**Department of Health and Human Services**
**Public Health Service**
**Food and Drug Administration**
**Center for Drug Evaluation and Research**
**Office of Surveillance and Epidemiology**

**Pediatric Postmarketing Pharmacovigilance and Drug Utilization Review**

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| **Product Name:** | Vyvanse (lisdexamfetamine dimesylate) |
| **Pediatric Labeling Approval Date:** | January 28, 2017 |
| **Application Type/Number:** | NDA 021977 (capsule), 208510 (chewable tablet) |
| **Applicant/Sponsor:** | Shire |
| **OSE RCM #:** | 2019-1210 |

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## EXECUTIVE SUMMARY

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for lisdexamfetamine dimesylate (Vyvanse) in pediatric patients less than 18 years of age. The Office of Surveillance and Epidemiology (OSE) conducted this review in accordance with the Food and Drug Administration Amendments Act (FDAAA) Pediatric Research Equity Act (PREA). This review focuses on serious unlabeled adverse events associated with lisdexamfetamine in pediatric patients.

The FDA approved lisdexamfetamine capsules on February 23, 2007 and it is indicated for the treatment of (1) Attention Deficit Hyperactivity Disorder (ADHD) and (2) moderate to severe Binge Eating Disorder (BED) in adults. The approved pediatric labeling is for ADHD in ages 6-17 years. On January 28, 2017, FDA approved lisdexamfetamine chewable tablets, a new formulation of lisdexamfetamine. The approval of this new formulation led to a pediatric labeling change that triggered this PREA review.

The Division of Pharmacovigilance (DPV) reviewed 202 U.S. FAERS reports with a serious outcome for lisdexamfetamine in the pediatric population from July 1, 2015 to April 30, 2019. During this time frame, an annual range of approximately 0.8 to 1.0 million pediatric patients younger than 18 years old received dispensed prescriptions for lisdexamfetamine, mostly 6-17 years old. Half of the FAERS reports described labeled adverse events for lisdexamfetamine. Of these labeled adverse events reported with lisdexamfetamine, we did not identify new pediatric safety signals and did not observe an apparent increased severity or frequency of any labeled adverse events.

We identified 23 serious pediatric cases with unlabeled adverse events for lisdexamfetamine. Three fatal cases reported completed suicide in adolescent patients; there is not enough information provided in these cases that suggests a causal association with lisdexamfetamine. Of the 20 non-fatal cases, we identified a potential safety signal of acute dystonic reactions reported with the use of lisdexamfetamine. Other movement disorders included in the ADVERSE REACTIONS section of the lisdexamfetamine labeling are dyskinesia, tics, bruxism, and tremor.

DPV will perform a review of acute dystonic reactions reported in association with the use of lisdexamfetamine to determine if any regulatory action is needed. DPV will also continue to monitor all adverse events associated with the use of lisdexamfetamine.

# 1 INTRODUCTION

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for lisdexamfetamine dimesylate (Vyvanse) in pediatric patients less than 18 years of age. The Office of Surveillance and Epidemiology (OSE) conducted this review in accordance with the Food and Drug Administration Amendments Act (FDAAA) Pediatric Research Equity Act (PREA). This review focuses on serious unlabeled adverse events associated with lisdexamfetamine in pediatric patients.

## 1.1 PEDIATRIC REGULATORY HISTORY

### Product Information and Dosing

Lisdexamfetamine is a central nervous system (CNS) stimulant indicated for the treatment of (1) Attention Deficit Hyperactivity Disorder (ADHD) and (2) moderate to severe Binge Eating Disorder (BED) in adults. On February 23, 2007, FDA approved new drug application (NDA) 021977 lisdexamfetamine for the treatment of ADHD in children 6 to 12 years of age.[1,2] On November 10, 2010, FDA extended the approval of lisdexamfetamine for ADHD in adolescents 13 to 17 years of age. On April 26, 2013, FDA approved lisdexamfetamine for the maintenance treatment of ADHD in pediatric patients 6 to 17 years of age. On January 30, 2015, FDA approved lisdexamfetamine for the treatment of moderate to severe BED in adults (18 to 55 years of age).

The recommended starting dose of lisdexamfetamine for the treatment of ADHD in pediatric and adult patients is 30 mg once daily in the morning.[2] The dose should be titrated in increments of 10 mg or 20 mg weekly up to a maximum dose of 70 mg; the recommended dose for ADHD treatment is 30 mg to 70 mg.

### Most Recent Pediatric Labeling Change

On January 28, 2017, FDA approved lisdexamfetamine chewable tablets (NDA 208510), a new formulation of lisdexamfetamine, for the treatment of ADHD in patients 6 years and above, and moderate to severe BED in adults.[3] The approval of this new formulation led to a pediatric labeling change that triggered this PREA review. Lisdexamfetamine chewable tablet was demonstrated to be bioequivalent to lisdexamfetamine capsule based on the following studies:[4,5,6]

- Study SHP489-126 (pharmacokinetic bioequivalence study): This Phase 1, randomized, open-label, 2-sequence, 4-period crossover study evaluated the bioavailability of lisdexamfetamine 60 mg capsule formulation compared to lisdexamfetamine 60 mg chewable tablet formulation in 18 healthy adults, ages 18 to 55. This study demonstrated that lisdexamfetamine chewable 60 mg tablet is bioequivalent to lisdexamfetamine 60 mg capsule when administered in a fasting state.
- Study SHP489-127 (food effects study): This Phase 1, randomized, open-label, 2-sequence, 3-period replicated crossover study consisted of a screening period and 3 treatment periods that enrolled 24 healthy adults, ages 18 to 55. This study supported the administration of lisdexamfetamine chewable tablet in a fasting or fed state.

There were no deaths, no serious or severe treatment-emergent adverse events (TEAEs) and no discontinuations due to TEAEs from studies SHP489-126 and SHP489-127. These studies demonstrated that the safety profile of lisdexamfetamine chewable tablets is consistent with the labeled safety information for lisdexamfetamine capsules. There were no new clinical safety or efficacy studies conducted.

Currently, lisdexamfetamine is available as capsules (10 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, and 70 mg) and chewable tablets (10 mg, 20 mg, 30 mg, 40 mg, 50 mg, and 60 mg).

**Past OSE Reviews**

FDA previously presented OSE's pediatric postmarketing safety reviews on lisdexamfetamine to the Pediatric Advisory Committee (PAC) in 2012 and 2016.

