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

Pediatric Postmarketing Pharmacovigilance Review

Date:	January 19, 2024
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Product Name:	Qelbree (viloxazine extended-release capsules)
Pediatric Labeling Approval Date:	April 2, 2021
Application Type/Number:	NDA 211964
Applicant:	Supernus Pharmaceuticals, Inc
TTT Record ID:	2023-6854

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EXECUTIVE SUMMARY

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Qelbree (viloxazine extended-release capsules) in pediatric patients less than 18 years of age. The Division of Pharmacovigilance (DPV) conducted this review in accordance with the Pediatric Research Equity Act (PREA). This review focuses on serious unlabeled adverse events associated with Qelbree in pediatric patients.

Qelbree (viloxazine extended-release capsules) is a selective norepinephrine reuptake inhibitor that was initially approved in the U.S. on April 2, 2021. Qelbree is currently indicated for the treatment of attention deficit hyperactivity disorder (ADHD) in adults and pediatric patients 6 years of age and older.

This pediatric postmarketing safety review was stimulated by pediatric labeling at initial FDA approval on April 2, 2021, that included a pediatric indication for use in patients aged 6 years and older.

DPV has not previously performed a pediatric postmarketing pharmacovigilance review for Qelbree for the Pediatric Advisory Committee.

DPV reviewed all serious FAERS reports with Qelbree in pediatric patients less than 18 years of age from April 2, 2021 – October 17, 2023, and identified 10 reports. However, DPV excluded all reports from further discussion.

There were no new safety signals identified, no increased severity or frequency of any labeled adverse events, and no deaths directly associated with Qelbree in pediatric patients less than 18 years of age.

DPV did not identify any new pediatric safety concerns for Qelbree at this time and will continue routine pharmacovigilance monitoring for Qelbree.

1 INTRODUCTION

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Qelbree (viloxazine extended-release capsules) in pediatric patients less than 18 years of age. The Division of Pharmacovigilance (DPV) conducted this review in accordance with the Pediatric Research Equity Act (PREA). This review focuses on serious unlabeled adverse events associated with Qelbree in pediatric patients.

1.1 PEDIATRIC REGULATORY HISTORY

Qelbree (viloxazine extended-release capsules) is a selective norepinephrine reuptake inhibitor that was initially approved in the U.S. on April 2, 2021. Qelbree is currently indicated for the treatment of attention deficit hyperactivity disorder (ADHD) in adults and pediatric patients 6 years of age and older.[1]

This pediatric postmarketing safety review was stimulated by pediatric labeling at initial FDA approval on April 2, 2021, that included a pediatric indication for use in patients aged 6 years and older.

DPV has not previously performed a pediatric postmarketing pharmacovigilance review for Qelbree for the Pediatric Advisory Committee.

1.2 RELEVANT LABELED SAFETY INFORMATION

The Qelbree labeling contains the following safety information excerpted from the Highlights of Prescribing Information and the *Pediatric Use* subsection. For additional Qelbree labeling information, please refer to the full prescribing information.[1]

WARNING: SUICIDAL THOUGHTS AND BEHAVIORS

See full prescribing information for complete boxed warning.

In clinical trials, higher rates of suicidal thoughts and behavior were reported in patients treated with Qelbree than in patients treated with placebo. Closely monitor for worsening and emergence of suicidal thoughts and behaviors (5.1).

----------CONTRAINDICATIONS----------

- Concomitant administration of monoamine oxidase inhibitors (MAOI), or dosing within 14 days after discontinuing an MAOI (4, 7.1)
- Concomitant administration of sensitive CYP1A2 substrates or CYP1A2 substrates with a narrow therapeutic range (4, 7.1)

----------WARNINGS AND PRECAUTIONS----------

- Blood Pressure and Heart Rate Increases: Assess heart rate and blood pressure prior to initiating treatment, following increases in dosage, and periodically while on therapy (5.2)
- Activation of Mania or Hypomania: Screen patients for bipolar disorder (5.3)
- Somnolence and Fatigue: Advise patients to use caution when driving or operating hazardous machinery due to potential somnolence (including sedation and lethargy) and fatigue (5.4)

----------ADVERSE REACTIONS----------

Most commonly observed adverse reactions (≥5% and at least twice the rate of placebo) were:

Pediatric patients 6 to 17 years of age: somnolence, decreased appetite, fatigue, nausea, vomiting, insomnia, and irritability (6.1)

Adult patients: insomnia, headache, somnolence, fatigue, nausea, decreased appetite, dry mouth and constipation (6.1)

8.4 Pediatric Use

The safety and effectiveness of Qelbree in pediatric patients 6 to 17 years of age with ADHD have been established based on randomized, placebo-controlled studies in pediatric patients [see Adverse Reactions (6.1) and Clinical Studies (14)].

The safety and effectiveness of Qelbree have not been established in pediatric patients younger than 6 years old.

Patients treated with Qelbree should be monitored for suicidal thoughts and behavior [see Warnings and Precautions (5.1)], and for changes in weight [see Adverse Reactions (6.1)].

