**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

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|---|---|
| **Date:** | January 19, 2024 |
| **Reviewer:** | Ivone Kim, MD, Medical Officer<br>Division of Pharmacovigilance I |
| **Team Leader:** | Carmen Cheng, PharmD<br>Division of Pharmacovigilance I |
| **Division Director:** | Monica Muñoz, PharmD, PhD<br>Division of Pharmacovigilance I |
| **Product Name:** | Evekeo ODT (amphetamine sulfate) orally disintegrating tablets |
| **Pediatric Labeling Approval Date:** | April 16, 2021 |
| **Application Type/Number:** | NDA 209905 |
| **Applicant:** | Azurity Pharmaceuticals |
| **TTT Record ID:** | 2023-6853 |

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## EXECUTIVE SUMMARY

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Evekeo ODT (amphetamine sulfate) orally disintegrating tablet 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 Evekeo ODT in pediatric patients.

Evekeo ODT (amphetamine sulfate) orally disintegrating tablet is a central nervous system stimulant initially approved in the U.S. on January 30, 2019. Currently, Evekeo ODT is indicated for the treatment of attention deficit hyperactivity disorder (ADHD) in pediatric patients aged 6 through 17 years of age.

At initial approval, Evekeo ODT was indicated for the treatment of ADHD in pediatric patients 6 to 17 years of age. On April 16, 2021, FDA approved the Applicant's supplemental new drug application (sNDA) (NDA 209905/S-001) that provided for a 2.5 mg strength of Evekeo ODT for the treatment of ADHD in pediatric patients 3 to 5 years of age. The Applicant subsequently discontinued the Evekeo ODT 2.5 mg dosage strength. On September 30, 2022, FDA approved an sNDA (NDA 209905/S-003) providing for the removal of the 2.5 mg dosage strength and related text (e.g., indication and information regarding use in pediatric patients 3 to 5 years old) from the Prescribing Information and Medication Guide.

This pediatric postmarketing safety review was prompted by the pediatric labeling on April 16, 2021, that extended the indication for use in patients 3 through 17 years of age. DPV has not previously performed a pediatric postmarketing pharmacovigilance review specific to Evekeo ODT for the Pediatric Advisory Committee (PAC). However, Evekeo ODT was included in three previous evaluations of ADHD medications presented to the PAC on September 15, 2020:

- A pediatric postmarketing pharmacovigilance review of all amphetamine and mixed salts of a single-entity amphetamine products
- An evaluation of ADHD stimulant medications and atomoxetine for a potential drug-drug interaction (DDI) with antipsychotic medications
- An evaluation of all ADHD stimulant medications and atomoxetine for acute dystonia

Following these evaluations, FDA identified a potential signal for a DDI for hyperkinetic movement disorder for methylphenidate products and risperidone. FDA recommended updating the Drug Interactions section of the product labeling for all respective methylphenidate and risperidone products. FDA did not identify sufficient evidence to support a signal of acute dystonia and ADHD medications, and FDA recommended continued ongoing, postmarketing safety monitoring. The PAC agreed with FDA on both recommendations.

DPV searched FAERS for all serious reports with Evekeo ODT in pediatric patients less than 18 years of age from January 30, 2019 – October 17, 2023, and did not identify any reports.

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

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

# 1 INTRODUCTION

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Evekeo ODT (amphetamine sulfate) orally disintegrating tablet 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 Evekeo ODT in pediatric patients.

## 1.1 PEDIATRIC REGULATORY HISTORY

Evekeo ODT (amphetamine sulfate) orally disintegrating tablet is a central nervous system stimulant initially approved in the U.S. on January 30, 2019. Currently, Evekeo ODT is indicated for the treatment of attention deficit hyperactivity disorder (ADHD) in pediatric patients aged 6 through 17 years of age.[1]

At initial approval, Evekeo ODT was indicated for the treatment of in pediatric patients 6 to 17 years of age.[2] On April 16, 2021, FDA approved the Applicant's supplemental new drug application (sNDA) (NDA 209905/S-001) that provided for a 2.5 mg strength of Evekeo ODT for the treatment of ADHD in pediatric patients 3 to 5 years of age.[3] The Applicant subsequently discontinued the Evekeo ODT 2.5 mg dosage strength. On September 30, 2022, FDA approved an sNDA (NDA 209905/S-003) providing for the removal of the 2.5 mg dosage strength and related text (e.g., indication and information regarding use in pediatric patients 3 to 5 years old) from the Prescribing Information and Medication Guide.[4]

This pediatric postmarketing safety review was prompted by the pediatric labeling on April 16, 2021, that extended the indication for use in patients 3 through 17 years of age. DPV has not previously performed a pediatric postmarketing pharmacovigilance review specific to Evekeo ODT for the Pediatric Advisory Committee (PAC). However, Evekeo ODT was included in three previous evaluations of ADHD medications presented to the PAC on September 15, 2020:

- A pediatric postmarketing pharmacovigilance review of all amphetamine and mixed salts of a single-entity amphetamine products[5]
- An evaluation of ADHD stimulant medications and atomoxetine for a potential drug-drug interaction (DDI) with antipsychotic medications[6]
- An evaluation of all ADHD stimulant medications and atomoxetine for acute dystonia[7]

Following these evaluations, FDA identified a potential signal for a DDI for hyperkinetic movement disorder for methylphenidate products and risperidone. FDA recommended updating the Drug Interactions section of the product labeling for all respective methylphenidate and risperidone products. FDA did not identify sufficient evidence to support a signal of acute dystonia and ADHD medications, and FDA recommended continued ongoing, postmarketing safety monitoring. The PAC agreed with FDA on both recommendations.[8]