In 2012, OSE evaluated postmarketing adverse event reports and drug utilization data for lisdexamfetamine in pediatric patients in two reviews.[7] The evaluation was triggered by the pediatric labeling change for lisdexamfetamine on November 10, 2010, which extended the pediatric ages for the treatment of ADHD to adolescents 13 to 17 years of age. The Division of Pharmacovigilance's (DPV's) evaluation was dated June 14, 2012.[8] Division of Epidemiology II (DEPI II) performed a drug utilization review in pediatric patients on July 9, 2012.[9] FDA presented OSE's evaluation to the PAC on September 11, 2012. OSE's evaluation did not identify any new safety concerns. The Committee recommended returning to standard, ongoing monitoring for adverse events and to be notified after class labeling for ADHD medications is completed.[7]

On February 17, 2016, OSE evaluated postmarketing adverse event reports and drug utilization data for lisdexamfetamine in pediatric patients.[10] OSE included pediatric postmarketing adverse event reports with: (1) a fatal outcome, (2) any adverse events in patients less than 6 years old, or (3) serious, unlabeled events in patients 6 to less than 17 years old. This evaluation was triggered by the pediatric labeling change on April 23, 2013 with the approval of lisdexamfetamine for the maintenance treatment of ADHD in pediatric patients 6 to 17 years of age. FDA presented OSE's evaluation to the PAC on April 12, 2016.[7] OSE identified a safety signal with alopecia reported in association with lisdexamfetamine and recommended to perform a review of this safety signal. The Committee members agreed with DPV's plans to (1) continue ongoing safety monitoring, and (2) review the safety signal for alopecia and bring the information to the committee at a future date. Additionally, (3) Committee members recommended that FDA should explore the use of claims database to obtain information regarding suicidality. Subsequent to the PAC presentation in 2016, DPV completed a postmarketing safety review of alopecia and selected amphetamine products (including lisdexamfetamine) that were not previously labeled for alopecia. On May 19, 2017, alopecia was added to the ADVERSE REACTIONS-Postmarketing Experience section of the labeling for lisdexamfetamine and selected amphetamine products not previously labeled for alopecia.[11] In addition, DEPI has been exploring the use of administrative claims database to evaluate suicide-related outcomes. Our DEPI colleagues, Swain et al., evaluated validated methods for suicidal outcome classification in electronic health care databases.[12] Their findings suggest that many pharmacoepidemiologic studies measuring suicide-related outcomes have poor sensitivity or positive predictive value.

### 1.2 RELEVANT LABELED SAFETY INFORMATION

The following information is an excerpt of the safety information from the Highlights of Prescribing Information section of the lisdexamfetamine labeling:[2]

**----------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, 7.2)

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

- *Serious Cardiovascular Reactions:* 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 arrhythmia, or coronary artery disease (5.2)
- *Blood Pressure and Heart Rate Increases:* Monitor blood pressure and pulse. Consider benefits and risks before use in patients for whom blood pressure increases may be problematic (5.3)
- *Psychiatric Adverse Reactions:* May cause psychotic or manic symptoms in patients with no prior history, or exacerbation of symptoms in patients with pre-existing psychosis. Evaluate for bipolar disorder prior to stimulant use (5.4)
- *Suppression of Growth:* Monitor height and weight in pediatric patients during treatment (5.5)
- *Peripheral Vasculopathy, including Raynaud's phenomenon:* Stimulants are associated with peripheral vasculopathy, including Raynaud's phenomenon. Careful observation for digital changes is necessary during treatment with stimulants (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).

**----------ADVERSE REACTIONS----------**

Most common adverse reactions (incidence ≥5% and at a rate at least twice placebo) in children, adolescents, 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)

Additionally, below is an excerpt from the human data in the Pediatric Use subsection (8.4) of the lisdexamfetamine labeling:[2]

ADHD

Safety and effectiveness 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 (14.1)]*. Safety and efficacy in pediatric patients below the age of 6 years have not been established.

BED

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

Growth Suppression
Growth should be monitored during treatment with stimulants, including VYVANSE, and children 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)]*.

# 2 METHODS AND MATERIALS

## 2.1 FAERS SEARCH STRATEGY

DPV searched the FAERS database with the strategy described in Table 1. We searched FAERS for all lisdexamfetamine reports initially received by the FDA from July 1, 2015 to April 30, 2019. We selected this beginning search date because the FAERS search period for the most recently completed OSE pediatric safety review for lisdexamfetamine ended on June 30, 2015.[10]

| **Table 1. FAERS Search Strategy*** | |
|---|---|
| Date of Search | May 2, 2019 |
| Time Period of Search | July 1, 2015† - April 30, 2019 |
| Search Type | FBIS Quick Query and Product-Manufacturer Reporting Summary |
| Product Terms | Product Active Ingredient: Lisdexamfetamine, Lisdexamfetamine dimesylate |
| MedDRA Search Terms (Version 21.1) | All Preferred Terms |
| * See Appendix A for a description of the FAERS database.<br>† The FAERS search period for the most recently completed OSE pediatric safety review for lisdexamfetamine ended on June 30, 2015.[10]<br>Abbreviations: FBIS=FDA Business Intelligence System, MedDRA=Medical Dictionary for Regulatory Activities | |

## 2.2 DRUG UTILIZATION

Proprietary drug utilization databases available to the Agency were used to conduct these analyses. Full database descriptions and limitations are provided in Appendix B

### *2.2.1 Data Source Used*

The IQVIA Total Patient Tracker™ data source was used to obtain estimated annual numbers of patients who received dispensed prescriptions for lisdexamfetamine from U.S. outpatient retail pharmacies from July 2015 through June 2019.

# 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 July 1, 2015 to April 30, 2019 with lisdexamfetamine.

| Table 2. Total Adult and Pediatric FAERS Reports* Received by FDA from July 1, 2015 to April 30, 2019 with Lisdexamfetamine | | | |
|---|---|---|---|
| | **All reports (U.S.)** | **Serious† (U.S.)** | **Death (U.S.)** |
| Adults (≥ 18 years) | 1387 (1251) | 532 (399) | 79 (70) |
| Pediatrics (0 - <18 years) | 1056‡ (881) | 377 (202§) | 14 (13) |

* 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, and other serious important medical events.

‡ Although the focus of this review is on U.S. pediatric reports with a serious outcome, we screened commonly reported Preferred Terms to identify potential new safety signals in all (serious and non-serious) foreign pediatric reports and non-serious U.S. pediatric reports. We did not identify additional new safety signals from this screening.

