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:	May 28, 2025
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Product Name:	Rexulti (brexpiprazole) tablets
Pediatric Labeling Approval Dates:	December 27, 2021, and May 7, 2024
Application Type/Number:	NDA 205422
Applicant:	Otsuka
TTT Record ID:	2025-13085

TABLE OF CONTENTS

EXECUTIVE SUMMARY

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Rexulti (brexpiprazole) 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 brexpiprazole in pediatric patients.

Rexulti (brexpiprazole) is an atypical antipsychotic initially approved in the U.S. on July 10, 2015, for use as an adjunctive therapy to antidepressants for the treatment of major depressive disorder (MDD) and the treatment of schizophrenia. Brexpiprazole is currently indicated for:

- Use as an adjunctive therapy to antidepressants for the treatment of MDD in adults
- Treatment of schizophrenia in adults and pediatric patients ages 13 years and older
- Treatment of agitation associated with dementia due to Alzheimer's disease

Rexulti is not indicated as an as needed treatment for agitation associated with dementia due to Alzheimer's disease.

On December 27, 2021, FDA approved expanding the indication for Rexulti to include use in the treatment of schizophrenia in patients aged 13 years and older.

On May 7, 2024, the Rexulti labeling was updated to include information on a clinical trial that failed to establish the safety and effectiveness of Rexulti in the treatment of irritability associated with autism spectrum disorder in pediatric patients.[4]

On May 9, 2025, the Rexulti labeling was updated to include new clinical trial data to support the indication for the treatment of schizophrenia in patients aged 13 and older.

This pediatric postmarketing safety review was prompted by pediatric labeling on December 27, 2021, and May 7, 2024.

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

DPV reviewed all U.S. serious FAERS reports with brexpiprazole in pediatric patients less than 18 years of age from July 10, 2015 – May 11, 2025, and identified 37 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 brexpiprazole in pediatric patients less than 18 years of age.

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

1 INTRODUCTION

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Rexulti (brexpiprazole) 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 brexpiprazole in pediatric patients.

1.1 PEDIATRIC REGULATORY HISTORY

Rexulti (brexpiprazole) is an atypical antipsychotic initially approved in the U.S. on July 10, 2015, for use as an adjunctive therapy to antidepressants for the treatment of major depressive disorder (MDD) and the treatment of schizophrenia.[1] Brexpiprazole is currently indicated for:[2]

- Use as an adjunctive therapy to antidepressants for the treatment of MDD in adults
- Treatment of schizophrenia in adults and pediatric patients ages 13 years and older
- Treatment of agitation associated with dementia due to Alzheimer's disease

Rexulti is not indicated as an as needed treatment for agitation associated with dementia due to Alzheimer's disease.

On December 27, 2021, FDA approved expanding the indication for Rexulti to include use in the treatment of schizophrenia in patients aged 13 years and older.[3]

On May 7, 2024, the Rexulti labeling was updated to include information on a clinical trial that failed to establish the safety and effectiveness of Rexulti in the treatment of irritability associated with autism spectrum disorder in pediatric patients.[4]

On May 9, 2025, the Rexulti labeling was updated to include new clinical trial data to support the indication for the treatment of schizophrenia in patients aged 13 and older.[5]

This pediatric postmarketing safety review was prompted by pediatric labeling on December 27, 2021, and May 7, 2024.

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

1.2 RELEVANT LABELED SAFETY INFORMATION

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

WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS AND SUICIDAL THOUGHTS AND BEHAVIORS

See full prescribing information for complete boxed warning.

- Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at increased risk of death. REXULTI is not approved for the treatment of patients with dementia-related psychosis without agitation associated with the dementia due to Alzheimer's disease. (5.1)
- Antidepressants increase the risk of suicidal thoughts and behaviors in pediatric and young adult patients. Closely monitor all antidepressant-treated patients for clinical worsening and emergence of suicidal thoughts and behaviors. Safety and effectiveness of REXULTI have not been established in pediatric patients with MDD. (5.2, 8.4)

----------CONTRAINDICATIONS----------
Known hypersensitivity to REXULTI or any of its components (4)

