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(s):	Vyvanse (lisdexamfetamine dimesylate)
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Applicant/Sponsor:	Shire
OSE RCM #:	2015-1958

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EXECUTIVE SUMMARY

In accordance with the Food and Drug Administration Amendments Act (FDAAA) Pediatric Research Equity Act (PREA), the Office of Surveillance and Epidemiology (OSE) evaluated unlabeled postmarketing adverse event reports with a serious outcome and drug utilization data for Vyvanse (lisdexamfetamine dimesylate) in pediatric patients. This review was triggered by the approval for Vyvanse in the maintenance treatment of Attention Deficit Hyperactivity Disorder (ADHD) in pediatric patients.

Vyvanse was first approved in 2007 and is indicated for ADHD and binge eating disorder (BED). The approved pediatric labeling is for ADHD in age 6-17 years.

In order to capture pediatric use of lisdexamfetamine and to provide context for the adverse event reports submitted to the FDA Adverse Event Reporting System (FAERS) database, drug utilization patterns were assessed. During the most recent 12-month period ending in June 2015, approximately 1.1 million pediatric patients (47% of total patients) received a prescription for lisdexamfetamine from U.S. outpatient retail pharmacies. Of pediatric patients, approximately 51% (549,000 patients) were aged 6-11 years, approximately 53% (566,000 patients) were aged 12-16 years, and 2% (21,000 patients) of pediatric patients were aged 0-5 years.[a] According to the U.S. office-based physician survey data, "attention deficit disorder" was the most common diagnosis associated with the use of lisdexamfetamine in all age groups.

A search of the FAERS database identified 215 pediatric cases received by FDA between April 10, 2012 and June 30, 2015. Of these 215 cases, 30 cases were identified in patients aged 0 to less than 6 years old, including 1 fatal case. In addition, 185 cases were identified in patients aged 6 to less than 17 years old, including 7 fatal cases. Of the eight total fatal pediatric cases, three cases reported an unknown cause of death or an alternative etiology as the likely cause of death, unrelated to lisdexamfetamine. Of the remaining five cases, four cases reported suicide as the cause of death and one case reported homicide. Three of the five cases that reported suicide or homicide were confounded by the patient's psychiatric history, non-compliance with a prescribed antidepressant, or psychological stressors.

The highest proportion of lisdexamfetamine cases in our case series reported suicidal or self-injurious thoughts or behaviors. A majority of these cases were confounded or did not contain enough information for assessment. About half of the children with ADHD may have coexisting conditions such as behavior or conduct problems, anxiety disorders, depression, and difficult peer relationships. Such conditions, as well as other psychiatric conditions including bipolar disorder, schizophrenia, psychotic disorders, aggression, substance use disorders, and impulsivity

[a] Patient age subtotals may not sum exactly (>100%) due to patients aging over the examined time, and may be counted more than once in the individual age categories. For this reason, summing across patient age bands is not advisable and will result in overestimates of patient counts.

are all risk factors for suicide. It is difficult to perform a causality assessment of suicide-related events and lisdexamfetamine from the postmarketing cases, because of the comorbid conditions, missing information regarding the patients' psychiatric history or social stressors, and the prevalence of youth suicides. Additionally, numerous placebo-controlled trials of lisdexamfetamine and other ADHD stimulants have not provided evidence that stimulants increase the risk of suicide-related events.

Based on the remaining cases, DPV identified a possible signal for alopecia in association with lisdexamfetamine. Although alopecia is not a life-threatening event, it has serious psychological consequences associated with increased anxiety and depression for both children and adults. Therefore, DPV will perform a review of alopecia reported in association with lisdexamfetamine to determine if any regulatory action is needed. DPV will also continue to monitor adverse events in the pediatric population associated with the use of lisdexamfetamine.

1 INTRODUCTION

1.1 PEDIATRIC REGULATORY HISTORY

Product Information and Dosing [1]

Vyvanse (lisdexamfetamine dimesylate) was approved for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) on February 23, 2007 in children 6 to 12 years of age, and on November 10, 2010, in adolescents 13 to 17 years of age. This triggered a Pediatric Research Equity Act (PREA) review for lisdexamfetamine, which was presented to the Pediatric Advisory Committee (PAC) in September 2012. [2]

On April 26, 2013, lisdexamfetamine was approved for the maintenance treatment of ADHD in pediatric patients 6 to 17 years of age. On January 30, 2015, the FDA approved an additional indication for lisdexamfetamine for the treatment of moderate to severe Binge Eating Disorder (BED) in adults (18 to 55 years of age).

The recommended starting dose of lisdexamfetamine for the treatment of ADHD is 30 mg once daily in the morning. The dose should be titrated in increments of 10 mg or 20 mg weekly up to a maximum dose of 70 mg daily. The recommended starting dose for the treatment of moderate to severe BED is 30 mg once daily. The dose should be titrated in increments of 20 mg weekly up to a maximum dose of 50 mg to 70 mg daily. Vyvanse is available as a capsule in 10 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, and 70 mg strengths.

Clinical Study

This PREA review was triggered by study SPD489-326, a long-term, placebo-controlled relapse prevention, maintenance efficacy study of lisdexamfetamine in the treatment of ADHD in pediatric patients 6 to 17 years of age. [3] The pediatric labeling change date was April 26, 2013. The following information is an excerpt from the lisdexamfetamine label regarding this study:[1]

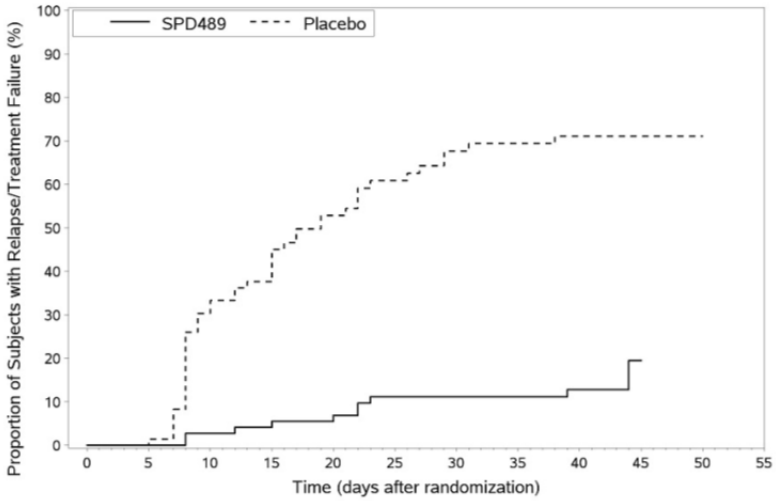
"Patients Ages 6 to 17 Years Old: Maintenance Treatment in ADHD

Maintenance of Efficacy Study (Study 6) - A double-blind, placebo-controlled, randomized withdrawal study was conducted in children and adolescents ages 6 to 17 (N=276) who met the diagnosis of ADHD (DSM-IV criteria). A total of 276 patients were enrolled into the study, 236 patients participated in Study 5 and 40 subjects directly enrolled. Subjects were treated with open-label VYVANSE for at least 26 weeks prior to being assessed for entry into the randomized withdrawal period. Eligible patients had to demonstrate treatment response as defined by [Clinical Global Impression Severity] CGI-S <3 and Total Score on the [ADHD Rating Scale] ADHD-RS ≤22. Patients that maintained treatment response for 2 weeks at the end of the open label treatment period were eligible to be randomized to ongoing treatment with the same dose of VYVANSE (N=78) or switched to placebo (N=79) during the double-blind phase. Patients were observed for relapse (treatment failure) during the 6 week double blind phase. A

significantly lower proportion of treatment failures occurred among VYVANSE subjects (15.8 %) compared to placebo (67.5%) at endpoint of the randomized withdrawal period. The endpoint measurement was defined as the last post-randomization treatment week at which a valid ADHD-RS Total Score and CGI-S were observed. Treatment failure was defined as a ≥50% increase (worsening) in the ADHD-RS Total Score and a ≥2-point increase in the CGI-S score compared to scores at entry into the double-blind randomized withdrawal phase.

Subjects who withdrew from the randomized withdrawal period and who did not provide efficacy data at their last on-treatment visit were classified as treatment failures (Study 6, Figure 5)."

Figure 5 Kaplan-Meier Estimation of Proportion of Patients with Treatment Failure for Children and Adolescent Ages 6-17 (Study 6)



1.2 HIGHLIGHTS OF LABELED SAFETY ISSUES

The following information is an excerpt from the Highlights of Prescribing Information and pertinent sections of the lisdexamfetamine label:[1]

Boxed Warning: Abuse and Dependence

- CNS stimulants (amphetamines and methylphenidate- containing products), including VYVANSE, have a high potential for abuse and dependence (5.1, 9.2, 9.3)
- Assess the risk of abuse prior to prescribing and monitor for signs of abuse and dependence while on therapy (5.1, 9.2)

Contraindications

- Known hypersensitivity to 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 in children and adolescents with serious heart problems, as well as sudden death, stroke, and myocardial infarction in adults 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)

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)

Drug Interactions

- *Acidifying and Alkalinizing Agents:* Agents that alter urinary pH can alter blood levels of amphetamine. Acidifying agents decrease amphetamine blood levels, while alkalinizing agents increase amphetamine blood levels. Adjust VYVANSE dosage accordingly (2.6, 7.1)

Use in Specific Populations

- Pediatric Use
  - 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 DRUG UTILIZATION DATA

2.1 METHODS

Proprietary drug utilization databases available to the Agency were used to conduct this analysis. (See Appendix A for detailed descriptions of the databases).

2.1.1 Determining Settings of Care

The IMS Health, IMS National Sales Perspectives™ database was used to determine the settings of distribution for lisdexamfetamine from July 2012 through June 2015. Sales data for lisdexamfetamine by the number of bottles sold from the manufacturer to all U.S. channels of distribution showed that approximately 92% of lisdexamfetamine bottles were distributed to outpatient retail pharmacies, 5% were to non-retail settings, and 3% were to mail-order/specialty pharmacies.[4] As a result, only outpatient retail pharmacy utilization patterns were examined for lisdexamfetamine. Mail-order/specialty pharmacy and non-retail pharmacy settings data were not included in this analysis.

2.1.2 Data Sources Used

The IMS, Total Patient Tracker™ (TPT) database was used to obtain the nationally estimated number of patients who received a dispensed prescription for lisdexamfetamine from U.S. outpatient retail pharmacies, stratified by patient age (0-5, 6-11, 12-16, and 17 years and older), from July 2012 through June 2015, yearly.

The IMS, National Prescription Audit™ (NPA) database was used to obtain nationally estimated number of prescriptions dispensed for lisdexamfetamine from U.S. outpatient retail pharmacies, stratified by prescriber specialty, from July 2012 through June 2015, cumulative.

Encuity Research, LLC, Treatment Answers™, a U.S. office-based physician survey database was used to obtain the top diagnoses associated with the use of lisdexamfetamine, stratified by patient age (0-5, 6-11, 12-16, and 17 years and older), from July 2012 through June 2015, cumulative. Diagnoses data by number of drug use mentions[b] were captured based on International Classification of Diseases (ICD-9-CM) codes) and 95% confidence intervals were applied to the estimates.

[b] The term "drug uses" refers to mentions of a drug in association with a diagnosis during a patient visit to an office-based physician. This term may be duplicated by the number of diagnosis for which the drug is mentioned. It is important to note that a "drug use" does not necessarily result in prescription being generated. Rather, the term indicates that a given drug was mentioned during an office visit.

2.2 RESULTS

2.2.1 Unique Patients

Table 2.2.1 below provides the nationally estimated number of patients who received a dispensed prescription for lisdexamfetamine from U.S. outpatient retail pharmacies, stratified by patient age (0-5, 6-11, 12-16, 17 years and older), from July 2012 through June 2015, yearly. During the 12-month period ending in June 2015, approximately 2.3 million patients received a dispensed prescription for lisdexamfetamine. Adult patients aged 17 years and older accounted for 54% (approximately 1.2 million patients) of total patients, while pediatric patients aged 0-16 years accounted for 47% (approximately 1.1 million patients) of total patients. Among the pediatric population, patients aged 0-5 years accounted for 2% (approximately 21,000 patients), followed by patients aged 6-11 and 12-16 years at 51 % and 53% of pediatric patients, respectively.

Table 2.2.1

Nationally estimated number of patients who received a dispensed prescription for lisdexamfetamine from U.S. outpatient retail pharmacies, stratified by patient age*, from July 2012 through June 2015, yearly

	July 2012 - June 2013		July 2013 - June 2014		July 2014 - June 2015	
	Patients N	Share %	Patients N	Share %	Patients N	Share %
Total Patients**	2,031,313	100.0%	2,148,049	100.0%	2,286,889	100.0%
0-16 years	1,062,931	52.3%	1,075,948	50.1%	1,079,272	47.2%
0 - 5 years	29,587	2.8%	24,601	2.3%	20,737	1.9%
6-11 years	555,107	52.2%	553,021	51.4%	548,503	50.8%
12-16 years	535,819	50.4%	555,859	51.7%	566,442	52.5%
17+ years	1,004,540	49.5%	1,110,657	51.7%	1,239,518	54.2%
Unknown age	720	0.0%	2,611	0.1%	18,721	0.8%

*Patient age groups are inclusive of all patients up to the day before their next birthday. For example, patients aged 0-16 years include patients less than 17 years of age (16 years and 11 months).
**Patient age subtotals may not sum exactly due to patients aging during the study, and may be counted more than once in the individual age categories. For this reason, summing across patient age bands or time periods is not advisable and will result in overestimates of patient counts.
Source: IMS Total Patient Tracker (TPT), JUL2012-JUN2015, extracted FEB2016, Source file: TPT 2015-1958 Vyvanse by Age 0-16 by MAT.xls

2.2.2 Prescriber Specialty

Table 2.2.2 below provides the nationally estimated number of lisdexamfetamine prescriptions dispensed from U.S. outpatient retail pharmacies, stratified by prescriber specialty, from July 2012 through June 2015, cumulative. During the examined time period, approximately 29 million lisdexamfetamine prescriptions were dispensed. Psychiatry was the top prescribing specialty accounting for 31% (approximately 9.2 million prescriptions) of the total lisdexamfetamine prescriptions dispensed. Pediatrics and General Practice/Family Practice/Osteopathic Medicine accounted for 26% (approximately 7.6 million prescriptions) and 22% (approximately 6.4 million prescriptions) of the total prescriptions, respectively.

