Department of Health and Human Services
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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:	April 25, 2023
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Product Name:	Aptensio XR (methylphenidate hydrochloride)
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Application Type/Number:	NDA 205831
Applicant:	Rhodes Pharmaceuticals LP
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EXECUTIVE SUMMARY

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Aptensio XR (methylphenidate hydrochloride) in pediatric patients through age 17 years. The Division of Pharmacovigilance (DPV) conducted this review in accordance with the Food and Drug Administration Amendments Act (FDAAA) and the Pediatric Research Equity Act (PREA). This review focuses on U.S. serious unlabeled adverse events associated with Aptensio XR in pediatric patients.

Aptensio XR is a central nervous system stimulant. FDA first approved Aptensio XR on April 17, 2015, for the treatment of attention deficit hyperactivity disorder (ADHD) in patients 6 years and older. This review was prompted by the June 14, 2019, pediatric labeling change that updated the Aptensio XR labeling to include findings from three clinical trials in patients under 6 years of age. NCT02683265 was a single-dose, open-label, randomized pharmacokinetic study of Aptensio XR capsules in children ages 4 to 5 years with ADHD in fed condition. NCT02470234 was a randomized, double-blind, placebo-controlled, flexible-dose titration study of Aptensio XR capsules in children ages 4 to 5 years diagnosed with ADHD. And NCT02677519 was a one-year pediatric open-label safety study for patients ages 4 to 5 years with ADHD. The studies failed to establish safety and effectiveness of Aptensio XR in children under 6 years of age.

DPV reviewed all U.S. serious FAERS reports with Aptensio XR in the pediatric population (ages 0-17 years) from January 1, 2018, through December 11, 2022. DPV identified no cases reporting an unlabeled adverse event with Aptensio XR. There were no new safety signals and no deaths associated with Aptensio XR.

DPV did not identify any new pediatric safety concerns for Aptensio XR at this time. DPV recommends no regulatory action at this time and will continue to monitor all adverse events associated with the use of Aptensio XR.

1 INTRODUCTION

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Aptensio XR (methylphenidate hydrochloride) in pediatric patients through age 17 years. The Division of Pharmacovigilance (DPV) conducted this review in accordance with the Food and Drug Administration Amendments Act (FDAAA) and the Pediatric Research Equity Act (PREA). This review focuses on U.S. serious unlabeled adverse events associated with Aptensio XR in pediatric patients.

1.1 PEDIATRIC REGULATORY HISTORY

Aptensio XR is a central nervous system stimulant. FDA first approved Aptensio XR on April 17, 2015, for the treatment of attention deficit hyperactivity disorder (ADHD) in patients 6 years and older.[1] Safety and efficacy for the use of Aptensio XR in pediatric patients ages 6 to 17 years derived from two well-controlled clinical trials including NCT01269463, a randomized, double-blind, single center, placebo-controlled, flexible-dose, cross over trial in pediatric patients ages 6 to 12 years and NCT01239030, a randomized, double-blind, multicenter, placebo-controlled, fixed-dose trial in pediatric patients 6 to 17 years old.

This review was prompted by the June 14, 2019, pediatric labeling change that updated the Aptensio XR labeling to include findings from three clinical trials in patients under 6 years of age. NCT02683265 was a single-dose, open-label, randomized pharmacokinetic study of Aptensio XR capsules in children ages 4 to 5 years with ADHD in fed condition. NCT02470234 was a randomized, double-blind, placebo-controlled, flexible-dose titration study of Aptensio XR capsules in children ages 4 to 5 years diagnosed with ADHD. And NCT02677519 was a one-year pediatric open-label safety study for patients ages 4 to 5 years with ADHD. The studies failed to establish safety and effectiveness of Aptensio XR in children under 6 years of age.[1]

DPV previously evaluated postmarketing adverse event reports with a serious outcome for Aptensio XR in pediatric patients for the Pediatric Advisory Committee (PAC). DPV's evaluation, dated May 24, 2018, was prompted by the pediatric labeling from the initial FDA approval of Aptensio XR.[2] DPV's evaluation did not identify any new safety concerns and recommended return to routine monitoring for adverse events with Aptensio XR. Additionally, Aptensio XR was included in the review of all methylphenidate products for the PAC. The Office of Surveillance and Epidemiology (OSE) presented methylphenidate products 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,[3] and 2) an evaluation of all ADHD stimulant medications and atomoxetine for acute dystonia.[4] 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 sections of the product labelings 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, postmarket safety monitoring. The PAC agreed with the FDA on both recommendations.

