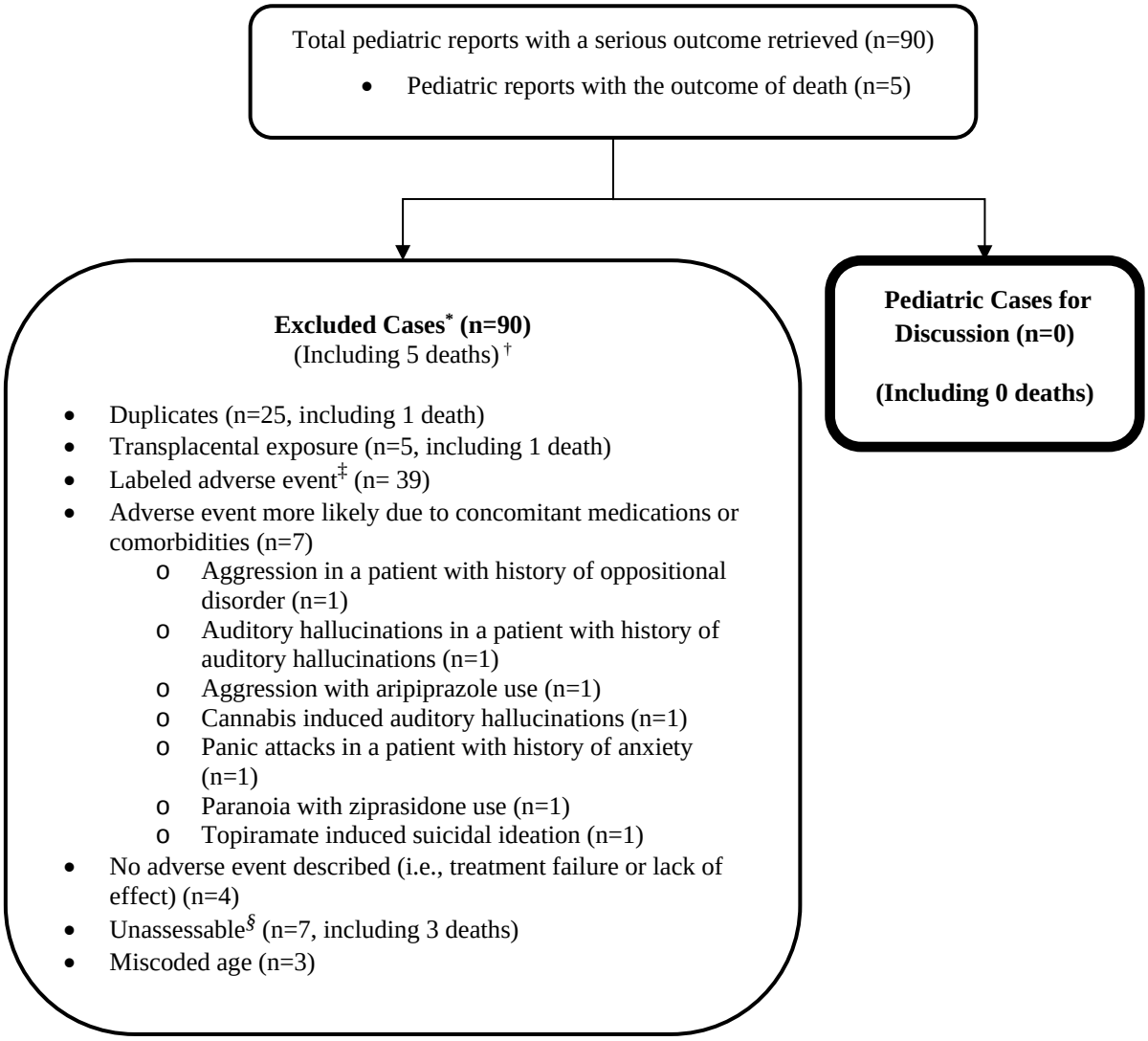
* May include duplicates and transplacental exposures, and have not been assessed for causality
† For the purposes of this review, the following outcomes qualify as serious: death, life- threatening, hospitalization (initial or prolonged), disability, congenital anomaly, required intervention, or other serious important medical events.
‡ See **Figure 1**. One additional report of pediatric death was identified among reports not reporting an age.