Table 2.2.2

Nationally estimated number of prescriptions dispensed for lisdexamfetamine from U.S. outpatient retail pharmacies, stratified by top prescriber specialties, from July 2012 to June 2015, cumulative

	July 2012 - June 2015	
	TRxs N	*Share %*
Total Prescriptions	**29,248,641**	**100.0%**
Psychiatry	9,179,859	31.4%
Pediatrics	7,594,952	26.0%
General Practice/Family Practice/Osteopathic Medicine	6,431,448	22.0%
Nurse Practitioner/Physician Assistant	3,223,542	11.0%
Internal Medicine	1,143,873	3.9%
Neurology	685,265	2.3%
Specialty Unspecified	233,932	0.8%
Internal Med/Pediatrics	199,119	0.7%
Emergency Medicine	55,047	0.2%
Obstetrics/Gynecology	48,103	0.2%
All Other Specialties	453,501	1.6%

Source: IMS Health, National Prescription Audit (NPA). July 2012-June 2015. Extracted Oct 2015. File: NPA 2015-1958 Vyvanse Rx Retail by Specialties, 11-27-2015

2.2.3 Diagnoses Associated with the Use of Lisdexamfetamine

Table 2.2.3 below provides the top diagnoses associated with the use of lisdexamfetamine by drug use mentions as reported by U.S. office-based physician surveys, stratified by patient age (0-5, 6-11, 12-16, 17 years and older), from July 2012 through June 2015, cumulative. A total of 13.7 million drug use mentions for lisdexamfetamine were captured during the cumulative time period. Among pediatric patients "attention deficit disorder" (ICD-9 code 314.0) was the most common diagnosis associated with the use of lisdexamfetamine in *all* the specified pediatric age groups, accounting for 96% of drug use mentions in patients 0-5 years old, 99% in patients aged 6-11 years old, and 99% in patients aged 12-16 years old. Although, there were other diagnoses associated with the use of lisdexamfetamine in the 0-5, 6-11, 12-16 years age groups, the number of drug use mentions were below the acceptable count to provide a reliable estimate of national use.

Table 2.2.3

Diagnoses associated with the use of lisdexamfetamine as reported by U.S. office-based physician surveys, stratified by patient age, from July 2012 through June 2015, cumulative

	July 2012-June 2015		
	Uses N	Share %	95% Confidence Interval
Total Uses	**13,650,000**	***100.0%***	**13,051,000 - 14,248,000**
0-5 years	140,000	*1.0%*	79,000 - 200,000
3140 ATTENTION DEFICIT DIS	135,000	*96.4%*	75,000 - 194,000
2967 BIPOLAR AFFECTIVE NOS	5,000	*3.6%*	<500 - 16,000
6-11 years	3,550,000	*26.0%*	3,244,000 - 3,855,000
3140 ATTENTION DEFICIT DIS	3,512,000	*98.9%*	3,208,000 - 3,816,000
2999 EARLY CHLD PSYCHOSIS NOS	14,000	*0.4%*	<500 -32,000
3138 OTH EMOTIONAL DIS CHILD	7,000	*0.2%*	<500-21,000
3129 CONDUCT DISTURBANCE NOS	7,000	*0.2%*	<500-21,000
2969 AFFECT PSYCHOSES NEC/NOS	5,000	*0.1%*	<500-17,000
2967 BIPOLAR AFFECTIVE NOS	5,000	*0.1%*	<500-16,000
12-16 years	3,727,000	*27.3%*	3,414,000 - 4,039,000
3140 ATTENTION DEFICIT DIS	3,678,000	*98.7%*	3,368,000 - 3,989,000
3138 OTH EMOTIONAL DIS CHILD	22,000	*0.6%*	<500-46,000
2999 EARLY CHLD PSYCHOSIS NOS	9,000	*0.3%*	<500-25,000
V623 EDUCATIONAL CIRCUMSTANCE	8,000	*0.2%*	<500-22,000
2780 OBESITY	5,000	*0.1%*	<500-17,000
2998 EARLY CHLD PSYCHOSES NEC	4,000	*0.1%*	<500-15,000
17+ years and older	5,635,000	*41.3%*	5,250,000 - 6,019,000
Unspecified Age	599,000	*4.4%*	474,000 - 725,000

***NEC: not elsewhere classifed**

****NOS: not otherwise specified**

Encuity Research, LLC, Treatment Answers™ recommends caution interpreting projected annual uses or mentions below 100,000 as the sample size is very small with correspondingly large confidence intervals.

Source: Encuity Research Treatment Answers™ Audit LLC. Extracted Oct 2015, File: PPDA 2015-1958 Vyvanse BPCA 0-5, 6-11, 12-16, 17+, Dx4, 10-16-2015.xls

3 POSTMARKET ADVERSE EVENT REPORTS

3.1 METHODS AND MATERIALS

3.1.1 FDA Adverse Event Reporting System (FAERS) Search Strategy

DPV searched the FAERS database with the strategy described in Table 3.1.1. See Appendix B for a description of the FAERS database.

Table 3.1.1 FAERS Search Strategy

Date of Search	September 24, 2015
Time Period of Search	April 10, 2012* - June 30, 2015
Search Type	FBIS Quick Query
Product Name(s)	Lisdexamfetamine, Lisdexamfetamine Dimesylate
Search Parameters	All ages, all outcomes, worldwide

** The search period in the previous OSE pediatric safety review for Vyvanse ended April 9, 2012.*

3.1.2 Inclusion Criteria

DPV included cases that reported:

- Fatal outcomes age 0 to less than 17 years, OR
- Any adverse events age 0 to less than 6 years old, OR
- Serious, unlabeled adverse events in age 6 to less than 17 years old

All FAERS reports retrieved were analyzed and reviewed. The reports that met the inclusion criteria above were included in the case series.

3.2 RESULTS

3.2.1 Total number of FAERS Reports by Age

Table 3.2.1 Total Adult and Pediatric FAERS reports* from April 10, 2012† to June 30, 2015 with Lisdexamfetamine

	All reports (US)	Serious† (US)	Death (US)
Adults (≥ 17 years)	600 (547)	349 (297)	27 (27)
Pediatrics (0 - <17 years)			
Age 0-<6 years	**40‡ (38)**	26 (24)	**1 (1)**
Age 6-<17 years	584 (507)	**389‡ (314)**	**24§ (23)**

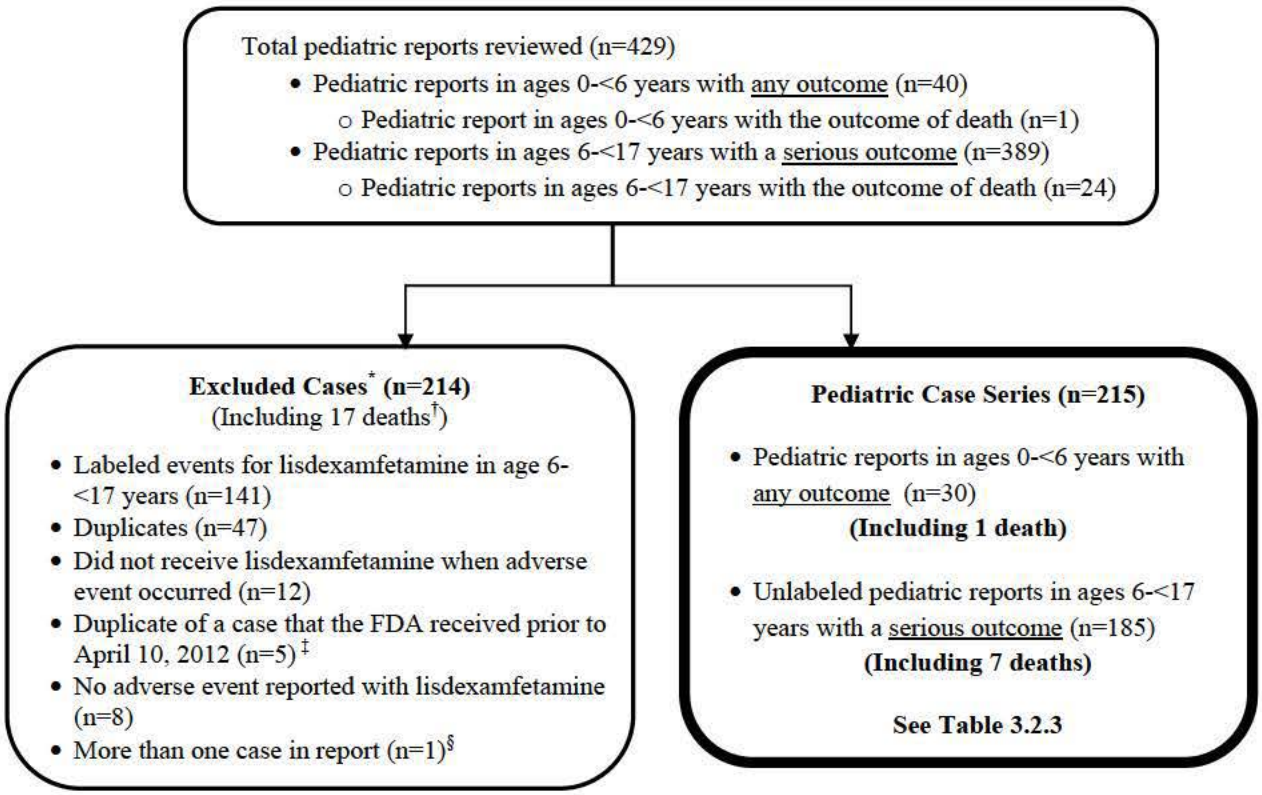
**** May include duplicates and transplacental exposures, and have not been assessed for causality***
† Serious adverse drug experiences per regulatory definition (CFR 314.80) include outcomes of death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, and other serious important medical events.
‡ See Figure 3.2.2
§ One additional report of pediatric death was identified among reports not providing an age.

3.2.2 Selection of Pediatric Cases in FAERS

For the purpose of this review, we focused on all reports in pediatric patients 0 to less than 6 years of age, as well as unlabeled reports in children 6 to less than 17 years of age with a serious outcome. The FAERS search included reports that the FDA received between April 10, 2012 and June 30, 2015.

A search of the FAERS database identified 40 pediatric reports with any outcome in patients 0 to less than 6 years of age, including 1 fatal report. In addition, 389 reports were identified in patients 6 to less than 17 years of age with a serious outcome, including 24 fatal reports. (Refer to **Table 3.2.1**). See **Figure 3.2.2** below for the specific selection of cases to be summarized in **Sections 3.3 and 3.4.**

Figure 3.2.2 Selection of Pediatric Cases with Vyvanse



* DPV reviewed these cases, but they were excluded from the case series for the reasons listed above

† Two death cases were excluded for the following reasons: 1) the patient did not receive lisdexamfetamine at the time of death, and 2) the case was a duplicate of another case that the FDA received prior to April 10, 2012 and presented to the PAC in September 2012. The patient had been switched to methylphenidate for more than three weeks prior to her death; only methylphenidate was detected in the patient's blood. An additional fifteen death cases were excluded because they were duplicates.

‡ April 10, 2012 is the beginning of the search period for this review. The search period in the previous OSE pediatric safety review for Vyvanse ended April 9, 2012.

§ One report contained information for more than one patient. A physician reported an increase in aggressive and violent behavior associated with lisdexamfetamine in at least 15 patients. Some patients had a history of aggressive behavior prior to the initiation of lisdexamfetamine.

3.2.3 Characteristics of Case Series for All Pediatric Patients

Appendix C lists all the FAERS case numbers, FAERS version numbers and Manufacturer Control Numbers for the pediatric case series.

Table 3.2.3 Characteristics of Pediatric Case Series with Vyvanse (N=215)

		Age 0-<6 years (n=30)	**Age 6-<17 years (n=185)**
Age	1 month - <2 years	3	0
	2- < 6 years	27	0
	6- <12 years	0	108
	12- < 17 years	0	77
Sex	Male	22	133
	Female	6	48
	Unknown	2	4
Country	United States	28	129
	Foreign	2	56
Reported Reason for Use	ADD/ADHD	16	118
	ADHD and oppositional defiant disorder (ODD)	1	1
	ADHD and Asperger's disorder	1	0
	ADHD and autism	1	0
	Abnormal behavior and psychomotor hyperactivity	0	1
	Abnormal behavior and disruptive behavior disorder	0	1
	Asperger's disorder	0	1
	Disturbance in attention	0	1
	"Help think better in school"	0	1
	Not applicable (accidental exposure, drug diversion)	5	3
	Unknown	6	58
Serious Outcome* (n=207)		(n=22)	(n=185)
	Death	1	7
	Hospitalization	8	41
	Life-threatening	1	5
	Disability	1	5
	Other serious	11	127

* Serious adverse drug experiences per regulatory definition (CFR 314.80) include outcomes of death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, and other serious important medical events. Reports may have more than one outcome.

