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:	January 19, 2024
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Product Name:	Xelstrym (dextroamphetamine) transdermal system
Pediatric Labeling Approval Date:	March 22, 2022
Application Type/Number:	NDA 215401
Applicant:	Noven Pharmaceuticals, Inc.
TTT Record ID:	2023-6851

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EXECUTIVE SUMMARY

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Xelstrym (dextroamphetamine) transdermal system 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 Xelstrym in pediatric patients.

Xelstrym (dextroamphetamine) transdermal system is a central nervous system stimulant first approved in the U.S. on March 22, 2022. Xelstrym is currently indicated for the treatment of attention deficit hyperactivity disorder (ADHD) in adults and pediatric patients aged 6 years and older.

This pediatric postmarketing safety review was prompted by the Xelstrym pediatric labeling on March 22, 2022, at initial approval that included a pediatric indication.

DPV has not previously performed a pediatric postmarketing pharmacovigilance review for Xelstrym for the Pediatric Advisory Committee.

DPV searched FAERS for all serious reports with Xelstrym in pediatric patients less than 18 years of age from March 22, 2022 – October 17, 2023, and identified two reports. However, DPV excluded these 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 Xelstrym in pediatric patients less than 18 years of age.

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

1 INTRODUCTION

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Xelstrym (dextroamphetamine) transdermal system 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 Xelstrym in pediatric patients.

1.1 PEDIATRIC REGULATORY HISTORY

Xelstrym (dextroamphetamine) transdermal system is a central nervous system stimulant first approved in the U.S. on March 22, 2022. Xelstrym is currently indicated for the treatment of attention deficit hyperactivity disorder (ADHD) in adults and pediatric patients aged 6 years and older.

This pediatric postmarketing safety review was prompted by the Xelstrym pediatric labeling on March 22, 2022, at initial approval that included a pediatric indication.

DPV has not previously performed a pediatric postmarketing pharmacovigilance review for Xelstrym for the Pediatric Advisory Committee.

1.2 RELEVANT LABELED SAFETY INFORMATION

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

WARNING: ABUSE, MISUSE, AND ADDICTION
See full prescribing information for complete boxed warning.

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

- **Before prescribing XELSTRYM, 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 XELSTRYM (4)
- Use with monoamine oxidase inhibitor (MAOI), or within 14 days of the last MAOI 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 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 XELSTRYM, screen patients for risk factors for developing a manic episode. If new psychotic or manic symptoms occur, consider discontinuing XELSTRYM (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 XELSTRYM treatment. Further clinical evaluation (e.g., rheumatology referral) may be appropriate for patients who develop signs or symptoms of peripheral vasculopathy (5.6)
- Serotonin Syndrome: Increased risk when co-administered with serotonergic agents (e.g., SSRIs, SNRIs, triptans), but also during overdosage situations. If it occurs, discontinue XELSTRYM and initiate supportive treatment (5.7, 10)
- Contact Sensitization: Use of XELSTRYM may lead to contact sensitization. Discontinue XELSTRYM if contact sensitization is suspected (5.8)
- Application Site Reactions: During wear time or immediately after removal of XELSTRYM, local skin reactions may occur. Select a different application site each day to limit the occurrence of skin reactions (5.9)
- External Heat: Avoid exposing XELSTRYM to external heat sources during wear because both the rate and extent of absorption are increased (5.10)
- Motor and Verbal Tics, and Worsening of Tourette's Syndrome: Before initiating XELSTRYM, 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 (5.11)

----------ADVERSE REACTIONS----------
Most common adverse reactions (incidence ≥2% and greater than the rate for placebo) in pediatric patients 6 to 17 years treated with XELSTRYM were decreased appetite, headache, insomnia, tic, abdominal pain, vomiting, nausea, irritability, blood pressure increased, and heart rate increased (6.1)

Most common adverse reactions (incidence ≥5% and at a rate at least twice placebo) in adults treated with lisdexamfetamine were decreased appetite, insomnia, dry mouth, diarrhea, nausea, and anxiety (6.1)

8.4 Pediatric Use

The safety and effectiveness of XELSTRYM have been established in pediatric patients with ADHD ages 6 to 17 years [see ADVERSE REACTIONS (6.1), CLINICAL PHARMACOLOGY (12.3), and CLINICAL STUDIES (14)].

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

Safety and efficacy of lisdexamfetamine were evaluated in a double-blind, randomized, parallel group, placebo-controlled, fixed-dose study in pediatric patients 4 to 5 years with ADHD, followed by a 1-year open-label extension study. In these studies, patients experienced elevated rates of adverse reactions, including weight loss, decreased BMI, decreased appetite, insomnia, infections (upper respiratory and nasopharyngitis), irritability, and affect lability.

Growth Suppression
Growth should be monitored during treatment with stimulants, including XELSTRYM, and pediatric patients who are not growing or gaining weight as expected may need to have their treatment interrupted [see WARNINGS AND PRECAUTIONS (5.5) and ADVERSE REACTIONS (6.1)].

Juvenile Animal Data
Juvenile rats treated with mixed amphetamine salts early in the postnatal period through sexual maturation demonstrated transient changes in motor activity. Learning and memory were impaired. No recovery was seen following a drug free period. A delay in sexual maturation was observed, 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) of 2, 6, or 20 mg/kg on days 7-13 of age; from day 14 to approximately day 60 of age, these doses were given twice daily for total daily doses of 4, 12, or 40 mg/kg. Post dosing 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	March 22, 2022† – October 17, 2023
Search type	Drug Safety Analytics Dashboard (DSAD) Quick Query
Product terms	Product name: Xelstrym NDA: 215401
MedDRA search terms (Version 26.0)	All Preferred Terms
* See Appendix A for a description of the FAERS database † Xelstrym 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 22, 2022 - October 17, 2023, with Xelstrym.

Table 2. Total Adult and Pediatric FAERS Reports* Received by FDA From March 22, 2022 – October 17, 2023, With Xelstrym			
	All Reports (U.S.)	**Serious† (U.S.)**	**Death (U.S.)**
Adults (≥ 18 years)	19 (17)	4 (2)	0 (0)
Pediatrics (0 - < 18 years)	10 (10)	2 (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 two serious pediatric reports from March 22, 2022 – October 17, 2023. We reviewed all FAERS pediatric reports with a serious outcome. We excluded both reports from the case series because they described labeled adverse events for Xelstrym. The reports 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 searched FAERS for all serious reports with Xelstrym in pediatric patients less than 18 years of age from March 22, 2022 – October 17, 2023, and identified two reports. However, DPV excluded these 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 Xelstrym in pediatric patients less than 18 years of age.

5 CONCLUSION

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

6 REFERENCES

1. Xelstrym (dextroamphetamine) transdermal system. [Prescribing information]. Miami, FL; Noven Pharmaceuticals, Inc.: 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 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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