Department of Health and Human Services
Public Health Service
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:	February 23, 2024
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Product Name:	Vyvanse (lisdexamfetamine dimesylate) capsule and chewable tablet
Pediatric Labeling Approval Date:	July 29, 2021
Application Type/Number:	NDA 021977 (capsule), 208510 (chewable tablet)
Applicant:	Takeda Pharmaceuticals
TTT Record ID:	2023-6857

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EXECUTIVE SUMMARY

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Vyvanse (lisdexamfetamine dimesylate) capsule and chewable tablet 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 U.S. serious unlabeled adverse events associated with lisdexamfetamine in pediatric patients.

Vyvanse (lisdexamfetamine dimesylate) is a central nervous system stimulant indicated for the treatment of attention deficit hyperactivity disorder (ADHD) in adults and pediatric patients 6 years and older and for the treatment of moderate to severe binge eating disorder (BED) in adults.

Vyvanse is available in capsules (NDA 021977) and chewable tablets (NDA 208510). The history of pediatric labelings for Vyvanse are summarized below:

- February 23, 2007: Initial FDA approval of Vyvanse capsule that included a pediatric indication for the treatment of ADHD in children 6 – 12 years old.
- November 10, 2010: FDA approved extending the indication of Vyvanse capsule for the treatment of ADHD in patients aged 13 – 17 years.
- April 26, 2013: FDA approved the indication of Vyvanse capsule for the maintenance treatment of ADHD in pediatric patients 6 – 17 years old.
- January 28, 2017: Initial FDA approval of Vyvanse chewable tablet that included a pediatric indication for the treatment of ADHD in children aged 6 years and older.
- July 29, 2021: Labeling change for Vyvanse capsule and chewable tablet included data from studies in pediatric patients ages 4-5 years with ADHD that failed to establish safety and effectiveness in patients below 6 years of age.

This review was prompted by the pediatric labeling on July 29, 2021. The Office of Surveillance and Epidemiology (OSE) previously presented three pediatric postmarketing pharmacovigilance assessments for lisdexamfetamine to the Pediatric Advisory Committee (PAC). Additionally, OSE presented two analyses of ADHD medications to the PAC that included lisdexamfetamine.

DPV reviewed all U.S. serious FAERS reports with lisdexamfetamine in pediatric patients less than 18 years of age from May 1, 2019 – October 17, 2023. Of the 54 reports reviewed, 1 case was included in our case series. The case described a patient who experienced acute angle closure glaucoma. An expanded review of the FAERS data and medical literature for glaucoma and lisdexamfetamine did not identify sufficient data to support a signal at this time.

Overall, there were no new safety signals identified, no increased severity or frequency of any labeled adverse events, and no deaths directly associated with lisdexamfetamine in pediatric patients less than 18 years of age.

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

1 INTRODUCTION

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Vyvanse (lisdexamfetamine dimesylate) capsule and chewable tablet 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 U.S. serious unlabeled adverse events associated with lisdexamfetamine in pediatric patients.

1.1 PEDIATRIC REGULATORY HISTORY

Vyvanse (lisdexamfetamine dimesylate) is a central nervous system stimulant indicated for the treatment of attention deficit hyperactivity disorder (ADHD) in adults and pediatric patients 6 years and older and for the treatment of moderate to severe binge eating disorder (BED) in adults.[1]

Vyvanse is available in capsule (NDA 021977) and chewable tablet (NDA 208510) formulations. The history of pediatric labelings for Vyvanse are summarized below:

- February 23, 2007: Initial FDA approval of Vyvanse capsule that included a pediatric indication for the treatment of ADHD in children 6 – 12 years old[2]
- November 10, 2010: FDA approved extending the indication of Vyvanse capsule for the treatment of ADHD in patients aged 13 – 17 years[3]
- April 26, 2013: FDA approved the indication of Vyvanse capsule for the maintenance treatment of ADHD in pediatric patients 6 – 17 years old[4]
- January 28, 2017: Initial FDA approval of Vyvanse chewable tablet that included a pediatric indication for the treatment of ADHD in children aged 6 years and older[5]
- July 29, 2021: Labeling change for Vyvanse capsule and chewable tablet included data from studies in pediatric patients ages 4-5 years with ADHD that failed to establish safety and effectiveness in patients below 6 years of age[6]

This review was prompted by the pediatric labeling on July 29, 2021. The Office of Surveillance and Epidemiology (OSE) previously presented three pediatric postmarketing pharmacovigilance assessments for lisdexamfetamine to the Pediatric Advisory Committee (PAC). Additionally, OSE presented two analyses of ADHD medications to the PAC that included lisdexamfetamine. **Table 1** describes past OSE evaluations of lisdexamfetamine products, OSE findings and recommendations, and PAC recommendations following the OSE presentations.