3.3 SUMMARY OF FATAL PEDIATRIC ADVERSE EVENT CASES (N=8)

DPV identified eight fatal pediatric cases reported with lisdexamfetamine in this case series. The causes of death were suicide (4), homicide (1), vascular disorder (1), and unknown (2). The median age of the patients was 14 years and ranged from 3 months to 16 years old. Five cases did not report the lisdexamfetamine dose; in the remaining three

cases, one case reported that the lisdexamfetamine dose was 30 mg daily and two cases reported that the dose was 50 mg daily. The three cases reporting the duration of lisdexamfetamine use at the time of death were 1 week, 11 months, and approximately two years. A summary of the eight cases is provided below, categorized by the cause of death.

3.3.1 Known/Reported Causes of Death (N=6)

Suicide (n=4)

Case # 8333111, USA, 2012: A 10-year-old female was taking lisdexamfetamine for ADHD. At an unknown time, the patient *completed suicide* by hanging herself. The patient had social stressors in her life; she was picked on at school and suspended from school the month prior for fighting. Three months prior to the event, the patient told her grandmother that she "ought to kill myself." The autopsy reported the cause of death was "asphyxia due to hanging." It was unknown if the patient was taking lisdexamfetamine at the time of death or if the patient was taking any medications concomitantly.

Case # 8350482, USA, 2012: The American Association of Poison Control Centers (AAPCC) National Poison Control Data System (NPDS) reported a 16-year-old female *completed suicide*. She was on lisdexamfetamine for an unknown indication. Additional suspect medications included morphine and an unspecified laxative. No additional clinical information was reported.

Case # 9769174, USA, 2013: A 14-year-old male *completed suicide* one week after lisdexamfetamine was initiated for ADHD. His lisdexamfetamine dose was 50 mg daily. No other medical conditions or additional clinical information were reported.

Case # 10537553, Canada, 2014: A 16-year-old male *completed suicide* on an unknown date. The patient was also prescribed unspecified antidepressants, but he was not compliant with them. The patient was "on and off" lisdexamfetamine for an unknown period of time. It was unknown if the patient was taking lisdexamfetamine at the time of death or if an autopsy was performed.

Reviewer's comment: Two of the four completed suicide cases were confounded by a history of depression, non-compliance with a prescribed antidepressant, or psychological stressors. Additionally, in both of the confounded cases, it was unknown if the patient was taking lisdexamfetamine at the time of death. The remaining two cases did not provide much information regarding the patient's medical history or if the patient experienced any social stressors.

Homicide (n=1)

Case # 10213468, USA, 2014: [redacted] (b) (6) Lisdexamfetamine was prescribed to the 10-year-old

(b) (6); the 10-year old girl had ADHD (b) (6)

Vascular Disorder (n=1)

Case # 10461502, USA, 2012: A 15-year-old female was prescribed guanfacine extended-release (ER) and lisdexamfetamine for "abnormal" and "impulsive" behavior, as well as for disruptive behavior disorder." Additional medical history included mild intellectual delay, developmental delay, congenital hypoplasia of corpus callosum, migraine, Crohn's disease, colitis, and moderate obesity. The patient was also taking propranolol for migraine. The patient had been on lisdexamfetamine for more than two years and guanfacine ER for approximately two months when she complained of abdominal pain for several days. Her lisdexamfetamine dose was 50 mg daily. She presented to the emergency department (ED) for evaluation of the abdominal pain. The patient was "severely anemic" (lab value for the hemoglobin was not reported). After treatment with a blood transfusion, she was discharged home with instructions to follow-up with a gastroenterologist. Later that day, the patient expired. Autopsy revealed that the patient died of *portal and splenic vein thromboses*. The reporting physician stated the thromboses were not related to guanfacine ER or lisdexamfetamine, but possibly due to a "transfusion reaction."

3.3.2 Unknown Cause of Death (N=2)

Case #8317964, USA, 2012: The AAPCC NPDS reported a 14-year-old male "*died of an unknown reason* after an acute on chronic ingestion" of codeine as the primary toxic substance. Additional suspect medications included morphine, hydrocodone, an unspecified laxative, sertraline, quetiapine, aripiprazole, valproic acid, lisdexamfetamine, amphetamine, diphenhydramine, penicillin, meloxicam, and clonidine. The patient experienced cardiac and/or respiratory arrest. The AAPCC assessed the medications alone would not have caused the death, but were partially responsible when combined with other factors.

Case #10426209, USA, 2014: An 8-year-old female was prescribed lisdexamfetamine 30 mg daily, clonidine 0.1 mg daily, and methylphenidate (Ritalin) daily as needed for ADHD. She was otherwise healthy and had no other medical history. When the patient's mother tried to wake her one morning for school, the patient was found face down, unresponsive, pulseless, and apneic. The patient's mother and emergency medical services attempted cardiopulmonary resuscitation, but the patient did not survive despite the resuscitative efforts. The autopsy reported the "*cause and manner of death was undetermined*." Toxicology report was positive for caffeine; lisdexamfetamine and clonidine were tested in the blood but both were negative. The patient did not have a family history of sudden

death. The autopsy did not identify any cardiac abnormalities, but stated "death from a cardiac dysrhythmia due to an inherited condition cannot be ruled out." She had been on lisdexamfetamine for about eleven months and clonidine for about nine months at the time of her death.

3.4 SUMMARY OF ALL NON-FATAL PEDIATRIC ADVERSE EVENT CASES IN AGE 0 TO LESS THAN 6 YEARS OLD WITH ANY OUTCOME (N=29)

We identified 29 non-fatal cases associated with lisdexamfetamine in the pediatric population less than 6 years of age, which is an unapproved patient population. Twenty-one cases reported a serious outcome including hospitalization (8), life-threatening (1), disability (1), and other serious medical events (11). Seventeen of the 29 cases reported adverse events consistent with the current labeling for Vyvanse such as mania, psychotic symptoms, or hallucination (7), affect lability (2), tic (2), psychomotor hyperactivity (1), dermatillomania (1), agitation (1), irritability (1), tachycardia (1), and palpitations (1). Twelve cases reported unlabeled adverse events such as accidental exposure (4), suicidal ideation or self-injurious behavior (2), drug ineffective (2), social avoidant behavior (1), drug effect increased (1), overdose (1), and dystonia (1).

Cases in this section are categorized by the Preferred Terms (PT) that best represent the reported adverse event(s). The PTs are then grouped by like terms and organized by System Organ Class (SOC).

3.4.1 Psychiatric Disorders (N=15)

Labeled Events: Mania, Psychotic Behaviour or Disorder, Hallucination (n=7)

Psychotic symptoms, mania, and hallucination are labeled in the Warnings and Precautions section. The reported PTs were mania (1), psychotic disorder (1), hallucination (2), psychotic behaviour/disorder and hallucination (2), and all three events (1). All were males aged four to five years old. The indications for lisdexamfetamine were ADHD (5), ADHD and Asperger's disorder (1), and unspecified (1). The lisdexamfetamine dose ranged from 10 mg to 40 mg daily in four cases; one additional case reported a dose of 30 mg with an unknown frequency, and two cases did not specify the dose. In five cases, the time to onset of the events ranged from within 1 day to 2 months. One additional case reported the time to onset for hallucination was a little over one year, but not specified for mania or psychosis. The remaining case did not report a time to onset.

Three cases were confounded by concomitant medications or medical history. One case reported psychotic symptoms in a patient with bipolar disorder. The two cases that reported hallucinations were confounded by a concomitant medication labeled for hallucinations (mirtazapine, clonidine ER). Additionally, one of these confounded cases reported a negative rechallenge. A 5-year-old male experienced symptoms of mania,

psychosis, and hallucinations. The events resolved after discontinuation of lisdexamfetamine. An unspecified time later in the same year, lisdexamfetamine was restarted, but he did not experience any side effects after the resumption of lisdexamfetamine.

Two cases reported a positive dechallenge. One case reported the resolution of hallucinations after lisdexamfetamine was discontinued. The second case reported a diagnosis of "amphetamine psychosis" and hallucinations in a 5-year-old male who had taken lisdexamfetamine for 24 days. The patient also took clonidine for an unknown duration, which is labeled for hallucinations. He recovered from the events after treatment with risperidone and diphenhydramine, and the discontinuation of lisdexamfetamine and clonidine.

Of the two remaining cases, one patient experienced mania and aggression after starting lisdexamfetamine for an unknown duration. As a result, lisdexamfetamine was discontinued, but the outcomes of the events were not reported. The second case reported a 4-year-old male who experienced acute psychosis after the first dose of lisdexamfetamine. Lisdexamfetamine was discontinued, but the patient additionally experienced hallucinations the next day. Despite the discontinuation of lisdexamfetamine, psychosis and hallucinations remained ongoing. He remained hospitalized for four weeks at the time of the report for the evaluation of psychotic symptoms.

Labeled Event: Affect Lability (n=2)

Affect lability is labeled in Adverse Reactions. Two cases reported emotional lability. The first case reported a 5-year-old male who experienced "emotional lability/became moody" and cried after the first dose of lisdexamfetamine for ADHD. The physician discontinued lisdexamfetamine and the events resolved the following day. The second case reported a 5-year-old male who experienced emotional lability an unknown date after starting lisdexamfetamine. Lisdexamfetamine was discontinued, and the outcome was not reported.

Labeled Event: Dermatillomania (n=1)

Dermatillomania is labeled in the Adverse Reactions section. A 4-year-old male picked at his fingers, hands, and other body parts, which led to bleeding. He was on an unknown dose of lisdexamfetamine for ADHD for a few months. He had no other past medical history.

Labeled Event: Agitation (n=1)

Agitation is labeled in the Adverse Reactions section. A 4-year-old male was on lisdexamfetamine 20 mg and escitalopram 20 mg at unspecified frequencies for unknown indications. On the day that the lisdexamfetamine dose was increased from 20 mg to 30

mg, the patient experienced acute agitation, restlessness, tachycardia (heart rate 120 bpm) and vomiting. The patient presented to the ED where he received one dose of lorazepam without relief. Otherwise, the patient was stable and alert at the time of reporting, without further information on the outcome.

Labeled Event: Irritability (n=1)

Irritability is labeled in the Adverse Reactions section. A 4-year-old male was on lisdexamfetamine and guanfacine ER for ADHD. After being on both medications for an unspecified duration, the patient experienced irritability, blurred vision, decreased appetite, as well as itching and eczema. No further information was provided.

Unlabeled Events: Suicidal Ideation, Self-injurious Behaviour (n=2)

One case reported suicidal ideation and another case reported self-injurious behavior.

In the first case, a 5-year-old female experienced suicidal ideation. She verbally expressed that she "did not want to live anymore." The report did not provide information on her medical history, lisdexamfetamine dose, time to onset, action with lisdexamfetamine, or the outcome of suicidal ideation.

In the second case, a 5-year-old male had self-injurious behaviors after the initiation of lisdexamfetamine 20 mg daily for ADHD. He lost his appetite, had nightmares, became violent (hit himself and others), and exhibited other self-injurious behaviors (bit his fingers and toenails until they bled, pulled his teeth out). The family was afraid lisdexamfetamine would cause "permanent damage," so lisdexamfetamine was changed to methylphenidate. The outcome was not reported, but the family was seeking psychiatric help for the patient. The patient was on lisdexamfetamine for about two years (he was 7 years old at the time of the report).

Unlabeled Event: Social Avoidant Behaviour (n=1)

A 5-year-old male with ADHD, autism, and sleep disorder was prescribed lisdexamfetamine 20 mg daily. He was on lisdexamfetamine for two months when the medication was discontinued for an unspecified reason and an alternative therapy was prescribed. Six months later, lisdexamfetamine was restarted at the previous dose. Two to three months after restarting lisdexamfetamine, the patient became "distant, kept to himself, and withdrawn." The events resolved the day after lisdexamfetamine was discontinued.

Reviewer's comment: This case is confounded by the patient's medical history of autism. The patient did not exhibit the social avoidant behavior when he was previously on lisdexamfetamine for two months.

3.4.2 Injury, Poisoning and Procedural Complications (N=5)

Unlabeled Event: Accidental Exposure to Product by Child (n=4)

An 8-month-old infant of an unknown sex experienced seizures after an accidental exposure to an unknown amount of lisdexamfetamine. The patient "nearly died." The outcome was unknown.

An 11-month-old male infant opened and chewed one or two of his mother's lisdexamfetamine 50 mg capsule(s). The patient was hospitalized for overnight observation. The patient had psychomotor hyperactivity and tachycardia (heart rate 182 bpm). Treatment included lorazepam and activated charcoal. The patient recovered, and the patient was discharged from the hospital.

A 2-year-old female had an accidental exposure to lisdexamfetamine "300 mg." No information was reported regarding the adverse event experienced or outcome.

A 3-year-old male ingested two or three lisdexamfetamine capsules of unknown strength (described as blue capsules). The capsules were left by a family friend staying overnight at the child's parents' house. The patient was hospitalized for three days. No information was reported regarding the adverse event experienced, treatment, or outcome.

Reviewer's comment: The 3-year-old male possibly ingested lisdexamfetamine 60 mg capsules, which are aqua blue in color. Other blue-colored lisdexamfetamine capsules are partially blue, such as the 40 mg strength (white body/blue green cap), 50 mg strength (white body/blue cap), and 70 mg strength (blue body/orange cap).

Unlabeled Event: Overdose (n=1)

A 3-year-old female was prescribed lisdexamfetamine 20 mg daily for ADHD. Shortly after the first dose, the patient experienced chills, tachycardia (heart rate 115 bpm), headache, ears and neck hurting, paranoia, and hallucinations (visual and auditory). The patient was diagnosed with lisdexamfetamine overdose at the hospital. Treatment included diphenhydramine and unspecified medications. Upon hospital discharge the following day, some of the adverse events resolved (such as chills, tachycardia, ears and neck hurting). However, other adverse events, such as paranoia and hallucinations, remained ongoing at the time of hospital discharge.

