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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:	Mydayis (mixed salts of a single-entity amphetamine product) extended-release capsules
Pediatric Labeling Approval Date:	September 13, 2019
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Applicant:	Takeda Pharmaceuticals, USA
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EXECUTIVE SUMMARY

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Mydayis (mixed salts of a single-entity amphetamine product) extended-release capsules in pediatric patients less than 18 years of age. The Division of Pharmacovigilance (DPV) conducted this review in accordance with the Best Pharmaceuticals for Children Act (BPCA) and the Pediatric Research Equity Act (PREA). This review focuses on serious unlabeled adverse events associated with Mydayis extended-release capsules in pediatric patients.

Mydayis (mixed salts of a single-entity amphetamine product) extended-release capsules is a central nervous system stimulant first approved in the U.S. on June 20, 2017. Mydayis is currently indicated for the treatment of attention deficit hyperactivity disorder (ADHD) in patients aged 13 years and older.

This pediatric postmarketing safety review was stimulated by pediatric labeling on September 13, 2019, which included information from two placebo-controlled safety and efficacy trials in patients aged 6 to 12 years old.

On September 15, 2020, the Office of Surveillance and Epidemiology (OSE) presented a pediatric postmarketing pharmacovigilance review on Mydayis and all other amphetamine and mixed salts of a single-entity amphetamine products to the Pediatric Advisory Committee (PAC). Mydayis was also included in two other evaluations of ADHD medications presented to the PAC: 1) an evaluation of ADHD stimulant medications and atomoxetine for a potential drug-drug interaction (DDI) with antipsychotic medications, 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. 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 recommended continued ongoing, postmarketing safety monitoring. The PAC agreed with FDA on both recommendations.

DPV reviewed all serious FAERS reports with Mydayis in pediatric patients less than 18 years of age from May 16, 2019 – 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 Mydayis in pediatric patients less than 18 years of age.

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

1 INTRODUCTION

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Mydayis (mixed salts of a single-entity amphetamine product) extended-release capsules in pediatric patients less than 18 years of age. The Division of Pharmacovigilance (DPV) conducted this review in accordance with the Best Pharmaceuticals for Children Act (BPCA) and the Pediatric Research Equity Act (PREA). This review focuses on serious unlabeled adverse events associated with Mydayis extended-release capsules in pediatric patients.

1.1 PEDIATRIC REGULATORY HISTORY

Mydayis (mixed salts of a single-entity amphetamine product) extended-release capsules is a central nervous system stimulant first approved in the U.S. on June 20, 2017. Mydayis is currently indicated for the treatment of attention deficit hyperactivity disorder (ADHD) in patients aged 13 years and older.[1]

This pediatric postmarketing safety review was stimulated by pediatric labeling on September 13, 2019, which included information from two placebo-controlled safety and efficacy trials in patients aged 6 to 12 years old.

On September 15, 2020, the Office of Surveillance and Epidemiology (OSE) presented a pediatric postmarketing pharmacovigilance review on Mydayis and all other amphetamine and mixed salts of a single-entity amphetamine products to the Pediatric Advisory Committee (PAC).[2] Mydayis was also included in two other evaluations of ADHD medications presented to the PAC: 1) an evaluation of ADHD stimulant medications and atomoxetine for a potential drug-drug interaction (DDI) with antipsychotic medications,[3] 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. 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 recommended continued ongoing, postmarketing safety monitoring. The PAC agreed with FDA on both recommendations.[5]

1.2 RELEVANT LABELED SAFETY INFORMATION

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

WARNING: ABUSE, MISUSE, AND ADDICTION

See full prescribing information for complete boxed warning.

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

- **Before prescribing MYDAYIS, 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 MYDAYIS. (4)
- Use with monoamine oxidase (MAO) inhibitors, or within 14 days of the last MAO inhibitor 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 MYDAYIS, screen patients for risk factors for developing a manic episode. If new psychotic or manic symptoms occur, consider discontinuing MYDAYIS. (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 MYDAYIS treatment. Further clinical evaluation (e.g., rheumatology referral) may be appropriate for patients who develop signs or symptoms of peripheral vasculopathy. (5.6)
- Seizures: May lower the convulsive threshold. If a seizure occurs, discontinue MYDAYIS. (5.7)
- Serotonin Syndrome: Increased risk when co-administered with serotonergic agents (e.g., SSRIs, SNRIs, triptans), but also during overdosage situations. If it occurs, discontinue MYDAYIS and initiate supportive treatment. (5.8)
- Motor and Verbal Tics, and Worsening of Tourette's Syndrome: Before initiating MYDAYIS, 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----------

Most common adverse reactions in patients with ADHD (incidence ≥5% and at a rate at least twice placebo) are:

- Pediatrics (13 years and older): insomnia, decreased appetite, decreased weight, irritability, and nausea. (6.1)
- Adults: insomnia, decreased appetite, decreased weight, dry mouth, increased heart rate, and anxiety. (6.1)

8.4 Pediatric Use

The safety and effectiveness of MYDAYIS in pediatric patients with ADHD ages 13 to 17 years have been established in two placebo-controlled clinical studies [see Adverse Reactions (6.1), Clinical Pharmacology (12.3), Clinical Studies (14)].