Table 1: Past OSE Lisdexamfetamine PAC Presentations, OSE Review Findings, and PAC Recommendations

PAC Presentation Date	OSE Review	OSE Review Findings/ Recommendations	PAC Recommendations
9/11/2012	Pediatric postmarketing pharmacovigilance review of Vyvanse (lisdexamfetamine dimesylate)[7]	• No new safety concerns • Recommend routine pharmacovigilance	• Agree with return to standard, ongoing monitoring for adverse events with lisdexamfetamine[8]

Table 1: Past OSE Lisdexamfetamine PAC Presentations, OSE Review Findings, and PAC Recommendations			
PAC Presentation Date	**OSE Review**	**OSE Review Findings/ Recommendations**	**PAC Recommendations**
4/12/2016	Pediatric postmarketing pharmacovigilance and drug utilization review of Vyvanse (lisdexamfetamine dimesylate)[9]	• Identified safety signal for alopecia • Recommended review of safety signal and bring information for the signal to the PAC at a future date	• Continue ongoing safety monitoring with lisdexamfetamine • Agree with plan to evaluate safety signal for alopecia and bring the information to the committee at a future date • Recommend FDA explore the use of claims databases to obtain information regarding suicidality[10]
9/15/2020	Pediatric postmarketing pharmacovigilance review of Vyvanse (lisdexamfetamine dimesylate)[11]	• Identified a potential safety signal of acute dystonic reactions	• Continue routine postmarketing safety surveillance[12]
9/15/2020	Integrated postmarket safety review of ADHD stimulants and atomoxetine & antipsychotics[13]	• Identified a potential signal for a drug-drug interaction for hyperkinetic movement disorder with methylphenidate products and risperidone • Recommended updating Drug Interactions section for all respective methylphenidate and risperidone products	• Agree with updating the Drug Interactions section of the product labeling for methylphenidate and risperidone products.[12]
9/15/2020	Integrated postmarket safety review of ADHD stimulants and atomoxetine & acute dystonia[14]	• No evidence to support a signal of acute dystonia	• Continued ongoing postmarketing pharmacovigilance.[12]

1.2 RELEVANT LABELED SAFETY INFORMATION

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

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

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

- **Before prescribing VYVANSE, 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 VYVANSE (4)
- Use with monoamine oxidase (MAO) inhibitor, 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 VYVANSE, screen patients for risk factors for developing a manic episode. If new psychotic or manic symptoms occur, consider discontinuing VYVANSE. (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 VYVANSE 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 VYVANSE and initiate supportive treatment (4, 5.7, 10)
- Motor and Verbal Tics, and Worsening of Tourette's Syndrome: Before initiating VYVANSE, 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. (5.8)

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

Most common adverse reactions (incidence ≥5% and at a rate at least twice placebo) in pediatric patients ages 6 to 17 years, and/or adults with ADHD were anorexia, anxiety, decreased appetite, decreased weight, diarrhea, dizziness, dry mouth, irritability, insomnia, nausea, upper abdominal pain, and vomiting (6.1)

Most common adverse reactions (incidence ≥ 5% and at a rate at least twice placebo) in adults with BED were dry mouth, insomnia, decreased appetite, increased heart rate, constipation, feeling jittery, and anxiety (6.1)

8.4 Pediatric Use

ADHD

Safety and effectiveness of VYVANSE have been established in pediatric patients with ADHD ages 6 to 17 years [see Dosage and Administration (2.3), Adverse Reactions (6.1), Clinical Pharmacology (12.3), and Clinical Studies (14.1)].

Safety and effectiveness of VYVANSE have not been established in pediatric patients below the age of 6 years.

Safety and efficacy of VYVANSE were evaluated in a double-blind, randomized, parallel-group, placebo-controlled, fixed-dose study in pediatric patients ages 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.

With the same VYVANSE dose, mean steady state exposure of dextroamphetamine was approximately 44% higher in pediatric patients ages 4 to 5 years compared to the pediatric patients ages 6 to 11 years.

BED
Safety and effectiveness of VYVANSE have not been established in pediatric patients with BED less than 18 years of age.

Growth Suppression
Growth should be monitored during treatment with stimulants, including VYVANSE, 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
Studies conducted in juvenile rats and dogs at clinically relevant doses showed growth suppression that partially or fully reversed in dogs and female rats but not in male rats after a four-week drug-free recovery period.