3.4.3 Nervous System Disorders (N=4)

Labeled Event: Tic (n=2)

Tic is labeled in the Adverse Reactions section. An 8-year-old male was initiated on lisdexamfetamine 20 mg daily for ADHD. The following month, the lisdexamfetamine

dose was titrated up to 50 mg daily. About one-and-a-half months after the lisdexamfetamine dosage increase, the patient experienced facial tics. Four days later, lisdexamfetamine was discontinued and the facial tics resolved.

An 8-year-old male developed tremors and tics following the first dose of lisdexamfetamine 20 mg for ADHD. As a result, the physician discontinued lisdexamfetamine. The outcome was unknown. The patient was not taking any concomitant medications and no other medical history was reported.

Labeled Event: Psychomotor Hyperactivity (n=1)

Psychomotor hyperactivity is labeled in the Adverse Reactions section. A 5-year-old male was on unknown doses of lisdexamfetamine and mixed amphetamine salts (Adderall XR) for an unspecified duration when he was hospitalized "due to hyperactivity." The physician stated the patient metabolized both medications faster "than what the literature said." No further information was provided regarding the clinical course during the hospitalization, treatment, outcome of event, or if the medications were continued.

Unlabeled Event: Dystonia (n=1)

A 5-year-old male was on lisdexamfetamine 15 mg for ADHD. The patient had been on lisdexamfetamine for eight days, with the last dose being on a Friday morning. On Saturday evening, the patient experienced "full body shaking/convulsing" during his sleep. Throughout the night, there were additional "smaller episodes." The patient was taken to the hospital on Sunday when the full body "convulsions" reappeared again. He was diagnosed with dystonia, and he was treated with diphenhydramine in the hospital. The patient was discharged home with a prescription for diphenhydramine. However, the "tremors/shaking" recurred the following day. He was admitted to the hospital for observation. His electroencephalogram was normal and seizures were ruled out. The neurologist confirmed a dystonic reaction to lisdexamfetamine.

Reviewer's comment: As reported, the lisdexamfetamine dose of 15 mg was administered from a 30 mg capsule.

3.4.4 General Disorders and Administration Site Conditions (N=3)

Unlabeled Event: Drug Ineffective (n=2)

A 4-year-old male with ADHD, aggression, and seasonal allergies was prescribed lisdexamfetamine for the treatment of ADHD. His concomitant medication included sertraline for an unspecified indication. The starting dose of lisdexamfetamine was 10 mg daily and titrated to 60 mg daily over an unspecified amount of time. It was reported that lisdexamfetamine was effective for ADHD, but not for aggression. As a result, guanfacine ER was added and the outcome of "drug ineffective" resolved.

A 5-year-old male was on lisdexamfetamine for about one month, but it was not effective for the treatment of ADHD. Previously, he was on methylphenidate ER oral suspension for about three months, but it was also not effective for treating ADHD. Eventually, methylphenidate was restarted with the combination of guanfacine ER, which was effective for the patient.

Unlabeled Event: Drug Effect Increased (n=1)

A 4-year-old female was taking lisdexamfetamine 20 mg (frequency unspecified) for about three to four months for an unknown indication. The 20 mg dose was determined to be "too much." The prescriber decreased the dose to 7 mg daily (compounded by a pharmacy). No further information was provided.

3.4.5 Cardiac Disorders (N=2)

Labeled Event: Tachycardia (n=1)

Tachycardia is labeled in the Warnings and Precautions section. A 5-year-old male was on an unspecified dosage of lisdexamfetamine for an unknown indication. On an unknown date, the patient was seen in the ED for tachycardia. No further information was available.

Labeled Event: Palpitations (n=1)

Palpitation is labeled in the Adverse Reactions section. A 5-year-old male with ADHD and ODD experienced palpitations, stomach cramps, and a loss of appetite while on lisdexamfetamine, mixed amphetamine salts, and atomoxetine at different times. A cardiologist evaluated the patient for the palpitations, but the outcome was not reported.

3.5 SUMMARY OF NON-FATAL PEDIATRIC SERIOUS, UNLABELED ADVERSE EVENT CASES IN AGE 6 TO LESS THAN 17 YEARS OLD (N=178)

We identified 178 non-fatal cases associated with lisdexamfetamine in the pediatric population aged 6 to less than 17 years of age that reported a serious, unlabeled adverse event. The serious outcomes included hospitalization (41), life-threatening (5), disability (5), and other serious medical events (127). The largest category of cases reporting hospitalization or life-threatening is in the Psychiatric Disorders SOC.

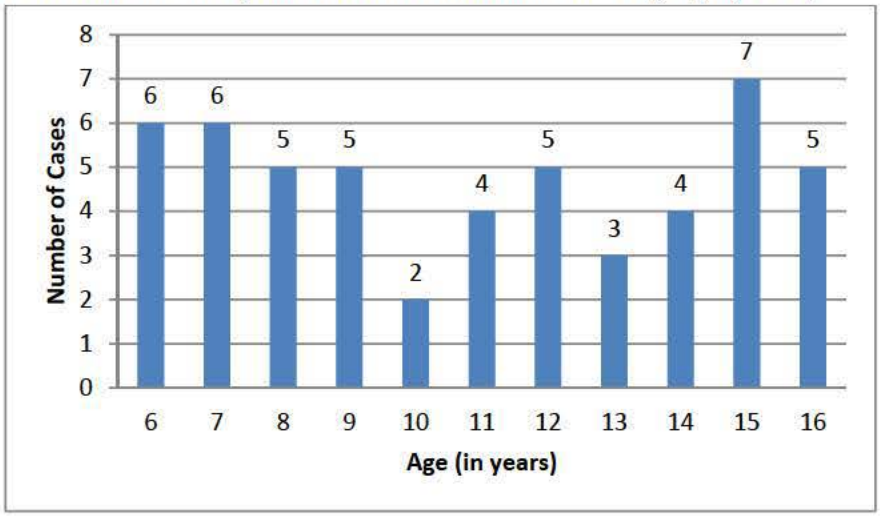
Cases in this section are categorized by PTs that best represent the reported adverse event(s). The PTs are then grouped by like terms and organized by SOC.

3.5.1 Psychiatric Disorders (N=73)

Suicidal Attempt, Suicidal Behavior, Suicidal Ideation, Self-injurious Behavior, Self-injurious Ideation, Intentional Overdose (n=52)

Fifty- two cases reported suicidal attempt/behavior/ideation (47), self-injurious behavior/ ideation (3), or intentional overdose (2) in patients ranging from 6 to 16 years old, with a median of 11 years old. See Figure 3.5.1 for the breakdown of the number of cases by age. The majority of the patients were male (n=38), and fourteen patients were female. There were 35 domestic cases and 17 foreign cases. The reported outcomes included hospitalization (9), life-threatening (5), and other serious (38).

Figure 3.5.1 Number of suicidal attempt/behavior/ideation, self-injurious behavior/ ideation, or intentional overdose cases by age (n=52)



The lisdexamfetamine daily dose ranged from 20 mg to 140 mg daily, as reported in 30 cases. An additional 13 cases provided the lisdexamfetamine dose, which ranged from 20 mg to 100 mg, but the frequency was not reported. The remaining nine cases did not report

a dose for lisdexamfetamine. In five of the 52 total cases, the prescribed lisdexamfetamine dose was above the maximum approved dose of 70 mg daily.

Eleven of the 52 cases were confounded by concurrent or past medical history (e.g., suicidal ideation, depression or a family history of depression, anxiety, anger, mood disorder, oppositional defiant disorder, or psychological stressors), or concomitant exposure to medications labeled for suicidal ideation (e.g. escitalopram, paroxetine), or both.

Five cases reported either a negative dechallenge, negative rechallenge, event resolved with the continuation of lisdexamfetamine, or the time to onset was greater than three years. Two of these five cases reported that the self-injurious or suicidal behavior continued after the discontinuation of lisdexamfetamine (negative dechallenge). The third case reported the suicidal ideation did not reappear when lisdexamfetamine was reintroduced (negative rechallenge). The fourth case reported the suicidal ideation resolved following an increased dosage of lisdexamfetamine, along with the initiation of additional treatments (an antidepressant and antipsychotic). In the fifth case, the time to onset of suicidal thoughts happened after the patient had been on lisdexamfetamine for three to four years (and more than one year since the last dosage increase).

Twelve cases reported the events abated after the discontinuation or a reduction in dose of lisdexamfetamine. Four of these twelve cases did not report the time to onset of the event and the patient's medical history. In the first case, an 8-year-old male experienced "thoughts of suicide" while on lisdexamfetamine 30 mg daily. In the second case, an 11-year-old female had "suicidal ideation, depressed mood, and hallucination" on an unknown date while on lisdexamfetamine 40 mg daily. The third and fourth cases reported depression and suicidal ideation in an 8-year-old male ("he wanted to run out in front of cars") and a 14-year-old female on lisdexamfetamine for ADHD. The remaining eight cases reported a median time to onset of 85 days (ranged from 1 day to 414 days) following the initiation of lisdexamfetamine. However, not all of these eight cases reported the patient's medical history. These eight cases are summarized below.

1. A 6-year-old male "complained of 'lows' and 'wanting to die/kill himself with something sharp'" two weeks after his lisdexamfetamine dose was increased from 20 mg to 30 mg daily. The patient had been on lisdexamfetamine for more than two months for ADHD at the time of the suicidal thoughts. The "symptoms improved or abated" after the discontinuation of lisdexamfetamine.

2. A 6-year-old male experienced suicidal ideation three months after initiating lisdexamfetamine 20 mg for ADHD. Initially, the patient improved in his

schoolwork, but he became withdrawn and spent more time alone at home. When he got into trouble, he would say things like "it would be better if I were dead." No stressors in his life were identified. Treatment with lisdexamfetamine was discontinued, and the events resolved.

3. A 9-year-old male had suicidal ideation (described as “suicidal remarks”), personality change, and “impulse breakout” after almost one month on lisdexamfetamine 30 mg. The events lasted three days until lisdexamfetamine was discontinued. The patient recovered from the events. The patient’s medical history was not reported.

4. A 9-year-old male experienced “nightmares, irritability, mood swings, depressive symptoms and self-harm ideation” after the first dose of lisdexamfetamine 30 mg for ADHD. The patient had no other medical history or psychological stressor. About four-and-a-half months later, treatment with lisdexamfetamine was discontinued, and all events resolved.

5. An 11-year-old male developed suicidal thoughts and depressive symptoms (sadness, crying, did not want to play). He also had increased anxiety and fought with other students. The patient had been on lisdexamfetamine 30 mg daily for about eight months when these symptoms appeared. Treatment with lisdexamfetamine was discontinued, and the events were resolving. The patient’s medical history was not reported.

6. A 13-year-old male had “suicidal ideation” for one evening. The patient had been on lisdexamfetamine for two months and the suicidal thought occurred about three weeks after an increase in the lisdexamfetamine dose from 30 mg to 40 mg daily. The following day, the patient’s mother stopped lisdexamfetamine without the physician’s awareness. The event resolved “immediately.” The patient’s medical history was not reported.

7. A 15-year-old male had suicidal thoughts, three days after an increase in the lisdexamfetamine dose from 30 mg to 40 mg daily. The patient had been on lisdexamfetamine for more than one year for the treatment of ADHD. On the same day of the event, psychiatry evaluated the patient and discontinued lisdexamfetamine. The event resolved by the following day. The patient had no other relevant medical history or psychological stressor.

8. A 17-year-old female abused alcohol, smoked marijuana, and became suicidal three months after starting lisdexamfetamine for ADHD. She was on lisdexamfetamine 60

mg daily. After the patient went to boarding school and lisdexamfetamine was discontinued, the patient became a "totally different person" one year later.

Six cases reported suicidal behavior or ideation with a possible temporal relationship to the initiation of lisdexamfetamine. The time to onset ranged from just after the first dose to 75 days. However, in three cases, the medical history and outcome of the event were not reported. In the fourth case, the patient's medical history was incomplete and the role of the discontinuation of risperidone during lisdexamfetamine therapy was unclear. In this case, on the same day that a 7-year-old male started treatment with lisdexamfetamine, he developed suicidal ideation and acute psychosis (depression, mood change, hallucination, aggression, compulsive crying). The patient was on risperidone for an unspecified indication, which was discontinued during treatment with lisdexamfetamine on an unknown date. In the fifth case, an 8-year-old male with ADHD and no other past medical history was initiated on lisdexamfetamine 30 mg daily. The following month, the dosage was increased to 70 mg daily and the patient developed suicidal thoughts. Lisdexamfetamine was continued and the event was ongoing. In the sixth case, a 9-year-old male started on lisdexamfetamine 20 mg daily for ADHD. One night, after taking lisdexamfetamine for two weeks, the patient told his parents that he did not have any friends and wanted to commit suicide. The patient had no other past medical history and was previously "a very happy child, full of life, and energy." The family discontinued lisdexamfetamine immediately, but the outcome was not reported.

The remaining 18 cases lacked sufficient information for assessment. None of the cases reported a time to onset. The majority of the cases did not report the patient's medical history, concomitant medications, action with lisdexamfetamine, and outcome of the event.

Anger (n=9)

Nine cases reported anger in patients ranging from 8 to 16 years old, with a median age of 10 years old. There were five females and four males. Seven cases were domestic and two were foreign. Five cases reported a positive dechallenge (anger resolved following the discontinuation of lisdexamfetamine), including one case of a positive rechallenge. Of these five cases, the medical history was not reported in three cases. The sixth case reported a negative dechallenge (adverse events such as auditory hallucinations and anger remained ongoing despite the discontinuation of lisdexamfetamine). The seventh case reported that the patient was diagnosed with depression when he was bullied at school; the patient experienced anger while on bupropion and lisdexamfetamine. The last two cases did not provide enough information regarding the patient's medical history for assessment.