Juvenile Animal Toxicity Data

Viloxazine was administered orally to juvenile rats from postnatal day (PND) 23 through PND 79 at doses of 43, 130, and 217 mg/kg/day, which are approximately 1, 2, and 3 times the MRHD of 400 mg in children, based on mg/m2, respectively. Viloxazine decreased body weight, weight gain, and food consumption in both sexes at 217 mg/kg/day. Sexual maturation, reproductive capacity, and learning and memory were not affected. The NOAEL for juvenile toxicity is 130 mg/kg/day, which is approximately 2 times the MRHD of 400 mg in children, based on mg/m2.

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	October 18, 2023
Time period of search	April 2, 2021† – October 17, 2023
Search type	Drug Safety Analytics Dashboard (DSAD) Quick Query
Product terms	Product name: Qelbree NDA: 211964
MedDRA search terms (Version 26.0)	All Preferred Terms
* See Appendix A for a description of the FAERS database † Qelbree U.S. approval date Abbreviations: MedDRA=Medical Dictionary for Regulatory Activities, NDA=New Drug Application	

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 through October 17, 2023, with Qelbree.

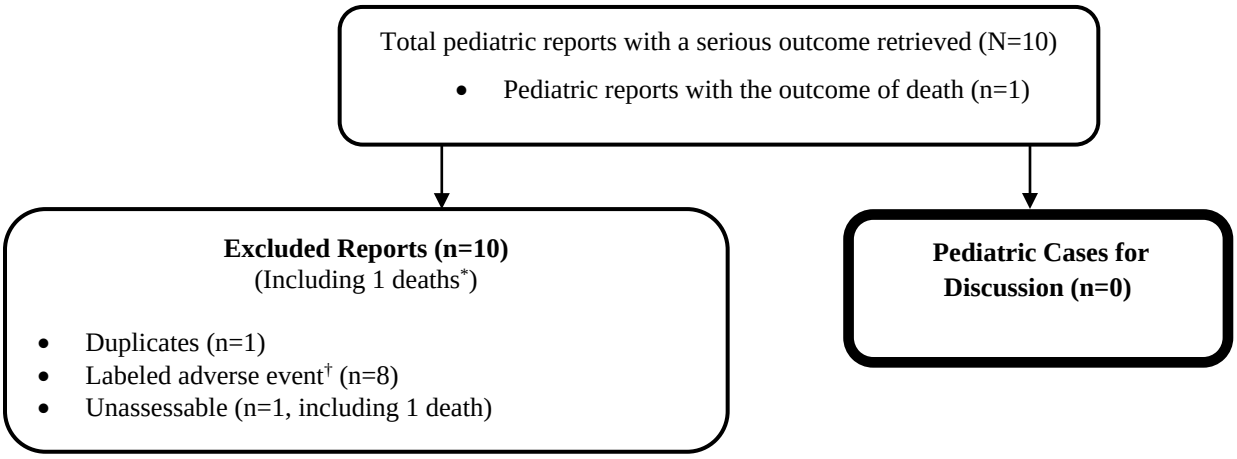
Table 2. Total Adult and Pediatric FAERS Reports* Received by FDA From April 2, 2021, Through October 17, 2023, With Qelbree			
	All Reports (U.S.)	**Serious† (U.S.)**	**Death (U.S.)**
Adults (≥ 18 years)	3 (3)	0 (0)	0 (0)
Pediatrics (0 - < 18 years)	25‡ (25)	10‡ (10)	1‡ (1)

* 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. This report is reflected in the counts of pediatric reports.

3.1.2 Selection of Serious Pediatric Cases in FAERS

Our FAERS search retrieved 10 serious pediatric reports from April 2, 2021 – October 17, 2023. We reviewed all FAERS pediatric reports with a serious outcome. We excluded all 10 reports from the case series for the reasons listed in **Figure 1**. **Figure 1** presents the selection of cases for the pediatric case series.

Figure 1. Selection of Serious Pediatric Cases With Qelbree



* One excluded FAERS report described a fatal outcome. The death described a 15-year-old male patient with a history of depression, suicidal ideation, anxiety, and environmental stressors (family and school) who was receiving psychiatric care and completed suicide. The patient had exposure to multiple medications including Qelbree and sertraline. The patient's underlying psychiatric conditions and social stressors contributed to the adverse event, but there was insufficient information to determine whether Qelbree also had a causal role in the event.
† Labeled adverse event does not represent increased severity or frequency.
‡ Unassessable: The report 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), the information is contradictory, or information provided in the report 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 Serious Non-Fatal Pediatric Cases (N=0)

There are no non-fatal pediatric adverse event cases for discussion.

4 DISCUSSION

DPV reviewed all serious FAERS reports with Qelbree in pediatric patients less than 18 years of age from April 2, 2021 – October 17, 2023, and identified 10 reports. However, DPV excluded all reports from further discussion.

There were no new safety signals identified, no increased severity or frequency of any labeled adverse events, and no deaths directly associated with Qelbree in pediatric patients less than 18 years of age.

5 CONCLUSION

DPV did not identify any new pediatric safety concerns for Qelbree at this time and will continue routine pharmacovigilance monitoring for Qelbree.

6 REFERENCES

1. Qelbree (viloxazine extended-release capsules). [Prescribing information]. Rockville, MD; Supernus Pharmaceuticals, Inc.: April 2022.

7 APPENDICES

7.1 APPENDIX A. 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 terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary.

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 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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