Department of Health and Human Services
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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:	January 3, 2023
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Product Name:	Jornay PM (methylphenidate hydrochloride)
Pediatric Labeling Approval Date:	August 8, 2018
Application Type/Number:	NDA 209311
Applicant:	Ironshore Pharmaceuticals, Inc.
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EXECUTIVE SUMMARY

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Jornay PM (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 unlabeled adverse events associated with Jornay PM in pediatric patients.

FDA approved Jornay PM on August 8, 2018. Jornay PM is a central nervous system stimulant indicated for the treatment of attention deficit hyperactivity disorder (ADHD) in patients aged 6 years and older. Safety and effectiveness for Jornay PM derived from two adequate and well-controlled clinical studies in pediatric patients aged 6 to 12 years, pharmacokinetic data in adults, and safety information from other methylphenidate-containing products. Safety and effectiveness in pediatric patients less than 6 years old have not been established.

This review was prompted by the August 8, 2018, approval of Jornay PM, which included an indication for pediatric patients. DPV has not prepared a Jornay PM-specific presentation to the Pediatric Advisory Committee (PAC) in the past.

DPV reviewed all FAERS reports with Jornay PM in the pediatric population (ages 0-17 years) through October 10, 2022. DPV identified no cases reporting an unlabeled adverse event with Jornay PM. There were no new safety signals and no deaths associated with Jornay PM.

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

1 INTRODUCTION

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Jornay PM (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 unlabeled adverse events associated with Jornay PM in pediatric patients.

1.1 PEDIATRIC REGULATORY HISTORY

FDA approved Jornay PM on August 8, 2018. Jornay PM is a central nervous system stimulant indicated for the treatment of attention deficit hyperactivity disorder (ADHD) in patients aged 6 years and older. Safety and effectiveness for Jornay PM derived from two adequate and well-controlled clinical studies in pediatric patients aged 6 to 12 years, pharmacokinetic data in adults, and safety information from other methylphenidate-containing products. Safety and effectiveness in pediatric patients less than 6 years old have not been established.[1]

This review was prompted by the August 8, 2018, approval of Jornay PM, which included an indication for pediatric patients. DPV has not prepared a Jornay PM-specific presentation to the Pediatric Advisory Committee (PAC) in the past. However, Jornay PM 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,[2] and 2) an evaluation of all ADHD stimulant medications and atomoxetine for acute dystonia.[3] 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[4]

The Jornay PM 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 JORNAY PM, 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 Reactions:* 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 JORNAY PM 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:* CNS 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

Based on accumulated data from other methylphenidate products, the most common (≥5% and twice the rate of placebo) adverse reactions for pediatric patients and adults are: appetite decreased, insomnia, nausea, vomiting, dyspepsia, abdominal pain, weight decreased, anxiety, dizziness, irritability, affect lability, tachycardia, and blood pressure increased.

Additional adverse reactions (≥5% and twice the rate of placebo) in pediatric patients 6 to 12 years treated with JORNAY PM: headache, psychomotor hyperactivity, and mood swings. (6.1)

8.4 Pediatric Use

The safety and effectiveness of JORNAY PM in pediatric patients less than 6 years have not been established.

The safety and effectiveness of JORNAY PM have been established in pediatric patients ages 6 to 17 years in two adequate and well-controlled clinical studies in pediatric patients 6 to 12 years, pharmacokinetic data in adults, and safety information from other methylphenidate-containing products [see Clinical Studies (14) and see Clinical Pharmacology (12.3)].

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 JORNAY PM. Pediatric patients who are not growing or gaining weight as expected may need to have their treatment interrupted [see Warnings and Precautions (5.7)].

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 11, 2022
Time period of search	All dates through October 10, 2022
Search type	Drug Safety Analytics Dashboard (DSAD) Quick Query
Product terms	Product name: Jornay PM Application: NDA 209311
MedDRA search terms (Version 25.0)	All PT terms
* See Appendix A for a description of the FAERS database. Abbreviations: 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 through October 10, 2022, with Jornay PM.