The safety and effectiveness of MYDAYIS have not been established in pediatric patients ages 12 years and younger.

MYDAYIS has been studied for the treatment of ADHD in pediatric patients 6 to 12 years in two placebo- controlled safety and efficacy trials. In the first trial, pediatric patients 6 to 12 years experienced higher rates of adverse reactions in some cases compared to patients 13 years and older, including higher rates of insomnia (30% vs 8%) and appetite decreased (43% vs 22%). In addition, amphetamine systemic exposures (both d- and l-) in pediatric patients 6 to 12 years following a single dose were higher than those observed in adults at the same dose (72 to 79% higher C_{max} and approximately 83% higher AUC). A second trial evaluated a lower dose than those approved for pediatric patients 13 to 17 years; efficacy was not demonstrated for the lower dose. Therefore, a safe and effective dose cannot be established in pediatric patients 12 years and younger.

Growth Suppression

Growth should be monitored during treatment with stimulants, including MYDAYIS, in pediatric patients 13 to 17 years who are not growing or gaining weight as expected may need to have their treatment interrupted [see Warnings and Precautions (5.5), Adverse Reactions (6.1)].

Juvenile Animal Toxicity Data

Juvenile rats treated with mixed amphetamine salts (same as in MYDAYIS) early in the postnatal period through sexual maturation demonstrated transient changes in motor activity. Learning and memory was impaired at approximately 8 times the maximum recommended human dose (MRHD) given to children on a mg/m2 basis. No recovery was seen following a drug-free period. A delay in sexual maturation was observed at a dose approximately 8 times the MRHD given to children on a mg/m2 basis, although there was no effect on fertility.

In a juvenile developmental study, rats received daily oral doses of amphetamine (d to l enantiomer ratio of 3:1, the same as in MYDAYIS) of 2, 6, or 20 mg/kg on days 7 to 13 of age; from Day 14 to approximately Day 60 of age these doses were given b.i.d. for total daily doses of 4, 12, or 40 mg/kg. The latter doses are approximately 0.8, 2, and 8 times the MRHD of 25 mg/day given to children on a mg/m2 basis. Postdosing hyperactivity was seen at all doses; motor activity measured prior to the daily dose was decreased during the dosing period but the decreased motor activity was largely absent after an 18-day drug-free recovery period. Performance in the Morris water maze test for learning and memory was impaired at the 40 mg/kg dose, and sporadically at the lower doses, when measured prior to the daily dose during the treatment period; no recovery was seen after a 19-day drug-free period. A delay in the developmental milestones of vaginal opening and preputial separation was seen at 40 mg/kg but there was no effect on fertility.

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	May 16, 2019† – October 17, 2023
Search type	Drug Safety Analytics Dashboard (DSAD) Quick Query
Product terms	Product name: Mydayis NDA: 022063
MedDRA search terms (Version 26.0)	All Preferred Terms
* See Appendix A for a description of the FAERS database † Data lock date from the last pediatric postmarketing pharmacovigilance review for Mydayis 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 May 16, 2019 - October 17, 2023, with Mydayis.

Table 2. Total Adult and Pediatric FAERS Reports* Received by FDA From May 16, 2019 – October 17, 2023, With Mydayis

	All Reports (U.S.)	Serious† (U.S.)	Death (U.S.)
Adults (≥ 18 years)	42 (38)	11 (11)	5 (1)
Pediatrics (0 - < 18 years)	20 (20)	1 (1)	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 one serious pediatric report from May 16, 2019 – October 17, 2023. We reviewed the pediatric report with a serious outcome and excluded it from further discussion as it described a labeled adverse event for Mydayis. 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 Mydayis in pediatric patients less than 18 years of age from May 16, 2019 – 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 Mydayis in pediatric patients less than 18 years of age.

5 CONCLUSION

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

6 REFERENCES

1. Mydayis (mixed salts of a single-entity amphetamine product) extended-release capsules. [Prescribing information]. Lexington, MA; Takeda Pharmaceuticals America, Inc.: October 2023.
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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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