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:	March 24, 2025
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Product Name:	Trintellix (vortioxetine) tablets
Pediatric Labeling Approval Dates:	January 22, 2021, and August 23, 2023
Application Type/Number:	NDA 204447
Applicant:	Takeda Pharmaceuticals America, Inc.
TTT Record ID:	2025-13086

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EXECUTIVE SUMMARY

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Trintellix (vortioxetine) tablets in pediatric patients less than 18 years of age. The Division of Pharmacovigilance (DPV) conducted this review in accordance with the Best Pharmaceuticals for Children Act (BPCA) and the Pediatric Research Equity Act (PREA). This review focuses on United States (U.S.) serious unlabeled adverse events associated with vortioxetine in pediatric patients.

Trintellix (vortioxetine) tablet is an antidepressant medication initially approved in the U.S. on September 30, 2013. Trintellix is currently approved for the treatment of major depressive disorder in adults. Trintellix is not approved for use in pediatric patients.

This pediatric postmarketing safety review was prompted by the pediatric labeling on January 22, 2021, and August 23, 2023, that included information on clinical trials that failed to establish safety and effectiveness for vortioxetine in pediatric patients.

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

DPV searched FAERS for all U.S. serious reports with vortioxetine in pediatric patients less than 18 years of age from September 30, 2013 – January 29, 2025 and identified 22 reports; however, all reports were excluded from further discussion.

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

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

1 INTRODUCTION

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Trintellix (vortioxetine) tablets in pediatric patients less than 18 years of age. The Division of Pharmacovigilance (DPV) conducted this review in accordance with the Best Pharmaceuticals for Children Act (BPCA) and the Pediatric Research Equity Act (PREA). This review focuses on United States (U.S.) serious unlabeled adverse events associated with vortioxetine in pediatric patients.

1.1 PEDIATRIC REGULATORY HISTORY

Trintellix (vortioxetine) tablet is an antidepressant medication initially approved in the U.S. on September 30, 2013.[1] Trintellix is currently approved for the treatment of major depressive disorder (MDD) in adults.[2] Trintellix is not approved for use in pediatric patients.

This pediatric postmarketing safety review was prompted by the pediatric labeling on January 22, 2021, and August 23, 2023, that included information on clinical trials that failed to establish safety and effectiveness for vortioxetine in pediatric patients.[2,3]

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

1.2 RELEVANT LABELED SAFETY INFORMATION

The Trintellix (vortioxetine) tablets labeling contains the following safety information excerpted from the Highlights of Prescribing Information and the *Pediatric Use* subsection. For additional Trintellix labeling information, please refer to the full prescribing information.[2]

> WARNING: SUICIDAL THOUGHTS AND BEHAVIORS
> See full prescribing information for complete boxed warning.
> - Increased risk of suicidal thinking and behavior in pediatric and young adult patients taking antidepressants.
> - Closely monitor all antidepressant-treated patients for clinical worsening and emergence of suicidal throughs and behaviors (5.1)
> - Trintellix is not approved for use in pediatric patients (8.4)

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

- Hypersensitivity to vortioxetine or any components of the TRINTELLIX formulation (4).
- Monoamine Oxidase Inhibitors (MAOIs): Do not use MAOIs intended to treat psychiatric disorders with TRINTELLIX or within 21 days of stopping treatment with TRINTELLIX. Do not use TRINTELLIX within 14 days of stopping an MAOI intended to treat psychiatric disorders. In addition, do not start TRINTELLIX in a patient who is being treated with linezolid or intravenous methylene blue (4).

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

- Serotonin Syndrome: Increased risk when coadministered with other serotonergic agents, but also when taken alone. If it occurs, discontinue TRINTELLIX and serotonergic agents and initiate supportive measures (5.2).
- Increased Risk of Bleeding: Concomitant use of aspirin, nonsteroidal anti-inflammatory drugs, other antiplatelet drugs, warfarin, or other drugs that affect coagulation may increase risk (5.3).

- Activation of Mania/Hypomania: Screen patients for bipolar disorder (5.4).
- Angle Closure Glaucoma: Angle closure glaucoma has occurred in patients with untreated anatomically narrow angles treated with antidepressants (5.6).
- Hyponatremia: Can occur in association with the syndrome of inappropriate antidiuretic hormone secretion (SIADH) (5.7).
- Sexual Dysfunction: TRINTELLIX may cause symptoms of sexual dysfunction (5.8).

----------ADVERSE REACTIONS----------
Most common adverse reactions (incidence ≥5% and at least twice the rate of placebo) were: nausea, constipation and vomiting (6).

8.4 Pediatric Use

The safety and effectiveness of TRINTELLIX have not been established in pediatric patients.

The safety and efficacy of TRINTELLIX were evaluated in two randomized, double-blind, placebo- and active-controlled 8-week studies in pediatric patients with major depressive disorder (MDD), one in patients 7 to 11 years of age (N=540 randomized) and one in patients 12 to 17 years of age (N=616 randomized). The primary efficacy endpoint for both studies was the change from baseline to week 8 in the Children's Depression Rating Scale-Revised (CDRS-R) total score. The CDRS-R assesses the severity of depression and change in depressive symptoms in children and adolescents with depression. TRINTELLIX was not superior to placebo in either study. Patients from the controlled 8-week studies were eligible to enroll in a 6-month open-label extension study (N=662 treated). Across the three studies, the most commonly observed adverse reactions to TRINTELLIX in pediatric patients 7 to 17 years of age were generally similar to those observed in adults [see Adverse Reactions (6)].