3.1.2 Selection of U.S. Serious Pediatric Cases in FAERS

Our FAERS search retrieved 90 U.S. serious pediatric reports from February 29, 2008 through May 31, 2021.

We reviewed all FAERS U.S. pediatric reports with a serious outcome. We excluded reports from the case series for various reasons, such as duplicate reporting, transplacental exposure, labeled adverse event, adverse event was more likely due to concomitant medications or comorbidities, no adverse event described, unassessable reports, or miscoded reports. Figure 1 presents the selection of cases for the pediatric case series.

Figure 1. Selection of Serious U.S. Pediatric Cases with Desvenlafaxine



* DPV reviewed these cases, but they were excluded from further discussion for the reasons listed above.

† Five excluded reports described fatal outcomes. One report described a neonate born at 26 weeks gestation with unspecified duration of transplacental exposure to desvenlafaxine and norethisterone who died from complications of extreme prematurity. The second report described a 15-year-old male with a significant history of depression who completed suicide with limited medical history to assess causality. The third report described a 17-year-old male who began desvenlafaxine 50 mg for major depressive disorder (MDD) at an unspecified time and completed suicide. Concomitant medications or time to event were not reported to assess causality. The fourth report was from a line listing of National Poison Data System data in the literature[3] that included a 3-year-old with a fatal outcome after unintentional exposure to more than 10 substances including desvenlafaxine; case details were not available for a causality assessment. The last report is a duplicate report.

‡ Labeled events include: diarrhea, nausea, vomiting, weight loss, tachycardia, interstitial lung disease, hypersensitivity, Stevens-Johnson syndrome, discontinuation syndrome, serotonin syndrome, overdose, suicidal ideation and behavior.

§ Unassessable: Case cannot be assessed for causality because there is insufficient information reported (i.e., unknown time to event, concomitant medications and comorbidities, clinical course and outcome) or the information is contradictory or information provided in the case cannot be supplemented or verified.

3.1.3 Summary of Fatal Pediatric Cases (N=0)

There are no fatal pediatric adverse event cases for discussion.

3.1.4 Summary of Non-Fatal Pediatric U.S. Serious Cases (N=0)

We did not identify any FAERS U.S. serious, unlabeled, non-fatal adverse event cases associated with desvenlafaxine in the pediatric population.

4 DISCUSSION

We reviewed 90 FAERS U.S. serious reports with desvenlafaxine in the pediatric population (ages 0 - < 18 years) from February 29, 2008 through May 31, 2021. We identified no new safety signals, no increased severity or frequency of any labeled adverse events, and no deaths directly associated with desvenlafaxine.

5 CONCLUSION

DPV did not identify any new pediatric safety concerns for desvenlafaxine at this time.

6 RECOMMENDATION

DPV recommends no regulatory action at this time and will continue to monitor all adverse events associated with the use of desvenlafaxine.

7 REFERENCES

1. Umhau J. Medical Officer Clinical Review of Pristiq® (desvenlafaxine). December 29, 2017. https://www.fda.gov/media/112547/download.
2. Pristiq® (desvenlafaxine) extended-release tablet [Prescribing Information] Philadelphia, PA: Wyeth Pharmaceuticals Inc.; February 2018.
3. Dalton A, Rynolds K. National poison data system fatalities involving pediatric exposures to single ingredient acetaminophen, 2007-2017. Clin Toxicol. 2019;57(10):888-9.

8 APPENDICES

8.1 APPENDIX A. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

FDA Adverse Event Reporting System (FAERS)

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support FDA's postmarketing safety surveillance program for drug and therapeutic biological products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Council on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary (FPD).

FAERS data have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population.

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