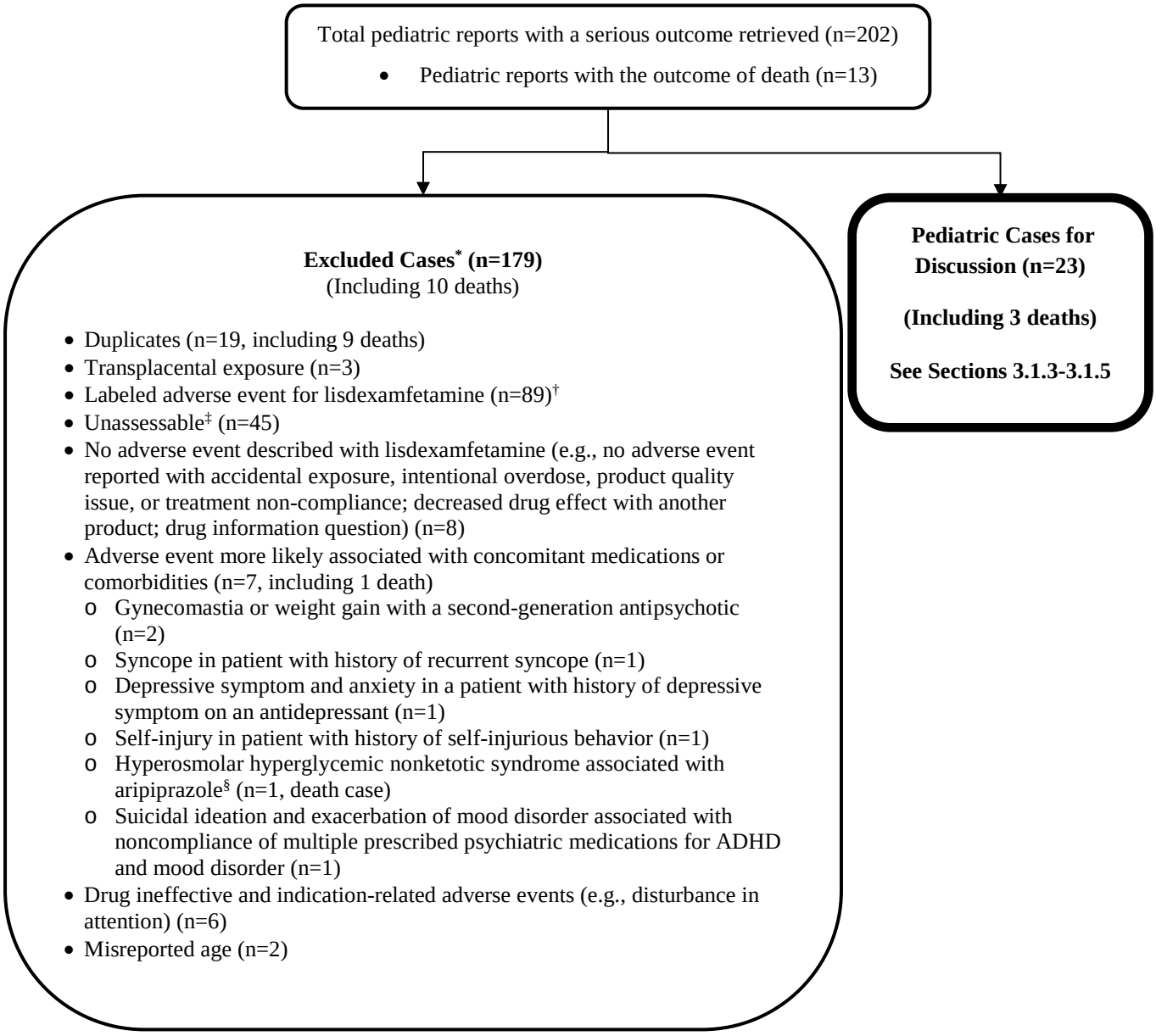
§ See Figure 1.

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

Our FAERS search retrieved 202 U.S. serious pediatric reports from July 1, 2015 to April 30, 2019.

We reviewed all U.S. FAERS pediatric reports with a serious outcome. Figure 1 presents the selection of cases for the pediatric case series. We excluded 179 cases from further discussion for reasons stated in Figure 1. We summarize the remaining 23 cases in the sections below.

**Figure 1. Selection of Serious U.S. Pediatric Cases with Lisdexamfetamine**




* DPV reviewed these cases, but they were excluded from further discussion for the reasons listed above. The FDA approval of a new formulation of lisdexamfetamine (chewable tablets) led to labeling change that triggered this PREA review. Seven of the 179 excluded cases reported the use of lisdexamfetamine chewable tablets. Upon review, the seven cases were excluded for one of the reasons listed above. No additional cases of lisdexamfetamine chewable tablets were included for further discussion.

† Labeled adverse events for lisdexamfetamine included: psychosis, mania, or hallucination (n=19); hypertension or tachycardia (n=15); decreased appetite, weight loss, or suppression of growth (n=8); anaphylactic reaction or hypersensitivity (n=7); dependence or withdrawal (n=7); depression (n=6); seizure (n=5); aggression (n=3); peripheral vasculopathy (n=3); rhabdomyolysis (n=3); chest pain (n=2); constipation (n=2); drug abuse (n=2); mood swing (n=2); dermatillomania (n=1); dyskinesia (n=1); logorrhea (n=1); somnolence (n=1); and tic (n=1).

‡ Unassessable: Case 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 case cannot be supplemented or verified.

§ This FAERS case was also published as an abstract in Clinical Toxicology.[13] A 14-year-old male experienced a fatal outcome as a result of hyperthermia associated with hyperglycemic hyperosmolar nonketotic syndrome. The patient's concomitant medications included aripiprazole. The authors speculated insulin administration also contributed to worsening hyperthermia. This is a labeled event for aripiprazole. The "Metabolic Changes" within the WARNINGS AND PRECAUTIONS section of the aripiprazole labeling state: "Hyperglycemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics."[14]

### *3.1.3 Characteristics of Pediatric Cases*

Appendix C contains a line listing of the 23 pediatric cases.

Table 3 summarizes the 23 FAERS cases in U.S. pediatric patients with lisdexamfetamine reporting a serious outcome received by FDA from July 1, 2015 to April 30, 2019.

