**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:** | Dyanavel XR (amphetamine) extended-release tablet |
| **Pediatric Labeling Approval Date:** | November 4, 2021 |
| **Application Type/Number:** | NDA 210526 |
| **Applicant:** | Tris Pharma, Inc. |
| **TTT Record ID:** | 2023-6852 |

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## EXECUTIVE SUMMARY

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Dyanavel XR (amphetamine) extended-release 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 Dyanavel XR in pediatric patients.

Dyanavel XR tablet is a central nervous system stimulant indicated for the treatment of attention deficit hyperactivity disorder (ADHD) in patients aged 6 years and older.

Dyanavel XR was first approved by FDA on October 19, 2015, as an extended-release oral suspension under New Drug Application (NDA) 208147. On November 4, 2021, FDA approved NDA 210526 for Dyanavel XR extended-release tablet formulation. Dyanavel XR extended-release oral suspension contains 2.5mg amphetamine base equivalents per mL. Dyanavel XR extended-release tablet is available in the following strengths: 5 mg, 10 mg, 15 mg, 20 mg.

This pediatric postmarketing safety review was prompted by pediatric labeling on November 4, 2021, at initial approval of Dyanavel XR extended-release oral tablet, which included a pediatric indication for use in patients aged 6 years and older. DPV has not previously performed a pediatric postmarketing pharmacovigilance review of Dyanavel XR extended-release tablet for the Pediatric Advisory Committee (PAC). However, DPV presented a pediatric postmarketing pharmacovigilance review of Dyanavel XR extended-release oral suspension for the PAC on June 13, 2018. DPV's evaluation did not identify any new safety signals with Dyanavel XR extended-release oral suspension. The Office of Surveillance and Epidemiology also presented three previous pharmacovigilance assessments to the PAC on September 15, 2020 that included Dyanavel XR extended-release oral suspension:

- 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 reviewed all serious FAERS reports with Dyanavel XR in pediatric patients less than 18 years of age from October 19, 2015 – October 17, 2023, and identified one report. However, DPV excluded this report 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 Dyanavel XR in pediatric patients less than 18 years of age.

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

# 1 INTRODUCTION

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Dyanavel XR (amphetamine) extended-release 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 Dyanavel XR in pediatric patients.

## 1.1 PEDIATRIC REGULATORY HISTORY

Dyanavel XR tablet is a central nervous system stimulant indicated for the treatment of attention deficit hyperactivity disorder (ADHD) in patients aged 6 years and older.[1]

Dyanavel XR was first approved by FDA on October 19, 2015, as an extended-release oral suspension under New Drug Application (NDA) 208147.[2] On November 4, 2021, FDA approved NDA 210526 for Dyanavel XR extended-release tablet formulation.[3] Dyanavel XR extended-release oral suspension contains 2.5 mg amphetamine base equivalents per mL. Dyanavel XR extended-release tablet is available in the following strengths: 5 mg, 10 mg, 15 mg, 20 mg.[1]

This pediatric postmarketing safety review was prompted by pediatric labeling on November 4, 2021, at initial approval of Dyanavel XR extended-release oral tablet, which included a pediatric indication for use in patients aged 6 years and older. DPV has not previously performed a pediatric postmarketing pharmacovigilance review of Dyanavel XR extended-release tablet for the Pediatric Advisory Committee (PAC). However, DPV presented a pediatric postmarketing pharmacovigilance review of Dyanavel XR extended-release oral suspension for the PAC on June 13, 2018.[4] DPV's evaluation did not identify any new safety signals with Dyanavel XR extended-release oral suspension. The Office of Surveillance and Epidemiology also presented three previous pharmacovigilance assessments to the PAC on September 15, 2020 that included Dyanavel XR extended-release oral suspension:

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

**WARNING: ABUSE, MISUSE, AND ADDICTION**
***See full prescribing information for complete boxed warning.***

**DYANAVEL XR 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 DYANAVEL XR, can result in overdose and death (5.1, 9.2, 10):**
**•Before prescribing DYANAVEL XR, 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 DYANAVEL XR (4)
- Use of monoamine oxidase inhibitor (MAOI) or within 14 days of the last MAOI dose (4, 7.1)