Reviewer's comment: Anger is not labeled in lisdexamfetamine, but anger is captured under the labeled term, "irritability." All of the cases reported other concurrent symptoms

such as hallucinations, aggression, irritability, or depression, which are labeled events for lisdexamfetamine.

Homicidal Ideation, Violence-Related Symptom (n=6)

Six cases reported homicidal ideation (5) or a violence-related symptom (1). Three of the patients with homicidal ideation also experienced suicidal ideation or self-injurious behavior. The patients ranged from 6 to 16 years old, with a median age of 9 years old. There were four males and two females. All were domestic cases.

The first case reported a 13-year-old female being on lisdexamfetamine for a few years, but she experienced depression and her personality changed once she hit puberty. The patient hallucinated that a girl was "telling her to do things" and instructed her to kill her mother with a knife. The patient almost stabbed her mother with a knife while her mother was sleeping. Lisdexamfetamine was discontinued, and the patient's condition was improving.

The patient's past medical history was confounded in four cases. The cases reported one or more of the following medical history: oppositional defiant disorder, adjustment disorder, bipolar disorder, and a history of violence. In one of the cases, the homicidal and suicidal thoughts resolved following a dosage increase in sertraline and continuation of lisdexamfetamine.

The remaining case reported a 7-year-old male who experienced "aggression, took a knife to his sister and had suicidal ideations." This case did not provide enough information for assessment.

Reviewer's comment: All of the cases reported other concurrent symptoms such as hallucinations, aggression, irritability, or depression, which are labeled events for lisdexamfetamine. There are many risk factors for the act of violence in youths, including ADHD and poor behavioral control.[5]

Trichotillomania (n=1)

An 11-year-old female on lisdexamfetamine picked at her scalp and pulled her hair out when she was nervous. When the patient was off from school in December, lisdexamfetamine was stopped. The events resolved, but the events resumed in January after lisdexamfetamine was restarted.

Reviewer's comment: Dermatillomania occurred concurrently with trichotillomania. Dermatillomania is labeled in the Adverse Reactions section of lisdexamfetamine.

Bipolar Disorder (n=1)
A 10-year-old male was prescribed lisdexamfetamine for ADHD. On an unknown date, the patient was seen in the ED for "possible bipolar disorder." Lisdexamfetamine was discontinued; the event resolved on an unspecified date.

Reviewer's comment: The details of the event "bipolar disorder" were not specified. Many of the symptoms of bipolar disorder (such as mania) are labeled events.

Head Banging (n=1)
An 11-year-old female with a medical history of "abnormal behaviour" and "mental impairment" was on risperidone in the past. The patient's concurrent medication, if any, is unknown. An unknown time after starting lisdexamfetamine for an unknown indication, the patient started "head banging," which led to bruising of her face. Lisdexamfetamine was discontinued and the event was resolving at the time of the report.

Reviewer's comment: The event is confounded by the patient's pre-existing psychiatric history.

Logorrhea (n=1)
An 8-year-old male was initiated on lisdexamfetamine for ADHD. Four days later, the patient was talking excessively. He had hoarseness and shortness of breath, but no breathing difficulties. The events resolved after the discontinuation of lisdexamfetamine.

Reviewer's comment: Logorrhea is not labeled in lisdexamfetamine, but labeled in the Adverse Reactions section of other amphetamine products (such as Adderall and Adderall XR). Logorrhea may also be related to the underlying ADHD.

Memory Impairment (n=1)
A 16-year-old male was on lisdexamfetamine for ADHD. The patient reported that he could "deal with the most common side effects like tachycardia, dry mouth, irritation, tics, etc." but he was "embarrassed and humiliated" about memory impairment. He had been on lisdexamfetamine since the age of 13 years old. After the lisdexamfetamine dose was increased from 50 mg to 60 mg, the patient experienced memory loss and forgetfulness, which he previously did not experience while on the 50 mg dose.

Social Avoidant Behaviour (n=1)
A 14-year-old male with a past medical history of aggression and autism initiated lisdexamfetamine 30 mg daily for ADHD. On an unknown date, the dosage was increased to 50 mg daily. On the same day of the dosage increase, the patient experienced mydriasis, social avoidant behavior, and "extreme aggression." Lisdexamfetamine was discontinued

the following day. The events resolved one week after the discontinuation of lisdexamfetamine.

Reviewer's comment: The event of social avoidant behavior is confounded by the patient's medical history of autism. Lisdexamfetamine is labeled for the other reported events (aggression and mydriasis).

3.5.2 Nervous System Disorders (N=25)

Loss of Consciousness/Syncope (n=12)

Twelve cases reported a loss of consciousness or syncope in patients ranging from 7 to 16 years old, with a median age of 12 years old. The majority of the patients were male (n=9); three were female. There were seven domestic cases and five foreign cases. In seven cases, the time to onset of the event ranged from two days to about one year following the initiation of lisdexamfetamine. The remaining five cases did not report a time to onset.

Four cases did not provide enough information for assessment. Of these four cases, two cases reported normal cardiac evaluations.

Five cases were confounded by the patient's medical history, concomitant medication labeled for syncope, or a possible alternative cause. Three patients were concomitantly on guanfacine ER or atomoxetine (both medications labeled for syncope in the Warnings and Precautions section). The fourth case reported a 13-year-old male, who had been on lisdexamfetamine for almost a year as part of a clinical trial, experienced syncope when he stood up and further episodes of dizziness; the patient had a prior history significant for dizziness as well as a history of anemia. Cardiac evaluation, including an ECG, was normal. The fifth case reported a 16-year-old male who experienced a "vasovagal episode with loss of consciousness" at school when he vomited. Additionally, the patient was dehydrated.

The three remaining cases did not report risk factors for loss of consciousness or syncope. One case was a 9-year-old male in a long-term safety study of lisdexamfetamine who experienced two episodes of syncope. The first episode occurred about three months after the initiation of lisdexamfetamine; the patient fainted while he was in a fight on the school bus. Syncope occurred a second time, about three months after the first episode; he had heart palpitations during gym class at school and shortly after, the patient experienced syncope for a brief period. The cardiac evaluation (ECG and echocardiogram [ECHO]) were normal. At the time of reporting, the plan was to restart lisdexamfetamine and follow-up with holter monitoring. The second case reported a 7-year-old male who passed out two hours after his second dose of lisdexamfetamine. ECG was "irregular" but the ECHO was normal. Lisdexamfetamine was discontinued and the patient's treatment was changed to methylphenidate with cardiac monitoring. The third case reported an 11-year-

old male who experienced "blacking out, fainting, and tachycardia" four days after the lisdexamfetamine dose was increased from 30 mg to 40 mg daily and more than one month after starting the medication. Two days later, lisdexamfetamine was discontinued. The events resolved and the ECG was normal on an unknown date. Another two days later, guanfacine was initiated and the patient did not experience any side effects.

Reviewer's comment: Although loss of consciousness or syncope are not labeled events for lisdexamfetamine, the Serious Cardiovascular Reactions section of the Warning and Precautions states to "further evaluate patients who develop exertional chest pain, unexplained syncope, or arrhythmias during VYVANSE treatment." The majority of the patients received further evaluation as recommended in the label. Of the patients who received further evaluation, none of the cases identified a cardiac etiology for the syncope.

Incoherent/Speech Disorder/Unresponsive to Stimuli (n=4)

Four cases reported the PTs incoherent, speech disorder, or unresponsive to stimuli in patients ranging from 6 to 13 years old, with a median age of 7 years old. All four patients were male. There were three foreign cases and one domestic case. The lisdexamfetamine dose ranged from 20 mg to 30 mg daily.

Three cases reported that the events occurred following the first dose of lisdexamfetamine. The first case reported that a 13-year-old male was incoherent, lethargic, looked "doped out," had poor coordination, and had nose tics; these events started a few hours after the first dose of lisdexamfetamine 20 mg. Lisdexamfetamine was discontinued, and all of the events resolved within two days. The second case reported a 6-year-old male with no past medical history or concomitant medications who started lisdexamfetamine 30 mg for ADHD. A few hours after the first dose, the patient experienced various adverse events such as irritability, agitation, "swollen tongue," "foaming mouth," incoherent speech, tachycardia, "psychotic outbreak," and dyskinesia. He was discharged home after he recovered in the ED. However, when the patient awoke the next morning, he vomited, had further involuntary movements of his arms, and fainted. The remaining symptoms were ongoing at the time of the report. The third case reported a 7-year-old male who was not responsive, "as if he was controlled remotely", after the first dose of lisdexamfetamine 30 mg. He was confused, restless, hyperventilated, and tachycardic (heart rate 96 bpm). The patient was admitted to the hospital, and lisdexamfetamine was discontinued. Treatment was not reported. The patient recovered from the events, and he was discharged home the next day.

The fourth case reported dyskinesia and "speech disorder" in a 7-year-old male; this case did not provide enough information for assessment.

Reviewer's comment: Three cases reported the onset of a constellation of symptoms following the first dose of lisdexamfetamine. Although these three patients initiated lisdexamfetamine according to the recommended 30 mg dose or less, some of the symptoms are expected adverse events (e.g., tics, irritability, agitation, dyskinesia, restlessness) or describe manifestations of possible overdose (e.g., rapid respiration, confusion, fatigue, vomiting). The second case reported "swollen tongue," possibly a sign of hypersensitivity, which is a labeled event for Vyvanse.

Hypoaesthesia (n=2)

One case reported a 13-year-old male who had been on lisdexamfetamine for about six months, and developed a rash on his arm, had "numbness and tingling on his face and arms," and "could not feel his arm or hand." On an unknown date, the patient also "could not feel his feet and was walking funny." An unspecified test showed a cyst in the temporal lobe of the brain. An MRI was "negative" and ruled out peripheral neuropathy. Lisdexamfetamine was discontinued, but the events remained ongoing.

The second case reported a 10-year-old patient of unknown sex who experienced dizziness, difficulty breathing, and numbness of both legs, one hour after the first dose of lisdexamfetamine 35 mg. The patient was evaluated at the hospital and the events were ongoing eleven hours after receiving the dose.

Reviewer's comment: Lisdexamfetamine is labeled for paresthesia in Adverse Reactions. In the first case, the events remained ongoing despite discontinuation of lisdexamfetamine; the numbness is possibly confounded by the cerebral cyst. In the second case, a temporal relationship was established. As reported, the lisdexamfetamine dose of 35 mg was administered from a 70 mg capsule.

Myasthenia Gravis (n=2)

Two male patients were diagnosed with myasthenia gravis within three months after the initiation of lisdexamfetamine for ADHD. Both of the patients exhibited ophthalmologic manifestations. The first patient, a 9-year-old male, experienced ptosis. A neurologist diagnosed the patient with "ocular myasthenia gravis" and lisdexamfetamine was discontinued. Treatment, if any, was not reported. The event resolved on an unknown date in the same year. On a follow-up report, the physician reported that the event was not related to treatment with lisdexamfetamine. The second patient, a 15-year-old male, complained of blurred vision in the month following initiation of lisdexamfetamine. The patient continued to experience blurred vision over the next two months, and then he developed ptosis. A Tensilon test was positive and a neurologist diagnosed the patient with myasthenia gravis.

Reviewer's comment: As of January 15, 2016, DPV had not identified any additional FAERS reports of lisdexamfetamine and the PT myasthenia gravis in any age group.

Neuroleptic Malignant Syndrome (n=2)

A 13-year-old male was on lisdexamfetamine for ADHD and sertraline for an unknown indication. Two weeks after the initiation of lisdexamfetamine and an unknown time after the initiation of sertraline, the patient experienced "neuroleptic malignant syndrome and extrapyramidal side effects which were not further clarified." The physician prescribed diphenhydramine and benztropine without response. The events remained ongoing for three weeks after a decrease in the lisdexamfetamine dose. Subsequently, lisdexamfetamine was discontinued and the patient started dextroamphetamine, but the events remained ongoing. The events resolved following the discontinuation of sertraline on an unspecified date.

The second case reported a 13-year-old female who experienced adverse events such as sweating, increased heart rate, and restlessness with uncontrollable leg movements after the first dose. The patient received aripiprazole for thirteen days before it was discontinued. The symptoms improved quickly after the discontinuation of aripiprazole. The case also reported propranolol, fluoxetine, and lisdexamfetamine as suspect products, but did not provide information regarding the treatment start dates.

Reviewer's comment: Both cases did not require hospitalization. In the first case, no information was reported regarding concomitant medications or a medical history. Additionally, the events resolved following the discontinuation of sertraline, but not lisdexamfetamine. The case also did not provide details regarding other symptoms of neuroleptic malignant syndrome besides the extrapyramidal side effects. In the second case, the event is likely attributed to aripiprazole based on a temporal relationship and positive dechallenge. Aripiprazole is labeled for neuroleptic malignant syndrome in Warnings and Precautions.

Extrapyramidal Disorder/Dystonia (n=2)

A 7-year-old male was prescribed aripiprazole 2 mg for bipolar disorder and Asperger's Syndrome. The patient also was prescribed unknown doses of lisdexamfetamine and clonidine for an unknown duration. The patient received 30 mg of aripiprazole (overdose due to an unspecified reason). He had an arched back and his mouth would not close. In the hospital, the patient was diagnosed with extrapyramidal syndrome. The condition improved after treatment with diphenhydramine; aripiprazole was discontinued.

A 6-year-old male initiated his first dose of lisdexamfetamine 30 mg for ADHD in the morning. Two hours after the first dose, the patient experienced abdominal pain, dyspnea,

and "uncontrollable facial movements" mainly with the mouth. The symptoms continued and he stayed overnight in the hospital. He was diagnosed with dystonia. The report also mentioned unspecified ECG changes, but no further information was provided. Treatment included diphenhydramine for five days. The patient was previously on methylphenidate (Concerta) and mixed amphetamine salts without adverse reactions.