**Table 3. Characteristics of the FAERS U.S. Serious Pediatric Cases with Lisdexamfetamine Received by FDA from July 1, 2015 to April 30, 2019 (N=23)**

| | | |
|---|---|---|
| Age | 2 - <6 years | 1 |
| | 6 - <12 years | 10 |
| | 12 - <18 years | 12 |
| Sex | Male | 16 |
| | Female | 7 |
| Reported Reason for Use (n=20) | ADHD | 18 |
| | Dyslexia | 1 |
| | Not applicable* | 1 |
| Serious Outcome† | Death | 3 |
| | Life-threatening | 4 |
| | Hospitalization | 5 |
| | Disability | 2 |
| | Other Serious | 16 |

* One case reported accidental exposure of lisdexamfetamine; therefore, the reported reason for use is not applicable.

† For the purposes of this review, the following outcomes qualify as serious: death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, required intervention, and other serious important medical events. A case may have more than one serious outcome.

### *3.1.4 Summary of Fatal Pediatric Cases (N=3)*

We identified three U.S. fatal pediatric cases reported with lisdexamfetamine in this case series. The patients' ages ranged from 15 to 17 years old. The cause of death included completed suicide by: hanging (n=2) and intentional multi-substance overdose (n=1). The limited information in these postmarketing cases preclude a causality assessment on whether lisdexamfetamine was directly associated with the cause of death. Missing information in these cases included one or more of the following: psychiatric history, social history, history of suicidal thoughts, presence of stressors, concomitant medications, lisdexamfetamine dose, and duration of lisdexamfetamine use. A summary of the three cases is provided below:

- FAERS Case #11555442: A 17-year-old female with a history of "mental disorder" was found unresponsive secondary to intentional overdose (suspected suicide). The patient ingested 54 lisdexamfetamine capsules and unknown quantities of quetiapine, diazepam, and an unspecified drug. She experienced a cardiac arrest and received cardiopulmonary

resuscitation and supportive treatment. She was transported to the hospital but subsequently experienced brain death on Day 2 of hospitalization. This case was also published in the 2015 Annual Report of the American Association of Poison Control Centers' National Poison Data System (NPDS): 33rd Annual Report.[15]

- FAERS Case #11934708: A consumer reported that her 15-year-old nephew with a history of ADHD started treatment with lisdexamfetamine 30 mg in the morning and mixed amphetamine salts 10 mg in the afternoon. Prior to this regimen, the patient had not been on medications for ADHD for 10 to 12 months. However, he had taken other unspecified ADHD medications in the past and experienced suicidal thoughts. One to two months after initiation, the lisdexamfetamine dose was titrated to 50 mg in the morning with mixed amphetamine salts 10 mg in the afternoon. About two months after treatment with lisdexamfetamine was initiated, the patient hung himself one to two hours after taking the afternoon dose of mixed amphetamine salts. Earlier the same day in school, the patient was interactive and seen laughing with classmates.

- FAERS Case #12075626: A physician reported that a 15-year-old male with a history of conduct disorder on lisdexamfetamine (unknown dose or frequency) for an unknown indication was found hanging. It was not reported whether the patient was taking any concomitant medications or whether the patient was compliant with the prescribed lisdexamfetamine. The patient was tachycardic and hypertensive (values not reported). He was admitted to the hospital, placed on mechanical ventilation, and received supportive care. The patient's magnetic resonance imaging showed irreversible brain hypoxia. On Day 7 of hospitalization, life support measures were withdrawn, and the patient expired from respiratory arrest. An autopsy and toxicology report were not provided.

#### *3.1.5 Summary of Non-Fatal Pediatric U.S. Serious Cases (N=20)*

We identified 20 non-fatal FAERS cases with lisdexamfetamine in the U.S. pediatric population reporting a serious outcome. Cases in this section are categorized by Preferred Terms (PTs) that best represent the reported adverse event(s).

##### 3.1.5.1 *Psychiatric Disorders (n=14)*

**Suicidal ideation or behavior (n=11):** Eleven non-fatal cases reported suicidal ideation or behavior, including nine cases of suicidal ideation and two cases of suicidal behavior. There were 6 males and 5 females. The median age was 12 years old (range: 8 to 17 years old). The reported reason for lisdexamfetamine use was treatment of ADHD in 10 cases and dyslexia (off-label use) in the remaining case. We did not identify a trend with the lisdexamfetamine dose among the seven cases that reported a dose (range: 20 mg daily to 50 mg daily); the remaining four cases provided incomplete or missing information regarding the lisdexamfetamine dose.

Five cases reported one or more risk factors for suicidal ideation or behavior such as a medical history of depression, mood disorder, psychological stressor, or the use of an antidepressant labeled with a BOXED WARNING for suicidal behavior. One of the five cases also reported that suicidal ideation was resolving with counseling and the ongoing use of lisdexamfetamine.

Six cases reported the suicidal ideation or behavior resolved following the discontinuation of lisdexamfetamine; however, in three cases this information was reported in a check box without further confirmatory details of the outcome in the narrative. All of the six cases were missing one or more of the following information: medical history, concomitant medication, dose, and time to event onset. Four cases additionally reported one or more of the following labeled adverse events while on lisdexamfetamine: depressed mood, anger, aggression, decreased appetite, and insomnia. Three of the six cases reported a time to event onset: within the first week of lisdexamfetamine initiation (n=2) and one year (two days after lisdexamfetamine dose was increased) (n=1). The remaining three cases did not report a time to event onset but stated the duration of lisdexamfetamine use (4 months, 5 months, and 1 year).

*Reviewer's comment: Suicidal ideation is labeled for lisdexamfetamine under the DRUG ABUSE AND DEPENDENCE section.[2] However, none of the cases reported information that was suggestive of lisdexamfetamine abuse or dependence.*

- **Intentional self-injury or self-injurious ideation (n=3):** Three cases described the occurrence of intentional self-injury or self-injurious ideation without reported suicidal intent in patients taking lisdexamfetamine. The first case reported intentional self-injury in the setting of psychosis in a 9-year-old male with autism spectrum disorder. The second case reported self-injurious ideation in a 9-year-old male with a history of anger, who concomitantly experienced aggravated anger, affect lability, and aggression. The third case reported self-injurious behavior (described as "cutting") in a 13-year-old female patient on lisdexamfetamine for ADHD. Information about the patient's medical history and concomitant medication were not provided. After taking lisdexamfetamine for two months, lisdexamfetamine was discontinued and the event resolved. Three months later, the patient resumed lisdexamfetamine, and she experienced a recurrence of the self-injurious behavior. Lisdexamfetamine was discontinued again and the outcome was not reported.