---------- WARNINGS AND PRECAUTIONS ----------
- Cerebrovascular Adverse Reactions in Elderly Patients with Dementia-Related Psychosis: Increased incidence of cerebrovascular adverse reactions (e.g., stroke, transient ischemic attack) (5.3)
- Neuroleptic Malignant Syndrome: Manage with immediate discontinuation and close monitoring. (5.4)
- Tardive Dyskinesia: Discontinue if clinically appropriate. (5.5)
- Metabolic Changes: Monitor for hyperglycemia/diabetes mellitus, dyslipidemia, and weight gain. (5.6)
- Pathological Gambling and Other Compulsive Behaviors: Consider dose reduction or discontinuation. (5.7)
- Leukopenia, Neutropenia, and Agranulocytosis: Perform complete blood counts (CBC) in patients with pre-existing low white blood cell count (WBC) or history of leukopenia or neutropenia. Consider discontinuing REXULTI if a clinically significant decline in WBC occurs in absence of other causative factors. (5.8)
- Orthostatic Hypotension and Syncope: Monitor heart rate and blood pressure and warn patients with known cardiovascular or cerebrovascular disease, and risk of dehydration or syncope. (5.9)
- Seizures: Use cautiously in patients with a history of seizures or with conditions that lower the seizure threshold. (5.11)
- Potential for Cognitive and Motor Impairment: Use caution when operating machinery. (5.14)

---------- ADVERSE REACTIONS ----------
Most common adverse reactions in adults were (6.1):
- MDD: Weight increased, somnolence, and akathisia (≥5% and at least twice the rate for placebo)
- Schizophrenia: Weight increased (≥4% and at least twice the rate for placebo)
- Agitation associated with dementia due to Alzheimer's disease: Nasopharyngitis, dizziness (≥4% and at least twice the rate for placebo)

8.4 Pediatric Use

Schizophrenia
The safety and effectiveness of REXULTI for treatment of schizophrenia have been established in pediatric patients 13 years of age and older. Use of REXULTI in this population is supported by evidence from adequate and well-controlled studies in adults with schizophrenia, pharmacokinetic data from adults and pediatric patients, and safety data in pediatric patients 13 to 17 years of age.

The safety and effectiveness of REXULTI for the treatment of schizophrenia have not been established in pediatric patients less than 13 years of age.

Major Depressive Disorder
The safety and effectiveness of REXULTI for treatment of major depressive disorder have not been established in pediatric patients. Antidepressants increased the risk of suicidal thoughts and behaviors in pediatric patients

Irritability Associated with Autism Spectrum Disorder
The safety and effectiveness of REXULTI for the treatment of irritability associated with autism spectrum disorder have not been established in pediatric patients. Effectiveness was not demonstrated, in an 8-week, double-blind, placebo-controlled, flexible-dose clinical study conducted in 119 REXULTI-treated pediatric patients 5 to 17 years of age with irritability associated with autism spectrum disorder diagnosed by the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition [DSM-5] criteria. In this study, somnolence (including sedation) occurred at a higher rate than reported in other REXULTI studies evaluating adults and elderly patients (16% in REXULTI-treated pediatric patients versus 5% for placebo). The mean increase in age-and-gender adjusted body weight z-score from baseline to last visit was 0.3 for REXULTI-treated patients versus 0.1 for placebo-treated patients. Increases in age-and-gender adjusted

body weight z-score of at least 0.5 SD from baseline was higher in REXULTI-treated patients versus placebo (19% versus 5%).

Of the 119 patients from this study, 95 patients entered the open-label treatment study and received up to 26 weeks of daily treatment with brexpiprazole. During the open-label treatment period, 2% of patients discontinued due to weight increase. In patients previously treated with REXULTI for 8 weeks, the mean increase in weight from the open-label study baseline to last visit was 4.5 kg. and 26% of patients had an increase in age-and-gender-adjusted body weight z-score of at least 0.5 SD from baseline.

Juvenile Animal Studies
Juvenile rats were administered oral doses of brexpiprazole of 3, 10, and 20 mg/kg/day once daily beginning from weaning (postnatal day 21) through adulthood (postnatal day 90), followed by a 4-week recovery (nondosing) period. Results were similar to those observed in previous repeat-dose toxicity studies in adolescent (8-week-old) rats. Mortality occurred at the high-dose of 20 mg/kg/day, as well as delayed sexual maturation in males and decreased rearing and motor activity. There was no evidence of neurotoxicity or effects on fertility and reproductive function. Histopathologic changes in reproductive organs and mammary glands occurred at all doses, were related to the pharmacology of brexpiprazole and were comparable to those in adult rats. All findings were at least partially reversible. Juvenile dogs were administered oral doses of brexpiprazole of 1, 3, and 30 mg/kg/day once daily starting at 8 or 9 weeks of age for 26 weeks, followed by an 8-week recovery (non-dosing) period. Decreases in body weight, lethargy, changes in heart rate, and immature male sex organs were observed at 30 mg/kg/day. These findings were at least partially reversible.