Hypersomnia (n=1)

An 8-year-old male was on methylphenidate (Ritalin) for two years for ADHD. Due to a short supply of Ritalin, the patient took one tablet (unknown dosage) of methylphenidate (Concerta). After one dose of Concerta, he slept for "two whole days and one night." He was evaluated at the hospital and received "saline solution" for treatment. After the incident, the patient was prescribed lisdexamfetamine one capsule (unknown dosage) daily. Again, the patient "slept all day long" and required gastric lavage. He remained in the hospital for two days for observation. The patient recovered and resumed Ritalin.

Reviewer's comment: This is an unusual case that is possibly lacking other pertinent information. Insomnia is one of the most common adverse reactions for lisdexamfetamine and other ADHD stimulants.

3.5.3 Cardiac Disorders (N=20)

Chest Discomfort, Chest Pain (n=12)

Twelve cases reported chest discomfort or chest pain in patients ranging from 6 to 16 years old, with a median age of 10 years old. The majority of the patients were male (n=9); three patients were female. All cases were domestic. In six cases, the time to onset ranged from the same day to about 2.5 years following the initiation of lisdexamfetamine. The remaining six cases did not report a time to onset.

Four cases did not provide enough information for assessment, including two patients who were seen in the hospital for further evaluation, but the outcome was not reported.

Three cases were confounded by the patient's medical history. Two of the confounded cases reported "chest discomfort" or "chest tightening" in addition to shortness of breath during physical activity, but the patients' underlying medical conditions included exercise-induced asthma or asthma. The third confounded case reported a 12-year-old female with celiac disease who experienced symptoms such as "trouble breathing, chest pressure, dizziness, and upset stomach (consistent with a reaction after ingesting gluten)," on the second day of lisdexamfetamine therapy.

In the five remaining cases, the patients received cardiac evaluation for the chest pain. Four cases reported a normal cardiac evaluation; including one case that was confounded by hypokalemia (potassium was 2.8). The last case reported an 11-year-old male with

ongoing shortness of breath, chest pain, and syncope after the discontinuation of lisdexamfetamine and an abnormal cardiac evaluation that showed "heart murmur and one artery of the heart was larger than the others."

Reviewer's comment: Although chest discomfort and chest pain are not labeled events for lisdexamfetamine, the Serious Cardiovascular Reactions section of the Warning and Precautions states to "further evaluate patients who develop exertional chest pain, unexplained syncope, or arrhythmias during VYVANSE treatment." The majority of the patients received further evaluation as recommended in the label. Of the patients who received further evaluation, with the exception of the last case, there was no identified cardiac etiology identified for the chest pain.

Arrhythmia, Extrasystoles, Bundle Branch Block Right (n=3)

The first case reported cardia arrhythmia but the case was confounded by the patient's medical history of atrial septal defect, a congenital condition that can cause arrhythmias. It was a clinical trial report of a 15-year-old male who participated in a phase 4, two-year safety study of lisdexamfetamine in children and adolescents aged 6-17 with ADHD. The patient had a normal baseline ECG when lisdexamfetamine was initiated. About 14 months after the initiation of lisdexamfetamine, a cardiac workup led to the diagnosis of cardiac arrhythmia and cardiomyopathy.

The second case reported a 15-year-old female who was diagnosed with right bundle branch block and sinus tachycardia on a routine visit to the physician's office. The patient had been on lisdexamfetamine for about seven months when the cardiac events were diagnosed. The events remained ongoing after the discontinuation of lisdexamfetamine.

The third case reported a 10-year-old male with an unknown medical history who experienced ventricular extrasystoles while he was on lisdexamfetamine, aripiprazole, risperidone, and other concomitant medications. Lisdexamfetamine was discontinued and the extrasystoles resolved on an unknown date. No information was provided regarding the patient's medical history, clinical course, duration of the extrasystoles, and treatment, if any.

Cardiac Failure Congestive, Cardiomegaly, Mitral Valve Stenosis/Pulmonary Valve Stenosis (n=3)

All three cases were confounded by the patient's cardiac history. The first case reported an 11-year-old female with atrioventricular block and pacemaker who experienced congestive heart failure. The patient was previously on lisdexamfetamine for an unknown duration of time and the medication was discontinued during the summer. The congestive heart failure occurred after the first or second dose when lisdexamfetamine was restarted. The

cardiologist discontinued lisdexamfetamine and the event resolved on an unknown date. The second case reported an 11-year-old male with atrial septal defect who developed cardiomegaly after being on lisdexamfetamine for 15 months. Lisdexamfetamine was discontinued and the patient required surgical intervention to repair the atrial septal defect. The third case reported a 14-year-old male with a history of ventral septal defect who developed pulmonary valve stenosis, mitral valve stenosis, and mild aortic regurgitation on an unknown date while on lisdexamfetamine; the patient remained on lisdexamfetamine and was under "cardiac care."

Bradycardia (n=1)

One case reported bradycardia and dizziness after a 9-year-old male restarted lisdexamfetamine and guanfacine ER without titration. The events resolved following the discontinuation of both medications.

Reviewer's comment: Lisdexamfetamine is associated with tachycardia. The event is likely associated with guanfacine ER, which is labeled for bradycardia in Warnings and Precautions.

Postural Orthostatic Tachycardia Syndrome (n=1)

A 15-year-old patient of unknown sex was on unknown doses of lisdexamfetamine and guanfacine ER for an unknown duration. On an unknown date, the patient discontinued guanfacine ER without the physician's awareness, leading to postural orthostatic tachycardia syndrome. As treatment, the physician discontinued lisdexamfetamine and prescribed a beta-blocker. The patient's past medical history and outcome of the event were not reported.

3.5.4 Injury, Poisoning and Procedural Complications (N=11)

Overdose, Prescribed Overdose, Toxicity to Various Agents (n=5)

Two cases reported patients who were diagnosed with an overdose of lisdexamfetamine, but the patients took a prescribed dose within the normal dosing range (less than the maximum dose of 70 mg daily). A 16-year-old male was initiated on lisdexamfetamine 30 mg daily for ADHD. He had no other past medical history and was not on any concomitant medications. After the second dose, the patient experienced dizziness, syncope, mental confusion, nausea, tingling in his scalp, and "intense" sweating in his hands and feet. The patient was hospitalized. He was diagnosed with "intoxication by the product [lisdexamfetamine]." The patient recovered from the events. The second case reported a diagnosis of possible overdose to lisdexamfetamine in a 16-year-old male prescribed lisdexamfetamine 20 mg daily. He was also taking methylphenidate (Ritalin) concomitantly and had been on lisdexamfetamine for six months when he experienced sensory disturbance described as "oversensitive to noise, lights and felt like his brain was

going to explode." Five days later, the physician discontinued lisdexamfetamine, and the event resolved the following day.

The third and fourth cases reported a prescribed overdose of lisdexamfetamine (above the maximum dose of 70 mg daily). A 13-year-old male was prescribed lisdexamfetamine 100 mg (frequency not reported) for an unknown indication. He was hyperactive, reported as "off the walls, racing." An unknown time later, the prescriber increased the dose to 120 mg (frequency not reported). The patient had been on the 120 mg dose for about three to four years, when he experienced six episodes of tremor and ataxia. He would lose control of his legs for about 15 seconds, but then able to stand up. Lisdexamfetamine was continued, and the events remained ongoing. In the second case of prescribed overdose, a 6-year-old male was prescribed lisdexamfetamine 70 mg in the morning and 20 mg in the afternoon. On an unknown date, the patient experienced "psychotic" behavior with tics and eye movements. As a result, the physician decreased the dose of lisdexamfetamine to 50 mg daily (along with decreasing the dose of other unspecified medications). The patient's medical history was not reported, but he was also on valproate semisodium, clonidine, and cyproheptadine. Mania persisted despite the dose reduction, and the outcome of other events were unknown.

The remaining case reported "toxicity to unspecified various agents" in a 7-year-old male, but the case did not provide enough information for assessment. The medical history, concomitant medications, time to onset, dose, and further information regarding the agents ingested were not reported.

Accidental Exposure to Product by Child, Accidental Overdose (n=4)

Three cases reported an accidental ingestion of a sibling's dose of lisdexamfetamine. The first case reported the patient's mother accidentally gave her 6-year-old son his older sibling's 30 mg dose of lisdexamfetamine. The patient experienced tics, blurred vision, anxiety, agitation, difficulty breathing, and a decreased blood pressure. He recovered following treatment in the hospital. The second case was an 8-year-old male who took his sibling's 70 mg dose of lisdexamfetamine. He experienced agitation and tachycardia. He was admitted to the hospital with "continued arrhythmia" and the outcome was not reported. The third case was a literature report of a 6-year-old female who ingested an unknown amount of her sibling's lisdexamfetamine. She experienced serotonin syndrome, and the patient recovered following treatment in the hospital.

The fourth case was a literature report of a 10-year-old male who was accidentally given a second 70 mg dose of lisdexamfetamine in the evening. The patient had insomnia and restlessness that evening. The next morning, the patient was given his daily 70 mg dose and went to school. The patient experienced uncontrollable, involuntary movements of his

body and extremities. The patient was treated with haloperidol for the choreoathetosis. The patient recovered and remained on a reduced dosage of lisdexamfetamine.

Drug Prescribing Error (n=2)

Two cases reported the patient took lisdexamfetamine 10 mg (half of a 20 mg capsule) daily. The patients were both 6 years old. In the first case, the patient initiated lisdexamfetamine 20 mg, but the drug prescribing error occurred when the dose was reduced to 10 mg. In the second case, the physician prescribed lisdexamfetamine 10 mg (half of a 20 mg capsule).

Reviewer's comment: The lisdexamfetamine label states in Section 2 Dosage and Administration, "Do not take anything less than one capsule per day, and a single capsule should not be divided." At the time of both of the reports, lisdexamfetamine 10 mg strength was not approved. Lisdexamfetamine is currently available as a 10 mg capsule.

3.5.5 Investigations (N=6)

Hepatic Enzyme Increased, Blood Creatine Phosphokinase Increased (n=4)

Four cases reported increased hepatic enzyme (2), increased creatine phosphokinase (CPK) (1), or increased hepatic enzyme and CPK (1). The cases provided limited information regarding medical history, concomitant medications, time to onset, clinical course, and lab values.

The first case reported a 14-year-old female with an unknown medical history on lisdexamfetamine 40 mg daily who had an elevated CPK of 849 (no units specified) on an unknown date. The second case reported a 6-year-old female with an unknown medical history on lisdexamfetamine 40 mg (frequency unspecified) who was hospitalized for increased alanine aminotransferase, increased aspartate aminotransferase, increased CPK) among other labeled adverse events. All events resolved on an unknown date. The action with lisdexamfetamine and lab values were not reported. The third case reported a 15-year-old male who had "elevated liver enzyme levels." Lisdexamfetamine was discontinued on an unspecified date and the event resolved on an unspecified date. However, the reporting physician was unsure of the cause of the event, because the patient was overweight (weighed about 300 lb). The last case reported a 10-year-old patient who was hospitalized for "slightly elevated liver enzymes due to viral infection."

Blood Pressure Decreased (n=1)

A 16-year-old of unknown sex was on lisdexamfetamine 30 mg daily for an unreported indication. His medical history was not reported, but the patient was concomitantly taking bupropion. Guanfacine ER was initiated on an unknown date and the dose was increased from 1 mg to 2 mg daily. On an unknown date, the patient had decreased blood pressure and increased heart rate, which resulted in hospitalization. Subsequently, the dose of

guanfacine ER was decreased to 1 mg daily. At the time of the report, the events continued and the patient remained hospitalized. The reporting physician related the events to guanfacine ER.

Reviewer's comment: Hypertension, rather than hypotension, is one of the cardiovascular risks associated with the use of lisdexamfetamine. Hypotension was likely associated with guanfacine ER (labeled for hypotension in Warnings and Precautions).

Weight Increased (n=1)

A 13-year-old male with obsessive-compulsive disorder was on escitalopram and lisdexamfetamine for unspecified indications. The patient gained 50 pounds since an unknown date.

Reviewer's comment: Lisdexamfetamine is associated with a decrease in appetite and weight loss. The report did not provide information on the time span of the 50 lb weight gain. With the concurrent medical history of OCD, it is possible that the patient had compulsive eating habits.

3.5.6 Skin and Subcutaneous Tissue Disorders (N=6)

Alopecia (n=3)

A 15-year-old female had a bald spot on her head after being on lisdexamfetamine for about two months. Her hair was "thinning all over" and she was "completely bald as if she was taking chemotherapy" within another month. The patient did not change her shampoo or conditioner. The pediatrician ruled out lupus. A dermatologist prescribed steroid injections that did not help with the hair growth. After lisdexamfetamine was discontinued for one month, her hair returned in "mass amounts."

An 8-year-old female had "alopecia areata" with a loss of hair on her scalp, as well as her eyebrows and eyelashes. Lisdexamfetamine was discontinued and the outcome was not reported.

A 9-year-old female had "severe hair loss and baldness" which began two months after starting ADHD treatment with lisdexamfetamine. The hair loss continued over the next three months until lisdexamfetamine was discontinued. Treatment, if any, was not reported. The outcome of the hair loss was resolving.

Reviewer's comment: Alopecia is not labeled in lisdexamfetamine, but it is labeled in the Adverse Reactions section of other amphetamine products (such as Adderall and Adderall XR). Two cases reported the event was resolving following the discontinuation of lisdexamfetamine.

Skin Exfoliation (n=2)

A 7-year-old male experienced the skin on his fingers, hands, and feet "peel[ed] off." The event was ongoing for one-and-a-half weeks at the time of the report. The patient's medical history, concomitant medications, and time to onset of the event after starting lisdexamfetamine were not reported.