----------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 DYANAVEL XR, screen patients for risk factors for developing a manic episode. If new psychotic or manic symptoms occur, consider discontinuing DYANAVEL XR (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)
- Peripheral Vasculopathy, including Raynaud's phenomenon: Careful observation for digital changes is necessary during DYANAVEL XR treatment. Further clinical evaluation (e.g., rheumatology referral) may be appropriate for patients who develop signs or symptoms of peripheral vasculopathy (5.6)
- Serotonin Syndrome: Increased risk when co-administered with serotonergic agents (e.g., SSRIs, SNRIs, triptans), but also during overdosage situations. If it occurs, discontinue DYANAVEL XR and initiate supportive treatment (5.7)
- Motor and Verbal Tics, and Worsening of Tourette's Syndrome: Before initiating DYANAVEL XR, 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. (5.8)

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

Most common adverse reactions observed with amphetamine products: dry mouth, anorexia, weight loss, abdominal pain, nausea, insomnia, restlessness, emotional lability, dizziness, tachycardia (6.1)

**8.4 Pediatric Use**

The safety and effectiveness have been established in pediatric patients with ADHD ages 6 to 17 years [see Adverse Reactions (6.1), Clinical Pharmacology (12), and Clinical Studies (14)].

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

*Long-Term Growth Suppression*

Growth should be monitored during treatment with stimulants, including DYANAVEL XR, and pediatric patients who are not growing or gaining weight as expected may need to have their treatment interrupted [see Warnings and Precautions (5.5)].

# 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 | October 19, 2015† - October 17, 2023 |
| Search type | Drug Safety Analytics Dashboard (DSAD) Quick Query |
| Product terms | Product name: Dyanavel XR<br>NDA: 210526 |
| MedDRA search terms (Version 26.0) | All Preferred Terms |
| * See Appendix A for a description of the FAERS database.<br>† U.S. approval date for the first Dyanavel XR extended-release oral suspension (NDA 208147)<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 October 19, 2015 – October 17, 2023, with Dyanavel XR.

| **Table 2. Total Adult and Pediatric FAERS Reports* Received by FDA From October 19, 2015 – October 17, 2023, With Dyanavel XR** | | | |
|---|---|---|---|
| | **All Reports (U.S.)** | **Serious† (U.S.)** | **Death (U.S.)** |
| Adults (≥ 18 years) | 1 (1) | 1 (1) | 0 (0) |
| Pediatrics (0 - < 18 years) | 14 (14) | 1 (1) | 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 one U.S. serious pediatric report from October 19, 2015 – October 17, 2023. We reviewed the FAERS pediatric report with a serious outcome, but we excluded the report from the case series as it described a labeled adverse event for Dyanavel XR. The report did not raise concern for increased severity or frequency for the labeled adverse event.

### *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 Dyanavel XR in pediatric patients less than 18 years of age from October 19, 2015 – October 17, 2023, and identified one report. However, DPV excluded this report 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 Dyanavel XR in pediatric patients less than 18 years of age.

## 5 CONCLUSION

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

## 6 REFERENCES


1. Dyanavel XR (amphetamine) extended-release oral suspension and extended-release tablets. [Prescribing information]. Monmouth Junction, NJ; Tris Pharma, Inc.: October 2023.
2. Approval letter. NDA 208147. October 19, 2015. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2015/208147Orig1s000ltr.pdf
3. Approval letter. NDA 210526. November 4, 2021. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2021/210526Orig1s000ltr.pdf
4. Chen A. Pediatric Postmarketing Pharmacovigilance Review. Dyanavel XR (amphetamine suspension) extended release and Adzenys XR-ODT (amphetamine tablet) orally disintegrating. NDA 208147 and NDA 204326. April 17, 2018. Available at: https://www.fda.gov/media/114080/download
5. Mohamoud M. Pediatric Postmarketing Pharmacovigilance and Drug Utilization Review. Mydayis and Adzenys ER. NDA 022063 and NDA 204325. July 30, 2020. Available at: https://www.fda.gov/media/142058/download
6. Mohamoud M. Integrated Postmarket Safety Review. ADHD Stimulants and Atomoxetine & Antipsychotics. March 19, 2020. Available at: https://www.fda.gov/media/142149/download
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
8. Pediatric Advisory Committee Meeting. September 15, 2020. Available at: https://www.fda.gov/advisory-committees/pediatric-advisory-committee/2020-meeting-materials-pediatric-advisory-committee

# 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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