  *Reviewer's comment: The first two cases reported intentional self-injury or self-injurious ideation related to one or more labeled adverse events for lisdexamfetamine (psychosis, anger, affect lability, and aggression). The third case did not report the patient's medical and social history.*

#### 3.1.5.2 *Nervous System Disorders (n=3)*

- **Dystonia (n=2):** Two cases reported acute dystonic reactions in pediatric patients while taking lisdexamfetamine. The first case was also reported in the literature[16] and described a 26-month-old male who presented to the emergency department with irritability and abnormal gait following accidental exposure to his relative's lisdexamfetamine (one pill of an unknown dose was reported missing). The patient developed "worsening agitation, tachycardia, and dystonia" despite treatment with diphenhydramine and lorazepam. He was also hypertensive. The urine test was positive for amphetamines and benzodiazepines; the positive test for benzodiazepines was presumed to be reflective of lorazepam administration in the hospital. Additional abnormal laboratory test results included elevated white blood count, anion gap metabolic acidosis, and elevated creatine

kinase. The patient was transferred to the pediatric intensive care unit and treated with intravenous dexmedetomidine; the event outcome was not reported.

In the second case, a physician reported the onset of headache and abdominal pain in an 11-year-old male when lisdexamfetamine was initiated for ADHD. Additional medical history included enuresis, color blindness, and gastroesophageal reflux disease. His concomitant medication included cetirizine (no further information on dosage, frequency, and duration of use). After taking lisdexamfetamine for a few months, the medication was discontinued during the summer break. When school resumed, the patient restarted lisdexamfetamine 40 mg daily. Three to four days later, the patient again experienced headache and abdominal pain, in addition to "hand tightness and inability to relax his hands from the flexed position." He experienced multiple episodes where he was "hunched over and hyperventilating." He also "became limp and developed nystagmus." The event resolved following the administration of an unknown medication, reported as possibly lorazepam. The results of an electroencephalogram (EEG) to evaluate for seizure activity and a computerized tomogram of the head were normal. No additional treatment was reported. The "dystonia" resolved, and the patient was discharged on Day 2 of hospitalization. Lisdexamfetamine was discontinued with plans to switch to another ADHD treatment.

*Reviewer's comment: The first case reported an acute dystonic reaction following the accidental ingestion of lisdexamfetamine. The case lacked clinical details to further describe the dystonic reaction, but the treatment was consistent with dystonia. The second case is atypical (preceding headache and abdominal pain), but otherwise consistent with an acute dystonic reaction. Although not much information was reported regarding the use of the patient's concomitant medication, dystonia has been reported with the use of cetirizine.[17] In addition, seizures cannot be ruled out as a differential diagnosis although the results of the EEG was negative, because the EEG was performed after the resolution of the event. With concern for a potential safety signal for acute dystonic reactions, we performed an expanded FAERS search for all lisdexamfetamine reports received by the FDA through July 23, 2019 in all ages with the PT Dystonia. We identified 48 additional reports, including 3 adults, 40 pediatric patients (including 16 duplicates), and 5 reports with an unknown age. A preliminary review of these cases suggests a temporal relationship of acute dystonic reactions reported with lisdexamfetamine. This is an adverse event that DPV has been monitoring with the use of ADHD stimulants based on previous postmarketing adverse event reports.*

- **Cerebrovascular accident (n=1):** A consumer reported that a 10-year-old male experienced a stroke after taking lisdexamfetamine 20 mg daily for two weeks as treatment for ADHD. He was hospitalized for 35 days. The patient was reported to be healthy prior to the event.

  *Reviewer's comment: Stroke is not specifically labeled for the pediatric population but is labeled for the adult population under "Serious Cardiovascular Reactions" within the WARNINGS AND PRECAUTIONS section of the lisdexamfetamine labeling. This is a class warning for the CNS stimulants. Additionally, the PATIENT COUNSELING INFORMATION section instructs healthcare providers to advise patients of the potential*

*serious cardiovascular risks including stroke. Although this report lacked clinical details regarding the type of stroke and clinical work-up, the reported event of stroke occurred without reported risk factors and occurred two weeks after the initiation of lisdexamfetamine.*

*We performed an expanded FAERS search for all reports received by the FDA through July 23, 2019 in all ages with the PT Cerebrovascular accident reported with lisdexamfetamine. The search identified 29 additional reports, including 18 adults (including 1 duplicate report), 7 pediatric patients, and 4 reports with an unknown age. No additional labeling changes are recommended based on a review of these reports. The majority of the pediatric reports included cases with an unconfirmed diagnosis of stroke or provided insufficient information for a causality assessment. In two reports that provided a time to onset, the event occurred four to five years after lisdexamfetamine use. One of the patients was tested positive for a genetic mutation associated with an increased risk of coronary artery disease. Similarly, the majority of the remaining reports (adults and unknown age) were unassessable, had an unconfirmed diagnosis of stroke, or reported risk factors for stroke.*

#### 3.1.5.3 *Other (n=3)*

- **Macular degeneration (n=1):** A physician reported that a 13-year-old male experienced a "blind spot in his vision" and *potential* macular degeneration while taking lisdexamfetamine 70 mg (unspecified frequency). He had been taking lisdexamfetamine for two years and his concomitant medication included bupropion. The event was ongoing at the time of the report.

  *Reviewer's comment: The event of macular degeneration was suspected but not confirmed; additionally, the case did not provide the patient's medical history or ophthalmological examination results. Accommodation abnormality has also been observed with bupropion.[18] Although this case provided limited details, we performed an expanded FAERS search to ensure this is not a safety signal concerning lisdexamfetamine because of the rarity of macular degeneration in the pediatric population. We searched FAERS for all lisdexamfetamine reports received by the FDA through July 23, 2019 in all ages with the PT Macular degeneration; we did not identify any additional reports. Note that other ophthalmic adverse events listed in the lisdexamfetamine labeling under the ADVERSE REACTIONS-Postmarketing Experience section include mydriasis, diplopia, difficulties with visual accommodation, and blurred vision.*

- **Aphthous ulcer (n=1):** A consumer reported that a 15-year-old male experienced canker sores following the initiation of lisdexamfetamine eight to nine years ago. Over the years, the number of occurrences of outbreaks increased, and the patient had "multiple mouth lesions on cheeks, lips, and back of throat." Lisdexamfetamine had been discontinued for four weeks prior to the reporting date. Since the discontinuation, the lesions have healed and have not reoccurred. The reporter inquired whether there were other reports of this adverse event in patients who took lisdexamfetamine.