One day after starting lisdexamfetamine, a 14-year-old female had swelling and "peeling" around her eyes. She also had erythema and a burning sensation on her face. Lisdexamfetamine was discontinued, and she was treated with diphenhydramine. The patient recovered from the events two days later.

Henoch-Schonlein Purpura (n=1)

A 9-year-old male with a medical history of eczema started treatment with lisdexamfetamine for ADHD. There was a prescribing error in which the patient was prescribed to take 5 mg from a 50 mg capsule; the dose was titrated up to 70 mg daily. In the same month that lisdexamfetamine was initiated, the patient had a generalized rash on his chest, arms, and abdomen. He was diagnosed with a viral syndrome. In the same month, the physician diagnosed the patient with Henoch-Schonlein purpura and prescribed corticosteroids for treatment. The purpura worsened over the next month; it was scattered on both legs. Lisdexamfetamine was continued and the outcome was unknown.

Reviewer's comment: As of January 15, 2016, DPV had not identified any additional FAERS reports of lisdexamfetamine and the PT Henoch-Schonlein purpura in any age group.

3.5.7 Eye Disorders (N=5)

Blindness, Blindness Transient (n=2)

A 6-year-old male developed blurred vision and "blindness" on an unspecified date while on lisdexamfetamine. The extent of blindness, diagnosis, duration of the events, time to onset, and outcome were not reported.

Eye Pain (n=1)

A 10-year-old male had burning pains in his eyes, and he was unable to see well. His eyes also twitched "uncontrollably." At the time of the report, a physician had not evaluated the patient. The patient had been on lisdexamfetamine for one month. The event occurred two days after a dosage increase from 30 mg to 40 mg daily.

Uveitis (n=1)

A 13-year-old male developed uveitis and had an increased human leukocyte antigen (HLA) while on lisdexamfetamine. The patient had no signs of inflammation or rheumatic

disease. Lisdexamfetamine was discontinued. After the events resolved, the patient resumed treatment with lisdexamfetamine.

Visual Acuity Reduced (n=1)

A 7-year-old female with an "eye disorder 'since her first year'" had a further loss of vision in both eyes a month after lisdexamfetamine was initiated. The vision in one eye reduced from "80% to 40%" and the other eye from "60% to 30%." Lisdexamfetamine was continued and the event remained ongoing.

Reviewer's comment: "Difficulties with visual accommodation" and "blurred vision" are labeled in the Adverse Reactions section.

3.5.8 Musculoskeletal and Connective Tissue Disorders (N=5)

Hypotonia (n=1)

A 13-year-old male with ADHD developed hypertensive crisis (blood pressure 140/80), increased sweating, hypotonia, and headache five days after starting lisdexamfetamine. He was not on any concomitant medications. The events resolved after an unspecified antihypertensive was initiated and the discontinuation of lisdexamfetamine. The patient did not have any adverse events while he was on previous unspecified medications for ADHD. No further details were provided regarding hypotonia.

Lower Limb Fracture (n=1)

A 13-year-old male had a broken leg while on lisdexamfetamine for ADHD. No further information was provided.

Muscular Weakness (n=1)

After the first dose of lisdexamfetamine 30 mg, an 11-year-old male experienced his "left eye [was] shut, weakness in both legs, and clonus of both hands." The patient was given lorazepam and cyclobenzaprine in the ED. Lisdexamfetamine was discontinued. Clonus remained ongoing while the muscular weakness and eye issue resolved.

Pain in Extremity (n=1)

A 7-year-old male was on lisdexamfetamine for ADHD. He did not have other medical history and was not on any concomitant medications. One-and-a-half years after starting lisdexamfetamine, the dose was increased to 40 mg daily (from an unspecified dose). After the dosage increase, the patient reported that his legs were in "excruciating pain." The next day, the patient reported pain in his arms. On unspecified dates in the following two months, the patient hallucinated that he saw bugs, thought spiders were in his shoes biting him, and thought his arms and hands were bleeding. As a result, the lisdexamfetamine dose was decreased to 20 mg daily. All events resolved. The case did not provide information on the diagnosis or etiology of reported pain, if treatment was required, or when the event resolved.

Tetany (n=1)

An 11-year-old male had been on lisdexamfetamine for an unknown duration when he experienced hallucinations, dizziness, unable to feel legs or walk, and unable to see well. At the hospital, he was diagnosed with "carpopedal spasms." The patient was recovering after treatment with diphenhydramine. The action with lisdexamfetamine was not reported.

3.5.9 Blood and Lymphatic System Disorders (N=4)

Neutropenia, Leukopenia (n=2)

A 12-year-old male was found to be neutropenic during routine testing while in the mental health ward. His neutrophil count dropped to 0.9 (units not specified). The patient previously experienced neutropenia while on methylphenidate. Treatment, if any, and the outcome were not reported. Lisdexamfetamine was discontinued.

A 12-year-old male had leukopenia while on lisdexamfetamine 30 mg. No additional information was reported.

Bone Marrow Failure (n=1)

A 10-year-old male was on lisdexamfetamine for ADHD. He had no other medical history. His concomitant medication was zinc. The patient was “pale and tired,” which increased gradually to “excessive tiredness.” Four months after the initial symptoms, the patient’s mother discontinued lisdexamfetamine (without medical advice). On an unknown date, labs showed low white blood cells (value not provided) and platelets (28,000, units not specified). A hematologist diagnosed the patient with bone marrow failure. The patient recovered following a bone marrow transfusion. Lisdexamfetamine was discontinued. The physician assessed the causality as not related to lisdexamfetamine.

Lymphadenopathy (n=1)

An 8-year-old male had posterior cervical and axillary lymphadenopathy after being on lisdexamfetamine for about six months. The patient did not have other symptoms. The physician prescribed treatment with antibiotics, but the outcome was not reported.

3.5.10 Metabolism and Nutrition Disorders (N=4)

Hypoglycaemia (n=3)

A 10-year-old male was diagnosed at the hospital with hypoglycemia due to decreased appetite. Lisdexamfetamine was temporarily interrupted because of the lack of appetite and hypoglycemia. The outcome was not reported.

A 7-year-old male had been on lisdexamfetamine for two years when he experienced hypoglycemic episodes where he was “lightheaded." The patient would also curl his hands toward his chest as if he was hypocalcemic. The symptoms resolved with orange juice or

soda. This occurred five times in the afternoon over the summer. The physician stated the patient was not eating enough during the day. An endocrinologist evaluated the patient and unspecified test results were pending at the time of the report. The patient continued lisdexamfetamine.

A 12-year-old male developed aggression after starting lisdexamfetamine; after two weeks, lisdexamfetamine was discontinued. Three months later, lisdexamfetamine was restarted for the treatment of ADHD. After the resumption of the first dose, the patient was hospitalized for chills, shortness of breath, low blood pressure, sweating, body tingling, loss of control of his legs, and delirium. The patient was found to be hypoglycemic in the hospital, with a blood glucose of 78 mg/dL. Treatment and the outcome of hypoglycemia were not reported.

Reviewer's comment: The first two cases reported hypoglycemia because of a decrease in appetite. In the third case, hypoglycemia occurred with a range of adverse events but the patient did not experience these symptoms when he was previously on lisdexamfetamine.

Obesity (n=1)

A litigation case reported that a 14-year-old male with ADHD, Asperger's disorder, autism, bipolar disorder, and asthma was diagnosed with gynecomastia (in 2011) after taking risperidone in 2007 for less than four months. The gynecomastia caused the patient to develop depression, and fluoxetine was prescribed for treatment. The patient started lisdexamfetamine in 2008; the patient's mother believed that the patient increased his food intake as a result of being on lisdexamfetamine. The patient was diagnosed with obesity in 2011. In March 2011, the patient's weight was 283 lb and his body mass index (BMI) was 36.71 kg/m^2. The patient exercised during football practice. In January 2012, the patient weighed 313 lb and his BMI was 38.12 kg/m^2. In September 2013, the patient had not taken lisdexamfetamine for three months because of the concern for weight gain. In May 2014, the patient was constantly eating and drinking, and he did not exercise. He was diagnosed with morbid obesity (his weight was 398.2 lb and his BMI was 46.7 kg/m^2). Lisdexamfetamine was discontinued. With lifestyle changes, the patient lost a few pounds in one month. The patient's baseline weight prior to starting lisdexamfetamine in 2008 was not reported.

3.5.11 Renal and Urinary Disorders (N=4)

Haematuria (n=1)

An 8-year-old male had gastroenteritis and hematuria. The patient's family history included benign familial hematuria. He was seen in the ED, but treatment was not reported. Lisdexamfetamine therapy continued. The patient had been on lisdexamfetamine for one year when the events occurred.

Nephrolithiasis (n=1)
A 15-year-old male had kidney stones in the right kidney after being on lisdexamfetamine for 12 months. The kidney stones were removed. The patient continued lisdexamfetamine.

Pollakiuria (n=1)
An 11-year-old male was initiated on lisdexamfetamine. On the same day, the patient urinated three times overnight and had auditory hallucinations at bedtime. The patient continued lisdexamfetamine. The events were ongoing at the time of the report.

Reviewer's comment: Pollakiuria is frequent urination during the daytime. It is unclear in the report whether the increased urination occurred only at night or during the day as well.

Urinary Retention (n=1)
A 16-year-old male was unable to urinate during the day while on lisdexamfetamine. The event would last for about eight hours during the day, even with liquid intake, and resolve in the evening. This happened for three to four days until the patient discontinued lisdexamfetamine. The symptoms subsided by the time the patient was seen by the physician. A urinalysis was negative for a urinary tract infection.

3.5.12 Infections and Infestations (N=3)

Paediatric Autoimmune Neuropsychiatric Disorders Associated With Streptococcal Infection (n=1)
An 11-year-old male was hospitalized for two days due to pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS) while on lisdexamfetamine. The physician assessed the causality as not related to lisdexamfetamine, but the root cause was a strep throat.

Superinfection Bacterial (n=1)
An 11-year-old male had a "papulopustular rash" for several weeks, particularly on his right hand. He had a recurrent pale rash on various parts of his body. After starting lisdexamfetamine, the patient had dyshidrotic eczema, recurrent rash throughout his body, and urticarial. Three months later, he was hospitalized for these events. The skin swab was positive for staphylococcus aureus and intravenous antibiotic was started for treatment. The dermatologist diagnosed the patient with a bacterial superinfection. The patient improved with additional prescribed treatment in the hospital, and he was discharged with outpatient dermatology re-evaluation. One month after the hospital discharge, lisdexamfetamine was stopped with a reported negative dechallenge.

Viral Infection (n=1)
A 7-year-old male became pale and non-responsive while on lisdexamfetamine. The patient was seen in the ED and he was diagnosed with a viral infection. The patient did not

receive any treatment and the patient was discharged home. The patient recovered with no further adverse events.

3.5.13 Respiratory, Thoracic, and Mediastinal Disorders (N=3)

Apnoea (n=1)

A 16-year-old male became apneic after starting a new medication, guanfacine ER 1 mg, and an increased dose of lisdexamfetamine from 15 mg to 30 mg. The school nurse gave mouth-to-mouth resuscitation, and the patient was taken to the ED, intubated and found to be unresponsive.

Choking Sensation (n=1)

A 16-year-old old male was on lisdexamfetamine for ADHD and ODD. About a year later, lisdexamfetamine dose was increased to 70 mg. The following month, the patient had tachycardia and "progressive pressure around the neck (like someone is choking him)." He was hospitalized for two days. Treatment, if any, was unknown. Lisdexamfetamine was discontinued and the events resolved.

Cough (n=1)

A 9-year-old male started coughing on the second day of lisdexamfetamine therapy. An unspecified medication was started for treatment. The patient had a persistent cough "which could have been a coughing tic." The patient stopped eating and drinking for hours. There was a positive dechallenge (event resolved upon discontinuation of lisdexamfetamine) and a positive rechallenge (the cough recurred when lisdexamfetamine was restarted).

3.5.14 Gastrointestinal Disorders (N=2)

Gastric Ulcer Perforation (n=1)

A 7-year-old male was admitted to the hospital for gastric ulcer perforation, two weeks after starting lisdexamfetamine. The patient was overweight and was not on any concomitant medications. Lisdexamfetamine was discontinued. The treatment, clinical course, and outcome were not reported.

Mouth Ulceration (n=1)

A 13-year-old female developed mouth ulcers after the lisdexamfetamine dose increased to 70 mg daily. The patient also experienced facial tics. The physician did not believe the mouth ulcers were related to lisdexamfetamine.

3.5.15 General Disorders and Administration Site Conditions (N=2)

Drug Effect Decreased (n=1)

An 11-year-old female was on lisdexamfetamine 50 mg daily. The patient reported lisdexamfetamine did not last "all day." The lisdexamfetamine dose was increased to 60 mg, but the lisdexamfetamine still did not last "all day."

Drug Ineffective (n=1)

A 12-year-old male was on lisdexamfetamine 70 mg daily for an unknown indication. The drug was "not working properly" and it did not help the patient. No additional information was provided.

3.5.16 Vascular Disorders (N=2)

Epistaxis (n=1)

A 10-year-old male had "increased nosebleeds" after starting lisdexamfetamine 50 mg daily. The patient experienced nosebleeds every morning for almost two months. The nosebleeds resolved following a dose reduction of lisdexamfetamine to 30 mg daily. This case is confounded by a recent diagnosis of iron deficiency prior to the initiation of lisdexamfetamine 50 mg dose; the patient started iron replacement therapy.

Haematoma (n=1)

An 8-year-old male initiated on lisdexamfetamine 20 mg daily and the dose was titrated to 40 mg daily on an unknown date. The patient's medical history included hemophilia, seasonal allergy, rhinitis, and sleep disturbance. While on lisdexamfetamine, the patient experienced "more frequent bleeds, described as once a month." The prior frequency of bleeds was not reported. In the following year, the patient was unable to walk due to the "blood collections behind knee." No treatment was reported, and the patient continued lisdexamfetamine.

