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Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Pharmacovigilance and Epidemiology

Pediatric Postmarketing Pharmacovigilance Review

Date:	February 21, 2024
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Product Name:	Azstarys (serdexmethylphenidate and dexmethylphenidate) capsules
Pediatric Labeling Approval Date:	March 2, 2021
Application Type/Number:	NDA 212994
Applicant:	Commave Therapeutics SA
TTT Record ID:	2023-6858

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EXECUTIVE SUMMARY

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Azstarys (serdexmethylphenidate and dexmethylphenidate) 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 Azstarys in pediatric patients.

Azstarys (serdexmethylphenidate and dexmethylphenidate) capsules is a central nervous system stimulant that was initially approved in the U.S. on March 2, 2021. Azstarys 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 the pediatric labeling at initial FDA approval on March 2, 2021, that included a pediatric indication for patients aged 6 years and older. DPV has not previously conducted a pediatric postmarketing pharmacovigilance review for Azstarys for the Pediatric Advisory Committee.

DPV reviewed all serious FAERS reports with Azstarys in pediatric patients less than 18 years of age from March 2, 2021 – October 17, 2023, and identified four reports. However, DPV excluded all reports 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 Azstarys in pediatric patients less than 18 years of age.

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

1 INTRODUCTION

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Azstarys (serdexmethylphenidate and dexmethylphenidate) 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 Azstarys in pediatric patients.

1.1 PEDIATRIC REGULATORY HISTORY

Azstarys (serdexmethylphenidate and dexmethylphenidate) capsules is a central nervous system stimulant that was initially approved in the U.S. on March 2, 2021. Azstarys 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 the pediatric labeling at initial FDA approval on March 2, 2021, that included a pediatric indication for patients aged 6 years and older. DPV has not previously conducted a pediatric postmarketing pharmacovigilance review for Azstarys for the Pediatric Advisory Committee.

1.2 RELEVANT LABELED SAFETY INFORMATION

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

WARNING: ABUSE, MISUSE, AND ADDICTION

See full prescribing information for complete boxed warning.

AZSTARYS 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 AZSTARYS, can result in overdose and death (5.1, 9.2, 10):

- **Before prescribing AZSTARYS, 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 serdexmethylphenidate, methylphenidate, or product components.
- Concurrent treatment with a monoamine oxidase inhibitor (MAOI), or use of an MAOI within the preceding 14 days.

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

- Risks to Patients with Serious Cardiac Disease: Avoid use in patients with known structural cardiac abnormalities, cardiomyopathy, serious cardiac arrhythmias, 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 AZSTARYS, screen patients for risk factors for developing a manic episode. If new psychotic or manic symptoms occur, consider discontinuing AZSTARYS. (5.4)
- Priapism: If abnormally sustained or frequent and painful erections occur, patients should seek immediate medical attention. (5.5)
- Peripheral Vasculopathy, including Raynaud's Phenomenon: Careful observation for digital changes is necessary during AZSTARYS treatment with ADHD stimulants. Further clinical evaluation (e.g., rheumatology referral) may be appropriate for patients who develop signs or symptoms of peripheral vasculopathy. (5.6)
- Long-Term Suppression of Growth in Pediatric Patients: Monitor height and weight at appropriate intervals in pediatric patients. (5.7)
- Acute Angle Closure Glaucoma: AZSTARYS-treated patients considered at risk for acute angle closure glaucoma (e.g., patients with significant hyperopia) should be evaluated by an ophthalmologist. (5.8)
- Increased Intraocular Pressure (IOP) and Glaucoma: Prescribe AZSTARYS to patients with open-angle glaucoma or abnormally increased IOP only if the benefit of treatment is considered to outweigh the risk. Closely monitor patients with a history of increased IOP or open angle glaucoma. (5.9)
- Motor and Verbal Tics, and Worsening of Tourette's Syndrome: Before initiating AZSTARYS, 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. (5.10)

----------ADVERSE REACTIONS ----------
Based on accumulated data from other methylphenidate products, the most common (>5% and twice the rate of placebo) adverse reactions are appetite decreased, insomnia, nausea, vomiting, dyspepsia, abdominal pain, weight decreased, anxiety, dizziness, irritability, affect lability, tachycardia, and blood pressure increased. (6)

8.4 Pediatric Use

The safety and effectiveness of AZSTARYS have been established in pediatric patients ages 6 to 17 years of age for the treatment of ADHD. Use of AZSTARYS in patients 6 to 12 years of age is supported by a randomized, double-blind, placebo-controlled, parallel group trial in 155 pediatric patients with ADHD and a 12-month open-label long term safety trial in 238 patients [see Adverse Reactions (6.1), Clinical Studies (14)]. Use of AZSTARYS in pediatric patients 13 to 17 years of age is supported by additional pharmacokinetics analysis showing similar plasma concentration-time profiles of dexmethylphenidate in adolescents and adults after administration of the same dose of AZSTARYS [see Clinical Studies (14)]. The long-term efficacy of methylphenidate in pediatric patients has not been established. The safety and effectiveness of AZSTARYS in pediatric patients less than 6 years have not been established.