*Reviewer's comment: Aphthous ulcers, or canker sores, are common conditions of the oral mucosa, and generally lasts up to 14 days with several episodes per year.[19, 20] Predisposing factors may include oral trauma, stress, and certain foods. However, this patient experienced frequent episodes with multiple lesions and the lesions resolved following the discontinuation of lisdexamfetamine. We performed an expanded FAERS search to determine whether there are additional reports that provided evidence of a causal association. We performed an expanded FAERS search for all reports received by the FDA through July 23, 2019 in all ages with the PT Aphthous ulcer reported with lisdexamfetamine. The search retrieved five additional reports, including four pediatric patients, one adult, and the remaining case did not report an age. The reports lacked sufficient information and did not suggest a potential safety signal.*

- **Hepatic enzyme increased (n=1):** A physician reported that a 9-year-old male experienced elevated hepatic enzymes while on lisdexamfetamine 60 mg daily for ADHD. He did not have any additional medical history. Additionally, the patient took mixed amphetamine salts 10 mg daily in the afternoon. About two and one-half years after the initiation of lisdexamfetamine and four months after the initiation of mixed amphetamine salts, the patient's yearly laboratory evaluation demonstrated elevated serum hepatic enzymes (aspartate aminotransferase 413 [unit not specified] and alanine aminotransferase 447 [unit not specified]. As a result, both lisdexamfetamine and mixed amphetamine salts were discontinued.

  *Reviewer's comment: Hepatic enzyme elevation is not labeled for lisdexamfetamine or other amphetamine products. This report is missing information on baseline values of the hepatic enzymes and event outcome. The patient was asymptomatic. Although this report lacked some pertinent information for assessment, we performed an expanded FAERS search for all reports received by the FDA through July 23, 2019 in all ages with the PT Hepatic enzyme increased reported with lisdexamfetamine. The search retrieved 27 additional reports, including one duplicate report. Of the 26 de-duplicated reports, there were 10 pediatric patients, 7 adults, and 9 reports with an unknown age. Elevated hepatic enzymes were reported in six patients with risk factors or possible alternative etiologies such as alcohol use, acetaminophen use, hepatic steatosis, and viral infection. The remaining 20 reports did not provide sufficient information for assessment such as missing information on past medical history, concomitant medication, time to onset, laboratory values, and event outcome. We did not identify a safety signal for serious hepatic events based on an evaluation of these reports.*

### 3.2 DRUG UTILIZATION

From July 2015 through June 2019, approximately 93% of lisdexamfetamine products were sold from manufacturers to U.S. retail channels of distribution, 5% to non-retail channels, and 2% to mail-order channels.[a] Accordingly, the patient data below included data from dispensed prescriptions from retail channels only; no data from mail-order, long-term care, or non-retail pharmacies (such as hospital pharmacies) were included.

[a] Source: IQVIA National Sales Perspectives™. Data time period July 2015 – June 2019. File: NSP Lisdexamfetamine July2015_June2019.xlsx

### *3.2.1 Number of Patients*

Annually from July 2015 through June 2019, approximately 2.0 million patients received dispensed prescriptions for lisdexamfetamine products, around 45% of whom were pediatric patients younger than 18 years old (Table 4 below). During the study period, approximately 60% of pediatric patients were 12-17 years old, and 45% were 6-11 years old.

**Table 4. Nationally estimated number of unique patients, stratified by age*, who received dispensed prescriptions for lisdexamfetamine products from U.S. outpatient retail pharmacies, July 2015 – June 2019 annually.**

| | Year ending June 2016 | | Year ending June 2017 | | Year ending June 2018 | | Year ending June 2019 | |
|---|---|---|---|---|---|---|---|---|
| | Patients (N) | Share (%) | Patients (N) | Share (%) | Patients (N) | Share (%) | Patients (N) | Share (%) |
| **Total** | **2,057,817** | **100%** | **2,061,535** | **100%** | **2,017,615** | **100%** | **1,991,554** | **100%** |
| ≤ 17 years old* | 1,001,281 | 49% | 940,312 | 46% | 891,152 | 44% | 848,433 | 43% |
| <2 years old | 74 | <1% | 65 | <1% | 65 | <1% | 72 | <1% |
| 2-5 years old | 9,849 | 1% | 8,730 | 1% | 7,849 | 1% | 6,824 | 1% |
| 6-11 years old | 455,673 | 46% | 424,182 | 45% | 396,297 | 44% | 372,861 | 44% |
| 12-17 years old | 595,484 | 59% | 564,234 | 60% | 540,880 | 61% | 520,527 | 61% |
| > 17 years old | 1,132,247 | 55% | 1,167,549 | 57% | 1,169,114 | 58% | 1,178,419 | 59% |
| Unspecified age | 2,903 | <1% | 8,751 | <1% | 13,638 | 1% | 3,645 | <1% |

Source: IQVIA Total Patient Tracker ™. Data time period July 2015 – June 2019. Data extracted December 2019.
* Patient age is calculated using patient's year of birth and the year of a prescription, and some age misclassification is possible.
Unique patient counts may not be added across time periods or age groups due to the possibility of double counting those patients who are receiving treatment over multiple time periods or age into the next age group during the time period.
Sums may add to more than 100% due to patients aging into the next age group during a calendar year.
Prescription data and resulting projected patient estimates have been adjusted to account for prescriptions that have been voided or reversed. This has resulted in a trend break between data through 12/2016 and data starting 1/2017.

## 4 DISCUSSION

DPV reviewed 202 U.S. FAERS reports with a serious outcome for lisdexamfetamine in the pediatric population (ages 0-17 years old) from July 1, 2015 to April 30, 2019. During this time frame, an annual range of approximately 0.8 to 1.0 million pediatric patients younger than 18 years old received dispensed prescriptions for lisdexamfetamine, mostly 6-17 years old. Half of the FAERS reports described labeled adverse events for lisdexamfetamine. Of these labeled adverse events reported with lisdexamfetamine, we did not identify new pediatric safety signals and did not observe an apparent increased severity or frequency of any labeled adverse events.

We identified 23 serious pediatric cases with unlabeled adverse events for lisdexamfetamine. Three fatal cases reported completed suicide in adolescent patients; there is not enough information provided in these cases that suggests a causal association with lisdexamfetamine. Of the 20 non-fatal cases, we identified a potential safety signal of acute dystonic reactions reported with the use of lisdexamfetamine. Other movement disorders included in the ADVERSE REACTIONS section of the lisdexamfetamine labeling are dyskinesia, tics, bruxism, and tremor.[2] Acute dystonic reactions are involuntary contractions that result in sustained or intermittent abnormal movements or postures.[21] Further review is necessary to assess whether

the reported events are consistent with the unlabeled event of acute dystonic reactions or are movement disorders adequately captured by the current labeling.