1.2 RELEVANT LABELED SAFETY INFORMATION[1]

The Aptensio XR labeling contains the following safety information excerpted from the Highlights section of the product labeling and the Pediatric Use subsection. For further labeling information, please refer to the full prescribing information.

WARNING: ABUSE AND DEPENDENCE

See full prescribing information for complete boxed warning.

- **CNS stimulants, including APTENSIO 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, 9.3)**

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

- *Serious Cardiovascular Events:* Sudden death has been reported in association with CNS stimulant treatment 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 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 APTENSIO 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)

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

The most common adverse reactions in double-blind clinical trials (> 5% and twice the rate of placebo) in pediatric patients 6 to 17 years were abdominal pain, decreased appetite, headache and insomnia. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Rhodes Pharmaceuticals L.P. at (1-888-827-0616); or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

8.4 Pediatric Use

The safety and effectiveness of APTENSIO XR in pediatric patients under 6 years have not been established.

Safety and efficacy of APTENSIO XR were evaluated in a multicenter, placebo-controlled, double-blind, parallel group study in 119 children 4 to <6 years of age with ADHD followed by a 12-month open-label extension in 44 of these children. In these studies, patients experienced high rates of adverse reactions, most notably weight loss. Comparing weights prior to initiation of APTENSIO XR (in the safety and efficacy study) to weights after 12 months of treatment (in the open-label extension), 20 of 39 patients with data (50%) had lost enough weight to decrease 10 or more percentiles on a

Centers for Disease Control growth chart for weight. In addition, systemic drug exposures in patients 4 to <6 years of age were higher than those observed in older children and adolescents at the same dose (2 to 3 fold higher Cmax and AUC). Therefore, the benefits of APTENSIO XR do not outweigh the risks in pediatric patients 4 to <6 years of age.

The safety and effectiveness of APTENSIO XR have been established in pediatric patients ages 6 to 17 years in two adequate and well-controlled clinical trials [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 APTENSIO 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 6 times the maximum recommended human dose (MRHD) of 60 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 6 times the MRHD of 60 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 (8 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 0.5 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	December 15, 2022
Time period of search	January 1, 2018† through December 14, 2022
Search type	DSAD Quick Query
Product terms	Product name: Aptensio XR Application: NDA 205831
MedDRA search terms (Version 25.0)	All PT terms

* See Appendix A for a description of the FAERS database.
† Data lock date from previous Aptensio XR PAC review
Abbreviations: DSAD=Drug Safety Analytics Dashboard, NDA=New Drug Application, MedDRA=Medical Dictionary for Regulatory Activities, PT=Preferred Term

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 1, 2018, through December 14, 2022, with Aptensio XR.

Table 2. Total Adult and Pediatric FAERS Reports[*] Received by FDA From January 1, 2018, through December 14, 2022, with Aptensio XR.

	All reports (U.S.)	Serious[†] (U.S.)	Death (U.S.)
Adults (≥ 18 years)	65 (23)	54 (12)	10 (3)
Pediatrics (0 - <18 years)	117[‡] (57)	**89[‡] (29)**	3[‡] (2)

