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:	Austedo (deutetrabenazine) tablets
Pediatric Labeling Approval Date:	June 24, 2021
Application Type/Number:	NDA 208082
Applicant:	Teva Branded Pharmaceutical Products R and D, LLC.
TTT Record ID:	2025-13419

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EXECUTIVE SUMMARY

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Austedo (deutetrabenazine) tablets in pediatric patients less than 17 years of age. The Division of Pharmacovigilance (DPV) conducted this review in accordance with the Best Pharmaceuticals for Children Act (BPCA). This review focuses on United States (U.S.) serious unlabeled adverse events associated with deutetrabenazine in pediatric patients.

Austedo (deutetrabenazine) tablets is a vesicular monoamine transporter 2 inhibitor initially approved in the U.S. on April 3, 2017, for the treatment of chorea associated with Huntington's disease.[1] On August 30, 2017, Austedo tablets was approved for the treatment of tardive dyskinesia.[2] On February 17, 2023, FDA approved Austedo XR (deutetrabenazine) extended-release tablets.[3] All Austedo and Austedo XR products are currently indicated for the treatment of 1) adults with chorea associated with Huntington's disease, and 2) adults with tardive dyskinesia.[4]

Deutetrabenazine is not indicated for the use in pediatric patients. On June 24, 2021, Austedo underwent a pediatric labeling change to include information from clinical trials and juvenile animal toxicity studies that failed to establish the safety and effectiveness of Austedo in pediatric patients.[5]

This review was prompted by the pediatric labeling on June 24, 2021. DPV has not previously performed a pediatric postmarketing pharmacovigilance review for deutetrabenazine.

DPV reviewed all U.S. serious FAERS reports with deutetrabenazine in pediatric patients less than 17 years of age from April 3, 2017 – February 9, 2025, and identified 3 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 deutetrabenazine in pediatric patients less than 17 years of age.

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

1 INTRODUCTION

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Austedo (deutetrabenazine) tablets in pediatric patients less than 17 years of age. The Division of Pharmacovigilance (DPV) conducted this review in accordance with the Best Pharmaceuticals for Children Act (BPCA). This review focuses on United States (U.S.) serious unlabeled adverse events associated with deutetrabenazine in pediatric patients.

1.1 PEDIATRIC REGULATORY HISTORY

Austedo (deutetrabenazine) tablets is a vesicular monoamine transporter 2 inhibitor initially approved in the U.S. on April 3, 2017, for the treatment of chorea associated with Huntington's disease.[1] On August 30, 2017, Austedo tablets was approved for the treatment of tardive dyskinesia.[2] On February 17, 2023, FDA approved Austedo XR (deutetrabenazine) extended-release tablets.[3] All Austedo and Austedo XR products are currently indicated for the treatment of 1) adults with chorea associated with Huntington's disease, and 2) adults with tardive dyskinesia.[4]

Deutetrabenazine is not indicated for the use in pediatric patients. On June 24, 2021, Austedo underwent a pediatric labeling change to include information from clinical trials and juvenile animal toxicity studies that failed to establish the safety and effectiveness of Austedo in pediatric patients.[5]

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1.2 RELEVANT LABELED SAFETY INFORMATION

The Austedo (deutetrabenazine) tablets labeling contains the following safety information excerpted from the Highlights of Prescribing Information and the *Pediatric Use* subsection. For additional Austedo labeling information, please refer to the full prescribing information.[4]

WARNING: DEPRESSION AND SUICIDALITY IN PATIENTS WITH HUNTINGTON'S DISEASE
See full prescribing information for complete boxed warning.

- **Increases the risk of depression and suicidal thoughts and behavior (suicidality) in patients with Huntington's disease (5.1)**
- **Balance risks of depression and suicidality with the clinical need for treatment of chorea when considering the use of AUSTEDO XR or AUSTEDO (5.1)**
- **Monitor patients for the emergence or worsening of depression, suicidality, or unusual changes in behavior (5.1)**
- **Inform patients, caregivers, and families of the risk of depression and suicidality and instruct to report behaviors of concern promptly to the treating physician (5.1)**
- **Exercise caution when treating patients with a history of depression or prior suicide attempts or ideation (5.1)**
- **AUSTEDO XR and AUSTEDO are contraindicated in patients who are suicidal, and in patients with untreated or inadequately treated depression (4, 5.1)**

CONTRAINDICATIONS

- Suicidal, or untreated/inadequately treated depression in patients with Huntington's disease (4, 5.1)

- Hepatic impairment (4, 8.6, 12.3)
- Taking reserpine, MAOIs, tetrabenazine, or valbenazine (4, 7.2, 7.3, 7.6)

_____ WARNINGS AND PRECAUTIONS _____

- QT Prolongation: Avoid use in patients with congenital long QT syndrome or with arrhythmias associated with a prolonged QT interval (5.3)
- Neuroleptic Malignant Syndrome (NMS): Discontinue if this occurs (5.4)
- Akathisia, agitation, restlessness, and parkinsonism: Reduce dose or discontinue if this occurs (5.5, 5.6)
- Sedation/somnolence: May impair the patient's ability to drive or operate complex machinery (5.7)

_____ADVERSE REACTIONS_____

- Most common adverse reactions (>8% of AUSTEDO-treated patients with Huntington's disease and greater than placebo): somnolence, diarrhea, dry mouth, and fatigue (6.1)
- Most common adverse reactions (that occurred in 4% of AUSTEDO treated patients with tardive dyskinesia and greater than placebo): nasopharyngitis and insomnia (6.1)

8.4 Pediatric Use

Chorea associated with Huntington's Disease and Tardive Dyskinesia

The safety and effectiveness of AUSTEDO XR and AUSTEDO have not been established in pediatric patients for the treatment of chorea associated with Huntington's disease or for the treatment of tardive dyskinesia.