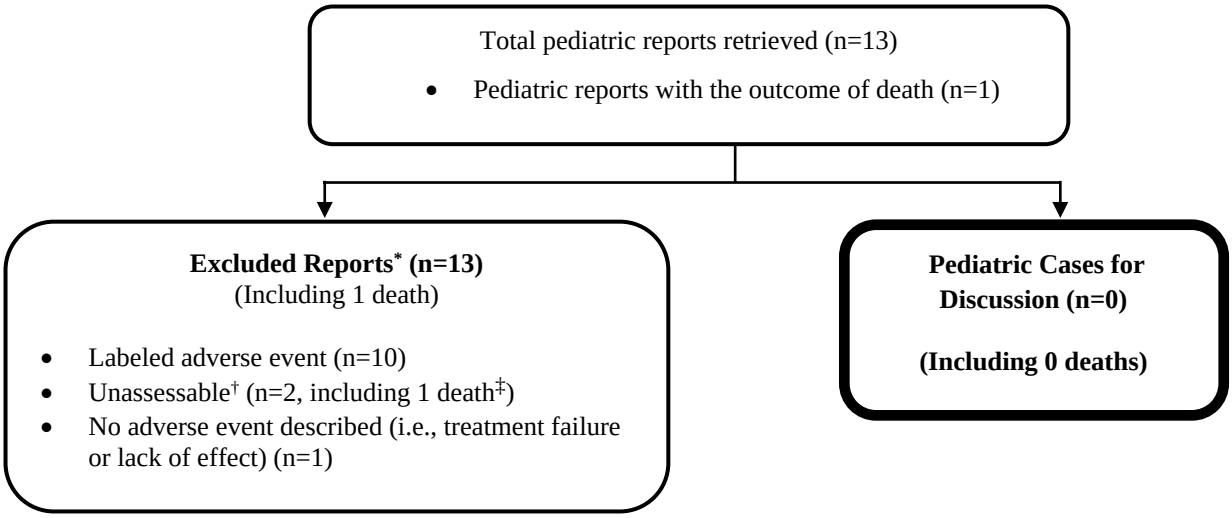
Table 2. Total Adult and Pediatric FAERS Reports* Received by FDA through October 10, 2022 With Jornay PM			
	All reports (U.S.)	**Serious† (U.S.)**	**Death (U.S.)**
Adults (≥ 18 years)	4 (4)	4 (4)	0 (0)
Pediatrics (0 - <18 years)	13 (13)	8 (8)	1 (1)
* May include duplicates and transplacental exposures, 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 Pediatric Cases in FAERS

The FAERS search retrieved 13 pediatric reports through October 10, 2022. Of the 13 reports, 8 were coded with a serious outcome. After hands-on review, all 13 pediatric reports were

excluded from the case series. Reasons for exclusion included description of labeled adverse events (n=10), unassessable causality (n=2), and having no adverse event described (n=1). **Figure 1** presents the selection of cases for the pediatric case series.

Figure 1. Selection of Pediatric Cases with Jornay PM



* DPV reviewed these reports, 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), the information is contradictory, or information provided in the report cannot be supplemented or verified.

‡ One report described a 13-year-old male with a history of ADHD, autism spectrum disorder, and seizure disorder who received other unspecified methylphenidate products in addition to Jornay PM and died in his sleep. Autopsy revealed "methylphenidate toxicity." There was no additional information available to determine if there was possible improper dosing, methylphenidate misuse or abuse, or if there were concomitant medications that may have contributed to the events. The narrative also lacked sufficient clinical detail to determine the degree to which Jornay PM contributed to the death compared with the other methylphenidate products.

3.1.3 Summary of Fatal Pediatric Cases (N=0)

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

3.1.4 Summary of Non-Fatal Pediatric Cases (N=0)

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

4 DISCUSSION

DPV reviewed all FAERS reports with Jornay PM in the pediatric population (ages 0-17 years) through October 10, 2022. DPV identified no cases reporting an unlabeled adverse event with Jornay PM. There were no new safety signals and no deaths associated with Jornay PM.

5 CONCLUSION

DPV did not identify any new pediatric safety concerns for Jornay PM 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 Jornay PM.

7 REFERENCES

1. Dickinson N. Clinical Review. Jornay PM (methylphenidate hydrochloride) NDA 209311. August 7, 2018. Available at: https://www.fda.gov/media/124194/download.
2. Mohamoud M. Integrated Postmarket Safety Review. ADHD Stimulants and Atomoxetine & Antipsychotics. March 19, 2020. Available at: https://www.fda.gov/media/142149/download
3. 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
4. Jornay PM (methylphenidate hydrochloride) extended-release capsules, for oral use (Prescribing Information). Ironshore Pharmaceuticals Inc; Cherry Hill, NJ: June 2021.

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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