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	May 12, 2025
Time period of search	July 10, 2015† - May 11, 2025
Search type	RxLogix Pediatric Focused Review Alert – DPV
Product terms	Product active ingredient: brexpiprazole
MedDRA search terms (Version 27.1)	All Preferred Terms
Other criteria‡	Case Seriousness: Serious Country Derived: USA

* See Appendix A for a description of the FAERS database.
† Rexulti 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

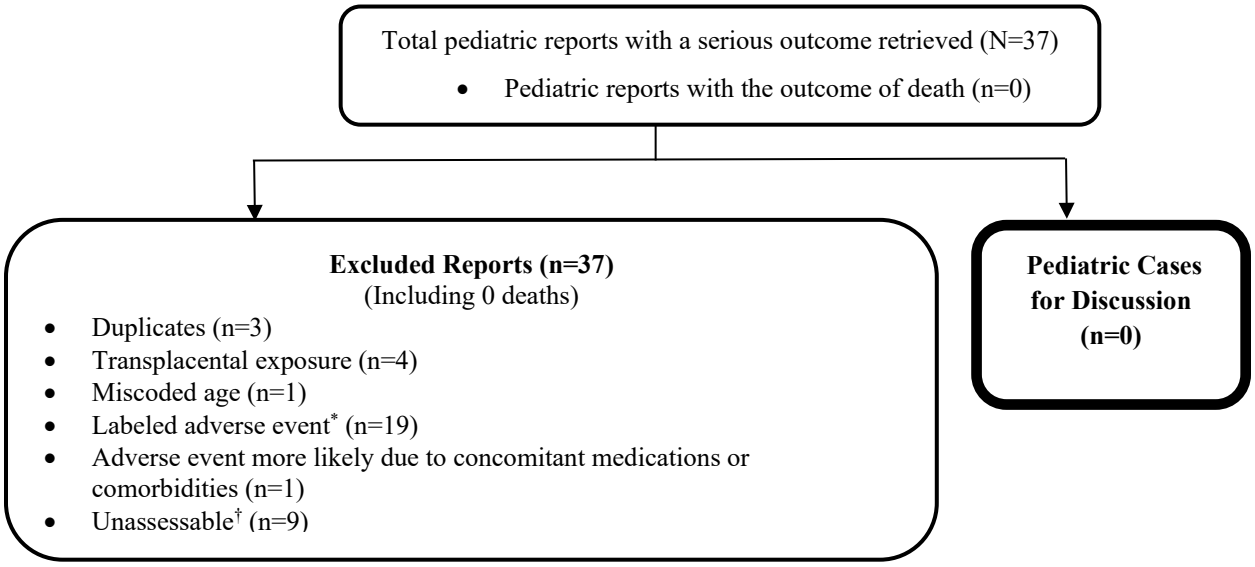
3 RESULTS

3.1 FAERS

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

Our FAERS search retrieved 37 U.S. serious pediatric reports for patients less than 18 years old from July 10, 2015 – May 11, 2025. We excluded all 37 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 Brexpiprazole



* 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.

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 reviewed all U.S. serious FAERS reports with brexpiprazole in pediatric patients less than 18 years of age from July 10, 2015 – May 11, 2025, and identified 37 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 brexpiprazole in pediatric patients less than 18 years of age.

5 CONCLUSION

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

6 REFERENCES

1. Rexulti (brexpiprazole) tablets. [Prescribing information]. Rockville, MD; Otsuka Pharmaceutical Co., Ltd.: July 2015.

2. Rexulti (brexpiprazole) tablets. [Prescribing information]. Deerfield, IL; Otsuka Pharmaceutical Co., Ltd.: May 2024.
3. Rexulti (brexpiprazole) tablets. [Prescribing information]. Deerfield, IL; Otsuka Pharmaceutical Co., Ltd.: December 2021.
4. Rexulti (brexpiprazole) tablets. [Prescribing information]. Deerfield, IL; Otsuka Pharmaceutical Co., Ltd.: May 2024.
5. Approval letter. NDA 205422/S-014. May 9, 2025.

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.