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:	October 24, 2023
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Product Name:	Adhansia XR (methylphenidate hydrochloride) extended-release capsules
Pediatric Labeling Approval Date:	February 27, 2019
Application Type/Number:	NDA 212038
Applicant:	Purdue Pharma LP
TTT Record ID:	2023-6237

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EXECUTIVE SUMMARY

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Adhansia XR (methylphenidate hydrochloride) extended-release capsules 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 Adhansia XR in pediatric patients.

Adhansia XR (methylphenidate hydrochloride) extended-release capsules is a central nervous system stimulant that was initially approved in the U.S. on February 27, 2019. It is currently indicated for the treatment of attention deficit hyperactivity disorder (ADHD) in patients 6 years of age and older.

This pediatric postmarketing safety review was prompted by pediatric labeling at initial U.S. approval on February 27, 2019, that included use in pediatric patients aged 6 years and older. The safety and effectiveness of Adhansia XR in pediatric patients under 6 years of age have not been established.

Of note, the Applicant for Adhansia XR requested that FDA withdrawal approval of the application under the process in 21 CFR 314.150(c). Adhansia XR has been withdrawn per the Federal Register effective January 9, 2023.

DPV has not previously presented a pediatric postmarketing pharmacovigilance review specific to Adhansia XR before the Pediatric Advisory Committee (PAC). However, Adhansia XR was included in previous reviews of all ADHD medications for the PAC. The Office of Surveillance and Epidemiology (OSE) presented Adhansia XR to the PAC on September 15, 2020, in the context of two analyses: 1) an evaluation of ADHD stimulant medications and atomoxetine for a potential drug-drug interaction (DDI) with antipsychotic medications, and 2) 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 and 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 recommended continued ongoing, postmarketing safety monitoring. The PAC agreed with the FDA on both recommendations.

DPV searched FAERS for all serious reports with Adhansia XR in pediatric patients less than 18 years of age from February 27, 2019 – August 31, 2023, and identified 11 reports. However, all reports were excluded 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 Adhansia XR in pediatric patients less than 18 years of age.

DPV did not identify any new pediatric safety concerns for Adhansia XR at this time.

1 INTRODUCTION

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Adhansia XR (methylphenidate hydrochloride) extended-release capsules 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 Adhansia XR in pediatric patients.

1.1 PEDIATRIC REGULATORY HISTORY

Adhansia XR (methylphenidate hydrochloride) extended-release capsules is a central nervous system stimulant that was initially approved in the U.S. on February 27, 2019. It is currently indicated for the treatment of attention deficit hyperactivity disorder (ADHD) in patients 6 years of age and older.[1]

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Of note, the Applicant for Adhansia XR requested that FDA withdrawal approval of the application under the process in 21 CFR 314.150(c). Adhansia XR has been withdrawn per the Federal Register effective January 9, 2023.[2]

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1.2 RELEVANT LABELED SAFETY INFORMATION

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

WARNING: ABUSE AND DEPENDENCE

See full prescribing information for complete boxed warning.

- **CNS stimulants, including ADHANSIA XR, other methylphenidate-containing products, and amphetamines, have a high potential for abuse and dependence (5.1, 9.2, 9.3)**
- **Assess the risk of abuse prior to prescribing, and monitor for signs of abuse and dependence while on therapy (5.1, 9.2)**

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

- Known hypersensitivity to methylphenidate or product components. (4) Concurrent treatment with a monoamine oxidase inhibitor (MAOI) or use of an MAOI within the preceding 14 days. (4)