Tourette Syndrome

The safety and effectiveness of AUSTEDO XR and AUSTEDO have not been established in pediatric patients for the treatment of Tourette syndrome.

Efficacy was not demonstrated in two randomized, double-blind, placebo-controlled studies in pediatric patients aged 6 to 16 years with Tourette syndrome. One study evaluated fixed doses of deutetrabenazine over 8 weeks (NCT03571256); the other evaluated flexible doses of deutetrabenazine over 12 weeks (NCT03452943). The studies included a total of 274 pediatric patients who received at least one dose of deutetrabenazine or placebo. The primary efficacy endpoint in both studies was the change from baseline to end-of-treatment on the Yale Global Tic Severity Scale Total Tic Score (YGTSS-TTS). The estimated treatment effect of deutetrabenazine on the YGTSS-TTS was not statistically significantly different from placebo in either study. The placebo subtracted least squares means difference in YGTSS-TTS from baseline to end-of-treatment was -0.7 (95% CI: -4.1, 2.8) in the flexible dose study and -0.8 (95% CI: -3.9, 2.3) for the primary analysis in the fixed dose study.

The following adverse reactions were reported in frequencies of at least 5% of pediatric patients treated with AUSTEDO and with a greater incidence than in pediatric patients receiving placebo (AUSTEDO vs placebo): headache (includes: migraine, migraine with aura, and headache; 13% vs 9%), somnolence (includes: sedation, hypersomnia, and somnolence; 11% vs 2%), fatigue (8% vs 3%), increased appetite (5% vs <1%), and increased weight (5% vs <1%).

Juvenile Animal Toxicity Data

Deutetrabenazine orally administered to juvenile rats from postnatal days 21 through 70 (at 2.5, 5, or 10 mg/kg/day) resulted in an increased incidence of tremor, hyperactivity, and adverse increases in motor activity at ≥5 mg/kg/day, and reduced body weight and food consumption at 10 mg/kg/day. There was no reproductive or early embryonic toxicity up to the highest dose. All drug-related findings were reversible after a drug-free period. The no observed adverse effect level (NOAEL) in juvenile rats was 2.5 mg/kg/day. These drug-related findings were similar to those observed in adult rats; however, the juvenile rats were more sensitive.

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	February 10, 2025
Time period of search	April 3, 2017† - February 9, 2025
Search type	RxLogix Pediatric Focused Review Alert – DPV
Product terms	Product active ingredient: Deutetrabenazine
MedDRA search terms (Version 27.1)	All Preferred Terms
Other search terms‡	Case Seriousness: Serious Country Derived: USA

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

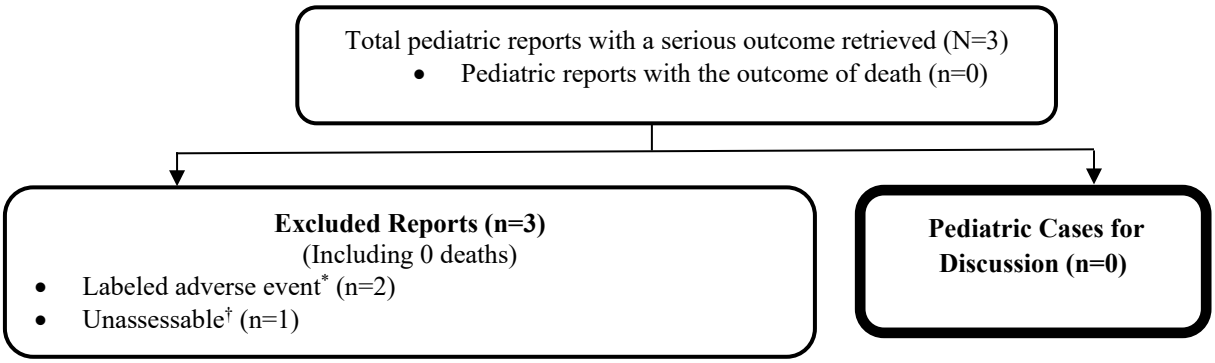
3 RESULTS

3.1 FAERS

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

Our FAERS search retrieved three U.S. serious pediatric reports for patients less than 17 years old from April 3, 2017 – February 9, 2025. We reviewed all U.S. FAERS pediatric reports with a serious outcome. We excluded all three 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 Deutetrabenazine



* 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 deutetrabenazine in pediatric patients less than 17 years of age from April 3, 2017 – February 9, 2025, and identified 3 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 deutetrabenazine in pediatric patients less than 17 years of age.

5 CONCLUSION

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

6 REFERENCES

1. Austedo (deutetrabenazine) tablets. [Prescribing information]. North Wales, PA; Teva Pharmaceuticals USA, Inc.: April 2017.
2. Austedo (deutetrabenazine) tablets. [Prescribing information]. North Wales, PA; Teva Pharmaceuticals USA, Inc.: August 2017
3. Austedo XR (deutetrabenazine) extended-release tablets. [Prescribing information]. Parsippany, NJ; Teva Neuroscience, Inc.: February 2023.
4. Austedo (deutetrabenazine) tablets. [Prescribing information]. Parsippany, NJ; Teva Neuroscience, Inc.: July 2024.
5. Austedo (deutetrabenazine) tablets. [Prescribing information]. Parsippany, NJ; Teva Pharmaceuticals USA, Inc.: June 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.