A study was conducted in which juvenile rats received oral doses of 4, 10, or 40 mg/kg/day of lisdexamfetamine dimesylate from day 7 to day 63 of age. These doses are approximately 0.3, 0.7, and 3 times the maximum recommended human daily dose of 70 mg on a mg/m2 basis for a child. Dose-related decreases in food consumption, bodyweight gain, and crown-rump length were seen; after a four-week drug-free recovery period, bodyweights and crown-rump lengths had significantly recovered in females but were still substantially reduced in males. Time to vaginal opening was delayed in females at the highest dose, but there were no drug effects on fertility when the animals were mated beginning on day 85 of age.

In a study in which juvenile dogs received lisdexamfetamine dimesylate for 6 months beginning at 10 weeks of age, decreased bodyweight gain was seen at all doses tested (2, 5, and 12 mg/kg/day, which are approximately 0.5, 1, and 3 times the maximum recommended human daily dose on a mg/m2 basis for a child). This effect partially or fully reversed during a four-week drug-free recovery period.

2 METHODS AND MATERIALS

2.1 FAERS SEARCH STRATEGY

DPV searched the FAERS database with the strategy described in **Table 2**.

Table 2. FAERS Search Strategy*	
Date of search	October 18, 2023
Time period of search	May 1, 2019† – October 17, 2023
Search type	RxLogix Quick Query
Product terms	Product active ingredient: lisdexamfetamine, lisdexamfetamine dimesylate
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 lisdexamfetamine
Abbreviations: MedDRA=Medical Dictionary for Regulatory Activities

3 RESULTS

3.1 FAERS

3.1.1 Total Number of FAERS Reports by Age

Table 3 presents the number of adult and pediatric FAERS reports from May 1, 2019 – October 17, 2023, with lisdexamfetamine.

Table 3. Total Adult and Pediatric FAERS Reports[*] Received by FDA From May 1, 2019 – October 17, 2023, With Lisdexamfetamine

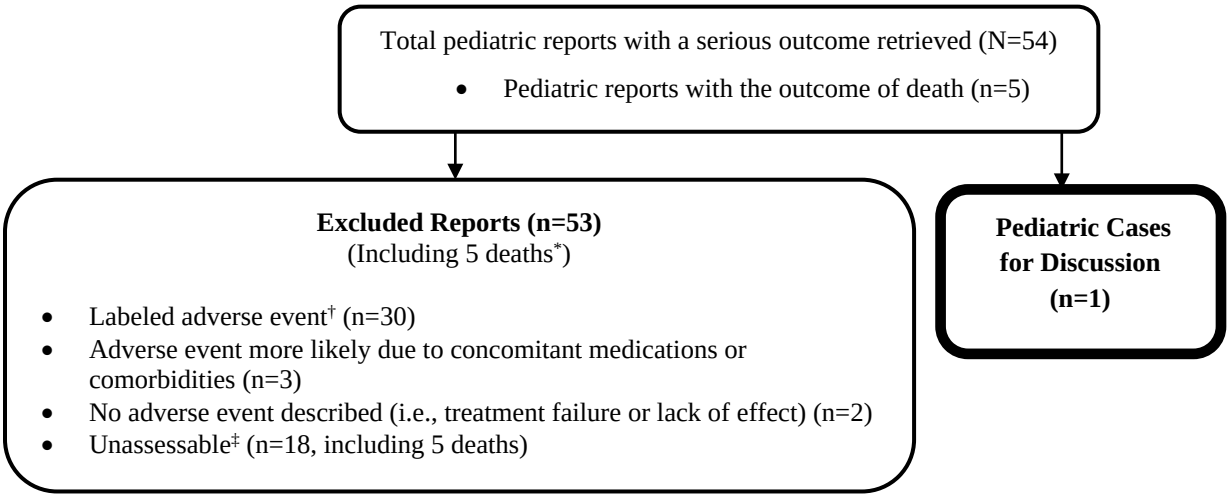
	All Reports (U.S.)	Serious[†] (U.S.)	Death (U.S.)
Adults (≥ 18 years)	667 (667)	174 (174)	7 (7)
Pediatrics (0 - < 18 years)	592[‡] (338)	305[‡] (54)	5[‡] (5)

* 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. Four additional reports of pediatric death were identified among reports not reporting an age. This report is reflected in the counts of pediatric reports.