Of the serious and unlabeled adverse event cases for lisdexamfetamine in the pediatric population, the most frequently reported adverse events were suicidal ideation or behaviors. This included cases reporting one or more risk factors for suicidal ideation or behavior, and cases with some missing information. In the general population, about half of the children with ADHD may have coexisting conditions such as behavior or conduct problems, anxiety disorders, depression, and difficult peer relationships.[22] Such conditions, as well as bipolar disorder, schizophrenia, psychotic disorders, aggression, substance use disorders, and impulsivity are all risk factors for suicide.[23,24] According to the Centers for Disease Control and Prevention, suicide was the second leading cause of death in 2017 for youths aged 10 to 24 years old (see Appendix D for the top ten leading causes of death in 2017).[25] Additionally, placebo-controlled trials of lisdexamfetamine and other ADHD stimulants have not provided evidence that ADHD stimulants increase the risk of suicide-related events. In September 2010, the FDA issued a draft guidance that the clinical protocols for any drug with a psychiatric indication (products managed by the Division of Psychiatry Products) should include a prospective assessment for suicidal ideation and behavior, such as the Columbia-Suicide Severity Rating Scale (C-SSRS).[26] The clinical trials that led to the approval of lisdexamfetamine in the treatment of moderate to severe BED in January 2015 utilized C-SSRS to assess the risk of suicidal behaviors and ideation. The results from this suicidal risk assessment were similar between lisdexamfetamine and placebo.[27] As discussed in the first pediatric review for lisdexamfetamine that was presented to the PAC in 2012,[8] Shire (the applicant of Vyvanse) completed two reviews in 2008 and 2009 that concluded there did not appear to be an increased risk of suicide-related events associated with lisdexamfetamine relative to the background risk in the general or ADHD populations. This review evaluated reports of suicide-related events associated with lisdexamfetamine in the Shire Global Safety System database received through January 31, 2009.

## 5 CONCLUSION

DPV identified a potential safety signal of acute dystonic reactions reported in association with the use of lisdexamfetamine. The labeled adverse events reported in FAERS for lisdexamfetamine in the pediatric population are consistent with the known adverse events described in the labeling, and no apparent increased severity was observed in these cases.

## 6 RECOMMENDATION

DPV will perform a review of acute dystonic reactions reported in association with the use of lisdexamfetamine to determine if any regulatory action is needed. DPV will also continue to monitor all adverse events associated with the use of lisdexamfetamine.

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# 8 APPENDICES

## 8.1 APPENDIX A. FDA ADVERSE EVENT REPORTING SYSTEM

**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.

## 8.2 APPENDIX B. DRUG UTILIZATION DATABASE DESCRIPTIONS AND LIMITATIONS

### IQVIA National Sales Perspectives™: Retail and Non-Retail

The IQVIA National Sales Perspectives™ measures the volume of drug products, both prescription and over-the-counter, and selected diagnostic products moving from manufacturers into various outlets within the retail and non-retail markets. Volume is expressed in terms of sales dollars, eaches, extended units, and share of market. These data are based on national projections. Outlets within the retail market include the following pharmacy settings: chain drug stores, independent drug stores, mass merchandisers, food stores, and mail service. Outlets within the non-retail market include clinics, non-federal hospitals, federal facilities, HMOs, long-term care facilities, home health care, and other miscellaneous settings.

### IQVIA Total Patient Tracker™ (TPT)

IQVIA Total Patient Tracker (TPT) is a national-level projected service designed to estimate the total number of unique (non-duplicated) patients across all drugs and therapeutic classes in the retail outpatient setting from U.S. retail pharmacies. Data are available back to January 2002 and are available 20 days after the close of the month. TPT uses prescription activity as part of its projection and integrates information from pharmacies and payers to eliminate duplicate patients and multiple prescription fills, producing quick and reliable unique patient counts. IQVIA has 92% coverage and a sample of ~58,900 retail pharmacies. IQVIA captures about 3.8 billion transactions annually. TPT is projected to the known universe of retail pharmacies.

Of note, the estimated prescription and/or patient counts provided are based on projections of sample prescription claims data and therefore have some degree of inherent sampling error. These estimates are not intended to be representations of exact enumerations and should be interpreted with caution particularly if they are based on a small sample size. In addition, the data cannot be validated due to lack of access to medical records in the data sources.

## 8.3 APPENDIX C. FAERS LINE LISTING OF THE PEDIATRIC CASE SERIES (N=23)

| | Initial FDA Received Date | FAERS Case # | Version # | Manufacturer Control # | Case Type | Age (years) | Sex | Country Derived | Serious Outcomes* |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 7/1/2015 | 11239657 | 1 | | Direct | 10 | MALE | USA | HO,LT |
| 2 | 8/18/2015 | 11392857 | 1 | US-SHIRE-US201510048 | Expedited (15-Day) | 13.695 | FEMALE | USA | OT |
| 3 | 9/25/2015 | 11555442 | 1 | US-SHIRE-US201511636 | Expedited (15-Day) | 17 | FEMALE | USA | DE,HO,OT |
| | 12/30/2016 | 13076609 (duplicate) | 1 | US-ASTRAZENECA-2016SF37671 | Expedited (15-Day) | 17 | FEMALE | USA | DE,HO |
| | 1/11/2017 | 13105111 (duplicate) | 1 | US-BAUSCH-BL-2017-000136 | Expedited (15-Day) | 17 | FEMALE | USA | DE,OT |
| | 1/12/2017 | 13110962 (duplicate) | 1 | US-APOTEX-2017AP005640 | Expedited (15-Day) | 17 | FEMALE | USA | DE,HO,OT |
| | 1/17/2017 | 13121050 (duplicate) | 1 | US-LANNETT COMPANY, INC.-US-2017LAN000263 | Expedited (15-Day) | 17 | FEMALE | USA | DE |
| | 1/25/2017 | 13151189 (duplicate) | 1 | US-PFIZER INC-2017029081 | Expedited (15-Day) | 17 | FEMALE | USA | DE |
| | 1/31/2017 | 13166469 (duplicate) | 1 | US-AUROBINDO-AUR-APL-2017-28630 | Expedited (15-Day) | 17 | FEMALE | USA | DE,HO,OT |
| | 4/24/2017 | 13471127 (duplicate) | 1 | US-ENDO PHARMACEUTICALS INC-2017-002072 | Expedited (15-Day) | 17 | FEMALE | USA | DE |
| | 11/13/2017 | 14182014 (duplicate) | 1 | US-TORRENT-00003769 | Expedited (15-Day) | 17 | FEMALE | USA | DE,HO,OT |
| | 6/6/2018 | 14980813 (duplicate) | 1 | US-SHIRE-US201820586 | Expedited (15-Day) | 17 | FEMALE | USA | DE,OT |
| 4 | 10/5/2015 | 11602999 | 1 | | Direct | 15 | FEMALE | USA | OT |
| 5 | 10/20/2015 | 11643264 | 1 | US-SHIRE-US201512658 | Expedited (15-Day) | 13 | FEMALE | USA | OT |
| 6 | 1/13/2016 | 11913162 | 1 | US-SHIRE-US201600075 | Expedited (15-Day) | 13 | MALE | USA | OT |
| 7 | 1/20/2016 | 11934708 | 1 | | Direct | 15 | MALE | USA | DE |
| 8 | 2/13/2016 | 12075626 | 1 | US-SHIRE-US201601701 | Expedited (15-Day) | 15 | MALE | USA | DE,HO,OT |