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

- Serious Cardiovascular Events: Sudden death has been reported in association with CNS stimulants at recommended doses in pediatric patients with structural cardiac abnormalities or other serious heart problems. In adults, sudden death, stroke, and myocardial infarction have been reported. Avoid use in patients with known structural cardiac abnormalities, cardiomyopathy, serious heart arrhythmias, or coronary artery disease. (5.2)
- Blood Pressure and Heart Rate Increases: Monitor blood pressure and pulse. Consider the benefits and risks in patients for whom an increase in blood pressure or heart rate would be problematic. (5.3)
- Psychiatric Adverse Reactions: Use of CNS stimulants may cause psychotic or manic symptoms in patients with no prior history, or exacerbation of symptoms in patients with pre-existing psychiatric illness. Evaluate for bipolar disorder prior to ADHANSIA XR use. (5.4)
- Priapism: Cases of painful and prolonged penile erections and priapism have been reported with methylphenidate products. Immediate medical attention should be sought if signs or symptoms of prolonged penile erections or priapism are observed. (5.5)
- Peripheral Vasculopathy, including Raynaud's Phenomenon: Stimulants used to treat ADHD are associated with peripheral vasculopathy, including Raynaud's phenomenon. Careful observation for digital changes is necessary during treatment with ADHD stimulants. (5.6)
- Long-Term Suppression of Growth: Monitor height and weight at appropriate intervals in pediatric patients. (5.7)
- Allergic-Type Reactions: FD&C Yellow No. 5: ADHANSIA XR 45 mg capsules contain FD&C Yellow No. 5 (tartrazine) which may cause allergic type reactions (including bronchial asthma) in certain susceptible persons. (5.8)

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

The most common (≥5% and twice the rate of placebo) adverse reactions occurring with ADHANSIA XR in adults are insomnia, dry mouth, nausea, and decreased appetite.

The most common (≥5% and twice the rate of placebo) adverse reactions occurring with ADHANSIA XR in pediatric patients are decreased appetite, insomnia, and weight decreased. (6.1)

----------DRUG INTERACTIONS----------

- Antihypertensive drugs: Monitor blood pressure. Adjust dosage of antihypertensive drug as needed. (7.1)

8.4 Pediatric Use

Safety and effectiveness of ADHANSIA XR in pediatric patients under the age of 6 years have not been established.

The safety and effectiveness of ADHANSIA XR have been established in one adequate and well controlled 6-week study in pediatric patients ages 6 to 12 years, and in one adequate and well-controlled 4-week study in pediatric patients ages 12 to 17 years [see Clinical Studies (14)]. The long-term efficacy of methylphenidate in pediatric patients has not been established.

Long Term Suppression of Growth
Growth should be monitored during treatment with stimulants, including ADHANSIA XR. Pediatric patients who are not growing or gaining weight as expected may need to have their treatment interrupted [see Warnings and Precautions (5.7)].

Juvenile Animal Toxicity Data
Rats treated with methylphenidate early in the postnatal period through sexual maturation demonstrated a decrease in spontaneous locomotor activity in adulthood. A deficit in acquisition of a specific learning task was observed in females only. The doses at which these findings were observed are at least 3 times the maximum recommended human dose (MRHD) of 85 mg/day given to children on a mg/m2 basis.

In the study conducted in young rats, methylphenidate was administered orally at doses of up to 100 mg/kg/day for 9 weeks, starting early in the postnatal period (postnatal day 7) and continuing through sexual maturity (postnatal week 10). When these animals were tested as adults (postnatal weeks 13-14), decreased spontaneous locomotor activity was observed in males and females previously treated with 50 mg/kg/day (approximately 3 times the MRHD of 85 mg/day given to children on a mg/m2 basis) or greater, and a deficit in the acquisition of a specific learning task was observed in females exposed to the highest dose (6 times the MRHD given to children on a mg/m2 basis). The no effect level for juvenile neurobehavioral development in rats was 5 mg/kg/day (approximately 0.25 times the MRHD given to children on a mg/m2 basis). The clinical significance of the long-term behavioral effects observed in rats is unknown.