3.1.2 Selection of Serious Pediatric Cases in FAERS

Our FAERS search retrieved 54 U.S. serious pediatric reports from May 1, 2019 – October 17, 2023. We reviewed all U.S. FAERS pediatric reports with a serious outcome. We excluded 53 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 U.S. Serious Pediatric Cases With Lisdexamfetamine



* Five excluded U.S. FAERS reports describe fatal outcomes. All five cases describe patients of unknown age and gender with completed suicide. Four cases report that the event "was possibly consistent with the underlying mental health condition" for the patient. However, causality with lisdexamfetamine is unassessable as none of cases provide any additional information about clinical or social history to determine whether lisdexamfetamine or other underlying medical conditions contributed to the adverse events.
† Labeled adverse event does not represent increased severity or frequency.
‡ Unassessable: The 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.

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=1)

DPV identified one case with lisdexamfetamine in the U.S. pediatric population reporting a non-fatal serious outcome. The case is summarized below.

FAERS 19034895, Expedited Report, United States, Other Serious Important Medical Event:[15] A 14-year-old male patient received lisdexamfetamine dimesylate 30 mg daily for ADHD for 2 years. The patient discontinued lisdexamfetamine for 6 months due to being out of school, but he restarted the medication at the same dose at the start of virtual learning during the COVID-19 pandemic. He then experienced blurry vision, headache, nausea, vomiting, and photophobia. He presented to the Emergency Department where his physical exam was consistent with acute angle closure (AAC) glaucoma with increased intraocular pressure (IOP) bilaterally (41 mmHg and 43 mmHg in the right eye and left eye, respectively). The patient was instructed to discontinue lisdexamfetamine. His IOP was lowered medically with repeat topical administration of dorzolamide 0.2%/timolol 0.5% and brimonidine 0.2% as well as intravenous acetazolamide over several hours. Approximately 12 hours later, he underwent a laser peripheral iridotomy (LPI) in the right eye resulting in a "dramatic rush of fluid through the patent iridotomy and immediate deepening of the anterior chamber." One week later, he had an LPI performed in the left eye. The patient self-restarted lisdexamfetamine daily 1 week after his second LPI and his ophthalmologic exam remained normal. Ocular coherence tomography, topography, and biometry 1 week after his second LPI showed normal retinal nerve fiber layer thickness for age without evidence of glaucomatous optic atrophy.

Reviewer comment: AAC glaucoma is unusual in young patients.[16] AAC glaucoma has been associated with some therapeutic drug products including angle narrowing medications (e.g., anticholinergic topical pupil dilators) and some systemic medications (e.g., sulfonamides, topiramate, phenothiazines).[17,18] The presence of bilateral AAC glaucoma suggests medication-induced AAC glaucoma. Lisdexamfetamine is not labeled for AAC glaucoma or increased IOP. Of note, no amphetamine ADHD drug product is labeled for AAC glaucoma; however, many methylphenidate ADHD drug products are labeled for AAC glaucoma and increased IOP in the WARNINGS AND PRECAUTIONS sections of their product labeling.[19-32] Although there was a temporal relationship between improvement of symptoms and lisdexamfetamine discontinuation, clinical improvement was also in the setting of medical and surgical interventions for AAC glaucoma. Notably, the patient was exposed to lisdexamfetamine for 2 years without incident, although this does not rule out a spontaneous, idiosyncratic drug reaction. DPV previously completed a pharmacovigilance review of glaucoma and increased IOP with all methylphenidate and amphetamine drug products including lisdexamfetamine on August 5, 2021.[33] DPV's evaluation found insufficient evidence to support inclusion of a warning for glaucoma or increased IOP. For completeness, DPV performed 1) a search of the FAERS data for all dates through October 25, 2023, for reports with lisdexamfetamine or lisdexamfetamine dimesylate coded with the PT Glaucoma and 2) a search of the medical literature for additional cases of glaucoma with lisdexamfetamine. Neither search identified additional cases with possible or probable causality with lisdexamfetamine. There is insufficient evidence to support a signal of glaucoma with lisdexamfetamine at this time.

4 DISCUSSION

DPV reviewed all U.S. serious FAERS reports with lisdexamfetamine in pediatric patients less than 18 years of age from May 1, 2019 – October 17, 2023. Of the 54 reports reviewed, 1 case was included in our case series. The case described a patient who experienced AAC glaucoma. An expanded review of the FAERS data and medical literature for glaucoma and lisdexamfetamine did not identify sufficient data to support a signal at this time.

There were no new safety signals identified, no increased severity or frequency of any labeled adverse events, and no deaths directly associated with lisdexamfetamine in pediatric patients less than 18 years of age.

5 CONCLUSION

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

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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 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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