Long Term Suppression of Growth

Growth should be monitored during treatment with stimulants, including AZSTARYS. Pediatric patients who are not growing or gaining weight as expected may need to have their treatment interrupted [see Warnings and Precautions (5.7) and Adverse Reactions (6.1)].

Juvenile Animal Toxicity Data

Rats treated with racemic 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 MRHD of 40 mg/day dexmethylphenidate hydrochloride given to children on a mg/m^2 basis.

In a study conducted in young rats, racemic methylphenidate hydrochloride 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 to14), decreased spontaneous locomotor activity was observed in males and females previously treated with 50 mg/kg/day racemic methylphenidate hydrochloride [approximately 3 times the maximum recommended human dose (MRHD) of 40 mg of dexmethylphenidate hydrochloride given to children on a mg/m^2 basis] or greater, and a deficit in the acquisition of a specific learning task was seen in females exposed to the highest dose (6 times the MRHD of 40 mg of dexmethylphenidate hydrochloride given to children on a mg/m^2 basis). The no effect level for juvenile neurobehavioral development in rats was 5 mg/kg/day racemic methylphenidate hydrochloride (less than the MRHD of 40 mg of dexmethylphenidate hydrochloride given to children on a mg/m^2 basis). The clinical significance of the long-term behavioral effects observed in rats is unknown.

Serdexmethylphenidate was administered orally to juvenile rabbits at doses up to 280 mg/kg/day (approximately 50 times the MRHD of 52 mg/day serdexmethylphenidate given to children on a mg/m^2 basis), respectively, for 6 months, starting at postnatal Day 28 and continuing through sexual maturity (postnatal Day 196). No adverse findings were observed at the highest dose of serdexmethylphenidate.

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	March 2, 2021† – October 17, 2023
Search type	Drug Safety Analytics Dashboard (DSAD) Quick Query
Product terms	Product name: Azstarys NDA: 212994
MedDRA search terms (Version 26.0)	All Preferred Terms

* See Appendix A for a description of the FAERS database.
† Azstarys U.S. approval date
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 March 2, 2021 – October 17, 2023, with Azstarys.

Table 2. Total Adult and Pediatric FAERS Reports* Received by FDA From March 2, 2021 – October 17, 2023, With Azstarys			
	All Reports (U.S.)	**Serious† (U.S.)**	**Death (U.S.)**
Adults (≥ 18 years)	24 (24)	2 (2)	0 (0)
Pediatrics (0 - < 18 years)	51 (51)	4 (4)	0 (0)

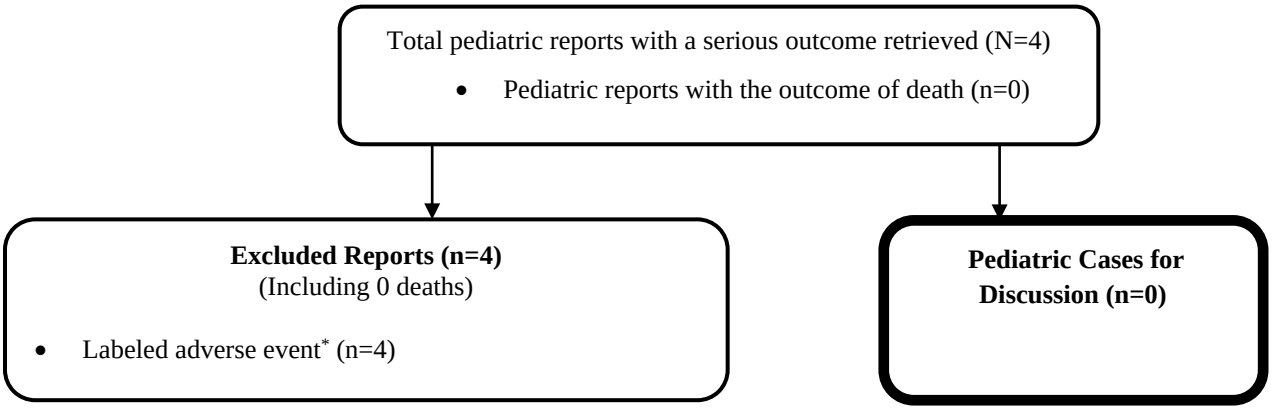
* May include duplicates and transplacental exposures, and have not been assessed for causality

† 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 four serious pediatric reports from March 2, 2021 – October 17, 2023. We reviewed all FAERS pediatric reports with a serious outcome. We excluded all four 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 Azstarys



* 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 reviewed all serious FAERS reports with Azstarys in pediatric patients less than 18 years of age from March 2, 2021 – October 17, 2023, and identified four reports. However, DPV excluded all reports 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 Azstarys in pediatric patients less than 18 years of age.

5 CONCLUSION

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

6 REFERENCES

1. Azstarys (serdexmethylphenidate and dexmethylphenidate) capsules. [Prescribing information]. Boston, MA; Corium, LLC: October 2023.

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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