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	September 5, 2023
Time period of search	February 27, 2019† - August 31, 2023
Search type	Drug Safety Analytics Dashboard (DSAD) Quick Query
Product terms	Product Name: Adhansia XR NDA: 212038
MedDRA search terms (Version 26.0)	All Preferred Terms
* See Appendix A for a description of the FAERS database. † Adhansia XR U.S. approval date Abbreviations: NDA=New Drug Application, MedDRA=Medical Dictionary for Regulatory Activities	

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 February 27, 2019 – August 31, 2023, with Adhansia XR.

Table 2. Total Adult and Pediatric FAERS Reports* Received by FDA From February 27, 2019 – August 31, 2023, with Adhansia XR			
	All Reports (U.S.)	**Serious† (U.S.)**	**Death (U.S.)**
Adults (≥ 18 years)	17 (8)	12 (3)	0 (0)
Pediatrics (0 - < 18 years)	29 (20)	11 (2)	0 (0)

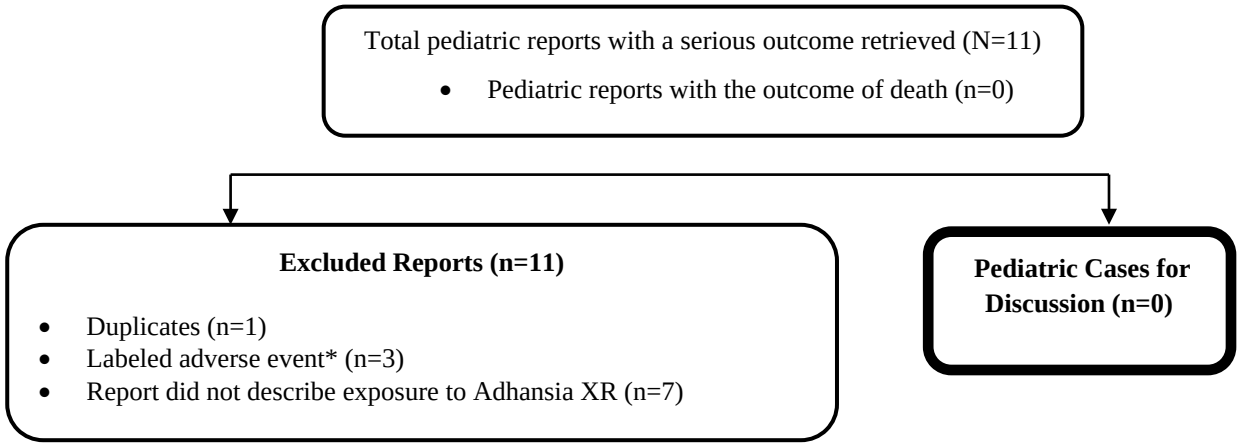
* May include duplicates and transplacental exposures, and have not been assessed for causality

† 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 11 serious pediatric reports from February 27, 2019 – August 31, 2023. We reviewed all FAERS pediatric reports with a serious outcome. We excluded all 11 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 Serious Pediatric Cases With Adhansia XR



* Labeled adverse event does not represent increased severity or frequency.

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 Adhansia XR in pediatric patients less than 18 years of age from February 27, 2019 – August 31, 2023, and identified 11 reports. However, all reports were excluded 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 Adhansia XR in pediatric patients less than 18 years of age.

5 CONCLUSION

DPV did not identify any new pediatric safety concerns for Adhansia XR at this time.

6 REFERENCES

1. Adhansia XR (methylphenidate hydrochloride) extended-release capsules. [Prescribing information]. Wilson, NC; Purdue Pharmaceuticals L.P.: June, 2021.
2. Federal Register. Vol 87, No 235. Thursday, December 8, 2022. (2022-26661). Available at: https://www.federalregister.gov/documents/2022/12/08/2022-26661/teva-branded-pharmaceutical-products-r-and-d-inc-et-al-withdrawal-of-approval-of-35-new-drug
3. Mohamoud M. Integrated Postmarket Safety Review. ADHD Stimulants and Atomoxetine & Antipsychotics. March 19, 2020. Available at: https://www.fda.gov/media/142149/download
4. 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

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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