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

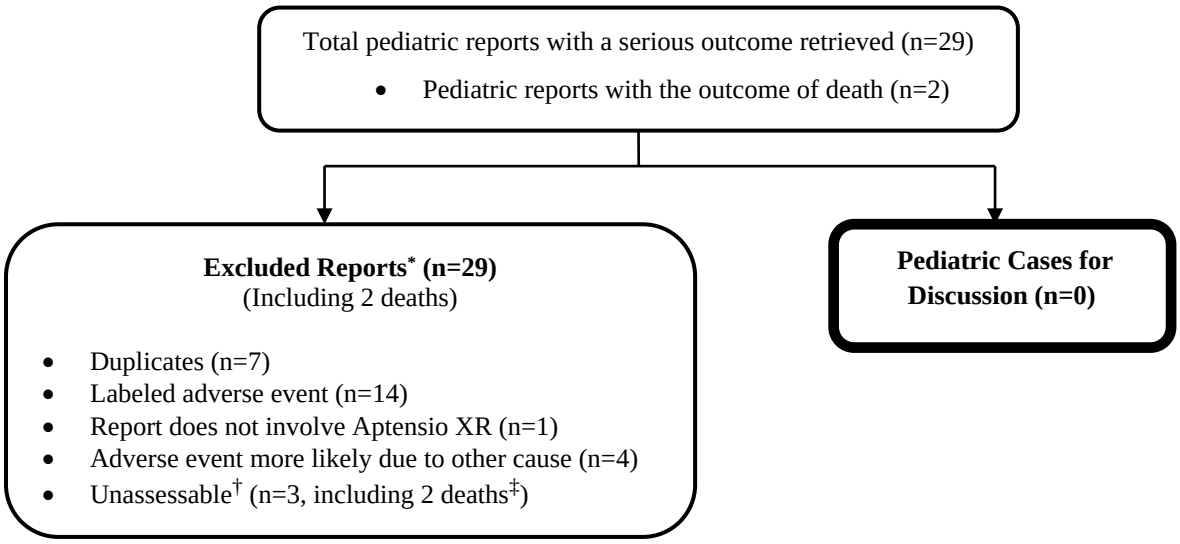
† For the purposes of this review, the following outcomes qualify as serious: death, life- threatening, hospitalization (initial or prolonged), disability, congenital anomaly, required intervention, or other serious important medical events.

‡ See Figure 1. One report of pediatric death was identified among reports not coded with an age. The report is reflected in the total count of pediatric reports.

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

The FAERS search retrieved 29 U.S. serious pediatric reports from January 1, 2018, through December 14, 2022. DPV screened the 29 reports and excluded them all from the case series for various reasons including duplicate reporting (n=7), adverse event already included in the Aptensio XR product labeling (n=14), report did not involve Aptensio XR (n=1), adverse event was more likely due to another cause (n=4), or report was unassessable (n=3). **Figure 1** presents the selection of cases for the pediatric case series.

Figure 1. Selection of Serious U.S. Pediatric Cases with Aptensio XR



* DPV reviewed these cases, but they were excluded from further discussion for the reasons listed above

† Unassessable: 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) or the information is contradictory or information provided in the report cannot be supplemented or verified.

‡ Two reports described fatal outcomes but were unassessable as there was no clinical information to inform causality.

3.1.3 Summary of Fatal Pediatric U.S. Cases (N=0)

There are no fatal pediatric adverse event U.S. cases for further discussion.

3.1.4 Summary of Non-Fatal Pediatric U.S. Serious Cases (N=0)

There are no non-fatal pediatric U.S. cases for further discussion.

4 DISCUSSION

DPV reviewed all U.S. serious FAERS reports with Aptensio XR in the pediatric population (ages 0-17 years) from January 1, 2018, through December 11, 2022. DPV identified no cases reporting an unlabeled adverse event with Aptensio XR. There were no new safety signals and no deaths associated with Aptensio XR.

5 CONCLUSION

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

6 RECOMMENDATION

DPV recommends no regulatory action at this time and will continue to monitor all adverse events associated with the use of Aptensio XR.

7 REFERENCES

1. Aptensio XR (methylphenidate hydrochloride) [package insert]. Coventry, RI: Rhodes Pharmaceuticals L.P. April 2015.
2. Cheng C. Pediatric postmarketing pharmacovigilance review. Aptensio XR and QuilliChew ER. May 24, 2018. Available at: https://www.fda.gov/media/114065/download
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

8 APPENDICES

8.1 APPENDIX A. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

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 (MedDRA) terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary (FPD).

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 or not 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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