## 1.2 RELEVANT LABELED SAFETY INFORMATION

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

**WARNING: ABUSE, MISUSE, AND ADDICTION**

***See full prescribing information for complete boxed warning.***

**EVEKEO ODT has a high potential for abuse and misuse, which can lead to the development of a substance use disorder, including addiction. Misuse and abuse of CNS stimulants, including EVEKEO ODT, can result in overdose and death (5.1, 9.2, 10):**

- **Before prescribing EVEKEO ODT, assess each patient's risk for abuse, misuse, and addiction.**
- **Educate patients and their families about these risks, proper storage of the drug, and proper disposal of any unused drug.**
- **Throughout treatment, reassess each patient's risk and frequently monitor for signs and symptoms of abuse, misuse, and addiction.**

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

- Known hypersensitivity to amphetamine products or other ingredients in EVEKEO ODT. (4)
- Use of monoamine oxidase inhibitor (MAOI) or within 14 days of the last MAOI dose. (4)

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

- Risks to Patients with Serious Cardiac Disease: Avoid use in patients with known structural cardiac abnormalities, cardiomyopathy, serious cardiac arrhythmia, coronary artery disease, or other serious cardiac disease. (5.2)
- Increased Blood Pressure and Heart Rate: Monitor blood pressure and pulse. (5.3)
- Psychiatric Adverse Reactions: Prior to initiating EVEKEO ODT, screen patients for risk factors for developing a manic episode. If new psychotic or manic symptoms occur, consider discontinuing EVEKEO ODT. (5.4)
- Long-term Suppression of Growth in Pediatric Patients: Closely monitor growth (height and weight) in pediatric patients. Pediatric patients not growing or gaining height or weight as expected may need to have their treatment interrupted. (5.5)
- Seizures: May lower the convulsive threshold. If a seizure occurs, discontinue EVEKEO ODT. (5.6)
- Peripheral Vasculopathy, including Raynaud's Phenomenon: Careful observation for digital changes is necessary during EVEKEO ODT treatment. Further clinical evaluation (e.g., rheumatology referral) may be appropriate for patients who develop signs or symptoms of peripheral vasculopathy. (5.7)
- Serotonin Syndrome: Increased risk when co-administered with serotonergic agents (e.g., SSRIs, SNRIs, triptans), but also during overdosage situations. If it occurs, discontinue EVEKEO ODT and initiate supportive treatment. (5.8)
- Motor and Verbal Tics, and Worsening of Tourette's Syndrome: Before initiating EVEKEO ODT, assess the family history and clinically evaluate patients for tics or Tourette's syndrome. Regularly monitor patients for the emergence or worsening of tics or Tourette's syndrome. Discontinue treatment if clinically appropriate. (5.9)

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

Most common adverse reactions (incidence ≥4% and at a rate at least twice placebo) in pediatric patients are: decreased appetite and insomnia. (6)

**8.4 Pediatric Use**

The safety and effectiveness of EVEKEO ODT have been established in pediatric patients 6 years and older. Use of EVEKEO ODT is based on one adequate and well-controlled study with another immediate-release amphetamine sulfate product (EVEKEO) in pediatric patients 6 to 12 years [see Clinical Studies (14)], along with dosing and safety information for other amphetamine products.

The safety and efficacy in pediatric patients less than 6 years have not been established.

Long-Term Growth Suppression

Growth should be monitored during treatment with stimulants, including EVEKEO ODT. Pediatric patients aged 6 to 17 years who are not growing or gaining weight as expected may need to have their treatment interrupted [see Warnings and Precautions (5.5), Adverse Reactions (6.1)].

# 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 | January 30, 2019† - October 17, 2023 |
| Search type | Drug Safety Analytics Dashboard (DSAD) Quick Query |
| Product terms | Product name: Evekeo ODT<br>NDA: 209905 |
| MedDRA search terms (Version 26.0) | All Preferred Terms |
| * See Appendix A for a description of the FAERS database<br>† Evekeo ODT U.S. approval date<br>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 from January 30, 2019 - October 17, 2023, with Evekeo ODT.

| **Table 2. Total Adult and Pediatric FAERS Reports* Received by FDA From January 30, 2019 – October 17, 2023, With Evekeo ODT** | | | |
|---|---|---|---|
| | **All Reports (U.S.)** | **Serious† (U.S.)** | **Death (U.S.)** |
| Adults (≥ 18 years) | 1 (1) | 0 (0) | 0 (0) |
| Pediatrics (0 - < 18 years) | 0 (0) | 0 (0) | 0 (0) |
| * May include duplicates and transplacental exposures, and have not been assessed for causality<br>† 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. | | | |

### *3.1.2 Selection of Serious Pediatric Cases in FAERS*

Our FAERS search retrieved no pediatric reports from January 30, 2019 – October 17, 2023.

### *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 searched FAERS for all serious reports with Evekeo ODT in pediatric patients less than 18 years of age from January 30, 2019 – October 17, 2023, and did not identify any reports.

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

## 5 CONCLUSION

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

## 6 REFERENCES


1. Evekeo ODT (amphetamine sulfate) orally disintegrating tablets. [Prescribing information]. Atlanta, GA; Arbor Pharmaceuticals, LLC.: October 2023.
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7. Kim I. Integrated Postmarket Safety Review. ADHD Stimulants and Atomoxetine and Acute Dystonia. June 15, 2020. Available at: https://www.fda.gov/media/142148/download
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# 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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