| | Initial FDA Received Date | FAERS Case # | Version # | Manufacturer Control # | Case Type | Age (years) | Sex | Country Derived | Serious Outcomes* |
|---|---|---|---|---|---|---|---|---|---|
| 9 | 4/21/2016 | 12289017 | 2 | US-SHIRE-US201604409 | Expedited (15-Day) | 9 | MALE | USA | OT |
| 10 | 4/25/2016 | 12303771 | 1 | | Direct | 14 | FEMALE | USA | LT |
| 11 | 4/29/2016 | 12317899 | 3 | US-SHIRE-US201604801 | Expedited (15-Day) | 8 | MALE | USA | LT,OT |
| 12 | 6/28/2016 | 12505444 | 1 | US-SHIRE-US201607488 | Expedited (15-Day) | 11.98631 | MALE | USA | DS,OT |
| 13 | 9/9/2016 | 12727268 | 2 | US-SHIRE-US201611686 | Expedited (15-Day) | 10.91034 | MALE | USA | HO |
| 14 | 10/26/2016 | 12891232 | 1 | | Direct | 9 | MALE | USA | LT |
| 15 | 11/18/2016 | 12956704 | 2 | US-SHIRE-US201617480 | Expedited (15-Day) | 9 | MALE | USA | OT |
| 16 | 2/16/2017 | 13242810 | 1 | | Direct | 13 | FEMALE | USA | OT |
| 17 | 5/6/2017 | 13521583 | 1 | | Direct | 16.57 | MALE | USA | OT |
| 18 | 5/26/2017 | 13586079 | 1 | | Direct | 9 | MALE | USA | OT |
| 19 | 5/31/2017 | 13597777 | 1 | US-SHIRE-US201711818 | Expedited (15-Day) | 9 | MALE | USA | OT |
| 20 | 8/29/2017 | 13919739 | 1 | | Direct | 15 | MALE | USA | DS |
| 21 | 1/26/2018 | 14448640 | 1 | US-SHIRE-US201801740 | Expedited (15-Day) | 10 | FEMALE | USA | OT |
| 22 | 12/12/2018 | 15714269 | 1 | US-SHIRE-US201847811 | Expedited (15-Day) | 2.16667 | MALE | USA | HO |
| 23 | 4/12/2019 | 16191888 | 1 | US-SHIRE-US201911441 | Expedited (15-Day) | 12 | MALE | USA | OT |

*As per 21 CFR 314.80, the regulatory definition of serious is any adverse drug experience occurring at any dose that results in any of the following outcomes: Death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect, and other serious important medical events. Those which are blank were not marked as serious (per the previous definition) by the reporter, and are coded as non-serious. A case may have more than one serious outcome.
Abbreviations: DE=Death, HO=Hospitalization, LT=Life-threatening, DS=Disability, OT=Other Medically Significant

## 8.1 APPENDIX D. TEN LEADING CAUSES OF DEATH IN 2017 FOR AGES 0-24 YEARS OLD

2017, All Races, Both Sexes

| | Age Groups | | | | |
|---|---|---|---|---|---|
| Rank | <1 | 1-4 | 5-9 | 10-14 | 15-24 |
| 1 | Congenital Anomalies 4,580 | Unintentional Injury 1,267 | Unintentional Injury 718 | Unintentional Injury 860 | Unintentional Injury 13,441 |
| 2 | Short Gestation 3,749 | Congenital Anomalies 424 | Malignant Neoplasms 418 | Suicide 517 | Suicide 6,252 |
| 3 | Maternal Pregnancy Comp. 1,432 | Malignant Neoplasms 325 | Congenital Anomalies 188 | Malignant Neoplasms 437 | Homicide 4,905 |
| 4 | SIDS 1,363 | Homicide 303 | Homicide 154 | Congenital Anomalies 191 | Malignant Neoplasms 1,374 |
| 5 | Unintentional Injury 1,317 | Heart Disease 127 | Heart Disease 75 | Homicide 178 | Heart Disease 913 |
| 6 | Placenta Cord Membranes 843 | Influenza & Pneumonia 104 | Influenza & Pneumonia 62 | Heart Disease 104 | Congenital Anomalies 355 |
| 7 | Bacterial Sepsis 592 | Cerebro-vascular 66 | Chronic Low. Respiratory Disease 59 | Chronic Low. Respiratory Disease 75 | Diabetes Mellitus 248 |
| 8 | Circulatory System Disease 449 | Septicemia 48 | Cerebro-vascular 41 | Cerebro-vascular 56 | Influenza & Pneumonia 190 |
| 9 | Respiratory Distress 440 | Benign Neoplasms 44 | Septicemia 33 | Influenza & Pneumonia 51 | Chronic Low. Respiratory Disease 188 |
| 10 | Neonatal Hemorrhage 379 | Perinatal Period 42 | Benign Neoplasms 31 | Benign Neoplasms 31 | Cerebro-vascular 168 |

Source: Centers for Disease Control and Prevention – Injury Prevention & Control: Data & Statistics (WISQARS™). http://www.cdc.gov/injury/wisqars/leading_causes_death.html. Accessed September 11, 2019.

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/s/

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CARMEN CHENG
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NILAR Z IORIO
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CORINNE M WOODS
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CINDY M KORTEPETER
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