Antidepressants, such as TRINTELLIX, increase the risk of suicidal thoughts and behaviors in pediatric patients [see Boxed Warning and Warnings and Precautions (5.1)].

Juvenile Animal Toxicity Data
Administration of vortioxetine to juvenile rats (oral doses of 10, 20, and 40 mg/kg/day twice daily from Postnatal Day 21 to 91) resulted in a neurobehavioral effect at the highest dose of 40 mg/kg twice daily (increased peak auditory startle amplitude) during the treatment period. The effect was not seen at the end of the recovery period. When animals were mated after the 4-week recovery period, viability was decreased in the offspring of mated pairs treated with 40 mg/kg twice daily. The no-observed adverse effect dose was 20 mg/kg twice daily based on both the neurobehavioral and reproductive effects. This dose was associated with plasma vortioxetine exposure (AUC) approximately 2 times that in pediatric patients.

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	January 30, 2025
Time period of search	September 30, 2013† - January 29, 2025
Search type	RxLogix Pediatric Focused Review Alert – DPV
Product terms	Product active ingredient: Vortioxetine, vortioxetine hydrobromide
MedDRA search terms (Version 27.1)	All Preferred Terms
Other search terms‡	Case Seriousness: Serious Country Derived: USA

Table 1. FAERS Search Strategy*
* See Appendix A for a description of the FAERS database. † Initial U.S. approval date. ‡ 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. Abbreviations: MedDRA=Medical Dictionary for Regulatory Activities; USA=United States of America

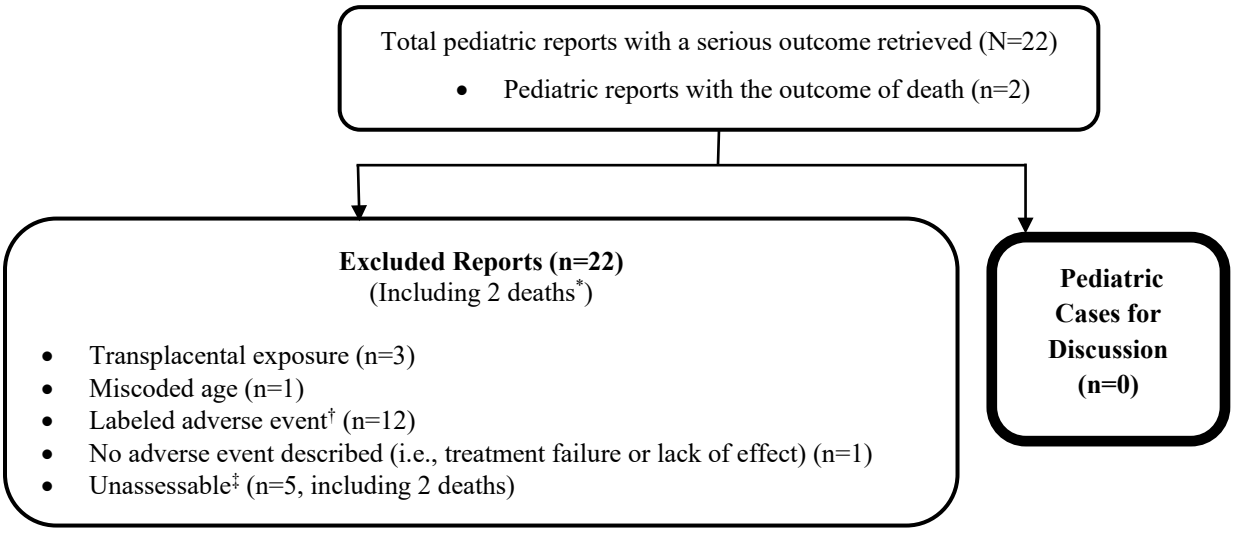
3 RESULTS

3.1 FAERS

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

Our FAERS search retrieved 22 U.S. serious pediatric reports for patients less than 18 years old from September 30, 2013 – January 29, 2025.[1] We reviewed all U.S. FAERS pediatric reports with a serious outcome. We excluded all 22 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 U.S. Serious Pediatric Cases With Vortioxetine



* Two excluded U.S. FAERS reports described fatal outcomes. Causality for the deaths is unassessable for both cases. The cases described adolescents with a history of depression with other chronic medical conditions and multiple concomitant medications who completed suicide. One of the patients had a history of suicidal ideation, and the other patient experienced social stressors prior to death. It is not possible to determine the extent to which vortioxetine may have contributed to the events based on available evidence.
† Labeled adverse event does not represent increased severity.
‡ 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.

3.1.2 Summary of U.S. Fatal Pediatric Cases (N=0)

There are no fatal pediatric adverse event cases for discussion.

[1] Includes one pediatric report that was identified among reports not coded with an age.

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

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

4 DISCUSSION

DPV searched FAERS for all U.S. serious reports with vortioxetine in pediatric patients less than 18 years of age from September 30, 2013 – January 29, 2025 and identified 22 reports; however, all reports were excluded from further discussion.

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

5 CONCLUSION

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

6 REFERENCES

1. Trintellix (vortioxetine) tablets. [Prescribing information]. Deerfield, IL: Takeda Pharmaceuticals America, Inc.: September 2013.
2. Trintellix (vortioxetine) tablets. [Prescribing information]. Lexington, MA; Takeda Pharmaceuticals America, Inc.: August 2023.
3. Trintellix (vortioxetine) tablets. [Prescribing information]. Lexington, MA; Takeda Pharmaceuticals America, Inc.: January 2021.

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.