3.5.17 Congenital, Familial, and Genetic Disorders (N=1)

Tourette's Disorder (n=1)

An 11-year-old male on lisdexamfetamine experienced "Tourette's disorder" among other adverse events (blepharospasm, hallucinations, dyskinesia, aggression, decreased appetite, and tic) on an unknown date, which resulted in hospitalization. The patient's medical history, concomitant medication, clinical course, treatment, action with lisdexamfetamine, and outcome of the events were not reported.

3.5.18 Reproductive System and Breast Disorders (N=1)

Gynaecomastia (n=1)

A 15-year-old male was developed gynecomastia after being on lisdexamfetamine for an unknown duration. The patient was scheduled for surgery.

3.5.19 Social Circumstances (N=1)

Drug Diversion (n=1)

A 14-year-old male with an unknown medical history took a lisdexamfetamine 20 mg dose from a friend, which improved his focus. The following day, the patient took seven doses and he was seen in the ED for tachycardia. The patient recovered.

4 DISCUSSION

A search of the FAERS database identified 215 pediatric cases received by FDA between April 10, 2012 and June 30, 2015. Of these 215 cases, 30 cases were identified in patients aged 0 to less than 6 years old, including 1 fatal case. In addition, 185 cases were identified in patients aged 6 to less than 17 years old, including 7 fatal cases. Of the eight total fatal pediatric cases, three cases reported an unknown cause of death or an alternative etiology as the likely cause of death, unrelated to lisdexamfetamine. Of the remaining five cases, four cases reported suicide as the cause of death and one case reported homicide. Three of the five cases that reported suicide or homicide were confounded by the patient's psychiatric history, non-compliance with a prescribed antidepressant, or psychological stressors.

The highest proportion of lisdexamfetamine cases in our case series reported suicidal thoughts or behaviors. A majority of these cases were confounded or did not contain enough information for assessment. 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.[6] Such conditions, as well as bipolar disorder, schizophrenia, psychotic disorders, aggression, substance use disorders, and impulsivity are all risk factors for suicide.[7, 8] The efficacy of lisdexamfetamine to reduce the symptoms of ADHD has been demonstrated in randomized clinical trials. It is well established that the treatment of ADHD can reduce impulsive and dangerous behaviors, as well as prevent some of the negative consequences of untreated ADHD such as poor school performances, inferior job performances, or relationship problems. Such behaviors and consequences of untreated ADHD may be risk factors for suicide.

It is difficult to perform a causality assessment of suicide-related events and lisdexamfetamine from the postmarketing cases, because of the comorbid conditions, missing information regarding the patients' psychiatric history or social stressors, and the prevalence of youth suicides. According to the Centers for Disease Control and Prevention, suicide was the second leading cause of death in 2014 for youths aged 10 to 24 years old (see Appendix D for the top ten leading causes of death in 2014).[9] As discussed in the previous pediatric review for lisdexamfetamine that was presented to the PAC in 2012, Shire (the sponsor 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 January31, 2009.[2]

Additionally, numerous placebo-controlled trials of lisdexamfetamine and other ADHD stimulants have not provided evidence that 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).[10] The clinical trials that led to the approval of lisdexamfetamine in the treatment of moderate to severe BED in January 2015 utilized the C-SSRS to assess the risk of suicidal behaviors and ideation. The results from the suicidal risk assessment were similar between lisdexamfetamine and placebo.[11] Furthermore, clinical trials to evaluate the safety and efficacy of lisdexamfetamine in the treatment of preschool children aged 4-5 years old are currently ongoing.[12, 13]

Based on the remaining cases, DPV identified a possible signal for alopecia in association with lisdexamfetamine. Three cases reported significant hair loss. Two of the three cases reported hair growth following the discontinuation of lisdexamfetamine. Alopecia is not a labeled event for lisdexamfetamine, but it is labeled for some of the other ADHD stimulants. Although alopecia is not a life-threatening event, it has serious psychological consequences associated with increased anxiety and depression for both children and adults.[14]

In order to capture pediatric use of lisdexamfetamine and to provide context for the adverse event reports submitted to the FAERS database for lisdexamfetamine, drug utilization patterns were assessed. During the most recent 12-month period ending in June 2015, the number of pediatric patients (0-16 years old) who received a dispensed prescription for lisdexamfetamine from outpatient retail pharmacies was approximately 47% of total patients. Among pediatric patients, approximately 51% (549,000 patients) were aged 6-11 years, approximately 53% (566,000 patients) were aged 12-16 years, and 2% (21,000 patients) of pediatric patients were aged 0-5 years. The drug utilization data provided in this review is consistent with the FAERS case series, with the majority of the cases in patients aged 6-11 years. According to the U.S. office-based physician survey data, "attention deficit disorder" was the most common diagnosis associated with the use of lisdexamfetamine in all age groups; this is also consistent with the most commonly reported reason for use of lisdexamfetamine in the case series.

5 CONCLUSION

The vast majority of adverse events reported to FDA in the 0 to less than 6-year-old age group were events that are well characterized in the labeling. Among the remaining cases in the 6 to less than 17-year-old age group, DPV identified a possible signal for alopecia in association with lisdexamfetamine.

6 RECOMMENDATIONS

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

7 REFERENCES

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8 APPENDICES

8.1 APPENDIX A. DRUG UTILIZATION DATABASE DESCRIPTIONS/LIMITATIONS

IMS Health, IMS National Sales Perspectives™: Retail and Non-Retail

The IMS Health, IMS 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.

IMS Health, Vector One®: Total Patient Tracker (TPT)

Total Patient Tracker (TPT) is a national-level projected audit designed to estimate the total number of unique patients across all drugs and therapeutic classes in the retail outpatient setting over time.

TPT derives its data from the Vector One® database which integrates prescription activity from a sample received from payers, switches, and other software systems that may arbitrage prescriptions at various points in the sales cycle. Vector One® receives over 2.1 billion prescription claims per year.

Unique patient counts may not be added across time periods due to the possibility of double counting those patients who are receiving treatment over multiple periods in the study. Furthermore, patient age subtotals may not sum exactly due to patients aging during the study period, and may be counted more than once in the individual age categories. For this reason, summing across time periods or patient age bands is not advisable and will result in overestimates of patient counts. Please note that subtotals may not sum exactly due to rounding. Because of patients aging during the study period, patients may be counted more than once in the individual age categories. For this reason, summing across years is not advisable and will result in overestimates of patient counts.

The estimates provided are national estimates, but no statistical tests were performed to determine statistically significant changes over time or between products. Therefore, all changes over time or between products should be considered approximate, and may be due to random error.

IMS Health, National Prescription Audit™ (NPA)

The National Prescription Audit (NPA™) measures the "retail outflow" of prescriptions, or the rate at which drugs move out of retail pharmacies, mail service houses, or long-term care facilities into the hands of consumers via formal prescriptions in the U.S. The NPA audit measures what is dispensed by the pharmacist. Data for the NPA audit is a national level estimate of the drug activity from retail pharmacies. NPA™ receives over 2.7 billion prescription claims per year, captured from a sample of the universe of approximately 57,000 pharmacies throughout the U.S. The pharmacies in the database account for most retail pharmacies and represent nearly 86% of retail prescriptions dispensed nationwide. The type of pharmacies in the sample are a mix of independent, retail, chain, mass merchandisers, and food stores with pharmacies, and include prescriptions from cash, Medicaid, commercial third-party and Medicare Part-D prescriptions. Data is also collected from approximately 40 - 70% (varies by class and geography) of mail service pharmacies and approximately 45-55% of long-term care pharmacies. Data are available on-line for 72- rolling months with a lag of 1 month.

Encuity Research, LLC., TreatmentAnswers™ with Pain Panel

Encuity Research, LLC., TreatmentAnswers™ and TreatmentAnswers™ with Pain Panel is a monthly survey designed to provide descriptive information on the patterns and treatment of diseases encountered in office-based physician practices in the U.S. The survey consists of data collected from over 3,200 office-based physicians representing 30 specialties across the United States that report on all patient activity during one typical workday per month. These data may include profiles and trends of diagnoses, patients, drug products mentioned during the office visit and treatment patterns. The Pain Panel supplement surveys over 115 pain specialists physicians each month. With the inclusion of visits to pain specialists, this will allow additional insight into the pain market. The data are then projected nationally by physician specialty and region to reflect national prescribing patterns.

Indications for use were obtained using a monthly survey of 3,200 office-based physicians. Although these data are helpful to understand how drug products are prescribed by physicians, the small sample size and the relatively low usage of these products limits the ability to identify trends in the data. In general, physician survey data are best used to identify the typical uses for the products in clinical practice. Results should not be overstated when nationally projected estimates of annual uses or mentions fall below 100,000 as the sample size is very small with correspondingly large confidence intervals.

8.2 APPENDIX B. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

FDA Adverse Event Reporting System (FAERS)

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Conference 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.

8.3 Appendix C. FAERS Case Numbers, FAERS Version Numbers And Manufacturer Control Numbers For The Pediatric Case Series With Lisdexamfetamine (N=215)

FAERS Case #	Version Number	Manufacturer Control #
8317964	1	US-PFIZER INC-2011310649
8324574*	1	US-JNJFOC-20111212387
8325201*	1	US-ABBOTT-11P-163-0887567-00
8335706*	1	US-SHIONOGI, INC-2012000003
8345197*	1	US-ROXANE LABORATORIES, INC.-2012-EU-00271GD
8346890*	1	US-B.I. PHARMACEUTICALS,INC./RIDGEFIELD-2012-EU-00271GD
8350416*	1	AVE_02165_2012
8350733*	1	IMP_05493_2012
8351354*	1	US-SHIRE-ALL1-2012-00259
8359917*	1	AUR-APL-2012-00149
8436205*	1	CHPA2012US003658
8749396*	1	2012MA009095
8325021	1	(blank)
8333111	3	US-SHIRE-ALL1-2012-00070
8347911	1	US-SHIRE-ALL1-2012-00251
8350482	1	US-SHIRE-ALL1-2012-00258
8345338*	1	US-ROXANE LABORATORIES, INC.-2012-EU-00280GD
8397042*	1	2012POI057500026
8402504*	1	US-COVIDIEN/TYCO
8750258*	1	HEALTHCARE/MALLINCKRODT-T201200098 2012MA009097
8371612	1	CA-SHIRE-ALL1-2012-00439
8371756	1	CA-SHIRE-ALL1-2012-00405
8374424	1	(blank)
9840761*	1	SPV1-2012-01200
8374529	1	CA-SHIRE-ALL1-2012-00399
8374530	1	CA-SHIRE-ALL1-2012-00412
8374532	1	BR-SHIRE-SPV1-2012-00062
8375018	1	CA-SHIRE-ALL1-2012-00396
8405719	1	(blank)
8419801	1	US-SHIRE-ALL1-2012-00803
8429169	1	(blank)
8437517	1	(blank)
8439663	2	US-SHIRE-ALL1-2012-01072
8443858	1	BR-SHIRE-SPV1-2012-00166
8445654	1	(blank)
8452486	1	US-SHIRE-ALL1-2012-01247
9841609*	1	ALL1-2012-01247
8480233	2	US-SHIRE-ALL1-2012-01543
8487117	1	(blank)
9840828*	1	SPV1-2012-01219
8524990	1	US-SHIRE-ALL1-2012-01993
8585832	1	US-SHIRE-ALL1-2012-02664
8589361	2	US-SHIRE-ALL1-2012-02670
8599576	1	US-SHIRE-ALL1-2012-02669
8600380	2	US-SHIRE-ALL1-2012-02710
8602825	1	US-SHIRE-ALL1-2012-02679
8610051	1	US-SHIRE-ALL1-2012-02719
8614962	1	US-SHIRE-ALL1-2012-02764
8619266	1	(blank)
8623111	1	US-SHIRE-ALL1-2012-02948
8676817	1	BR-SHIRE-SPV1-2012-00661
8716819	1	ALL1-2011-04160
8756303	1	(blank)
8784353	2	US-SHIRE-ALL1-2012-04137
8785399	2	US-SHIRE-ALL1-2012-04339
8785400	3	US-SHIRE-ALL1-2012-04323
8791773	2	US-SHIRE-ALL1-2012-04231
8833623	1	CA-SHIRE-ALL1-2012-04650
8838836	1	(blank)
8912165	1	US-SHIRE-ALL1-2012-05496
8915666	1	US-SHIRE-ALL1-2012-05548
8950826	1	(blank)
8956628	1	US-SHIRE-ALL1-2012-06133
8958268	1	US-SHIRE-ALL1-2012-05936
8969493	1	US-BRISTOL-MYERS SQUIBB COMPANY-16257966
8972881	1	CA-SHIRE-ALL1-2012-06020
8975038	1	US-SHIRE-ALL1-2012-06127
8988481	1	(blank)
9001255	1	US-SHIRE-ALL1-2012-06581
9030590	3	HU-SHIRE-ALL1-2013-00167

FAERS Case #	Version Number	Manufacturer Control #
9034240	1	(blank)
9074921	1	US-ROXANE LABORATORIES, INC.-2013-RO-00137RO
9026197*	2	2012AP004417
8951217*	1	2012P1065399
8931700*	2	US-SHIRE-ALL1-2012-05663
9122817*	1	2013SUN00043
9084556	1	US-SHIRE-ALL1-2013-00338
9093176	1	US-SHIRE-ALL1-2013-00522
9051887*	1	(blank)
9106970	2	US-SHIRE-ALL1-2013-00962
9123898	1	US-SHIRE-ALL1-2013-00274
9154379	4	ES-SHIRE-ALL1-2013-01177
9162815	1	US-SHIRE-ALL1-2013-01259
9170890	1	US-SHIRE-ALL1-2013-01436
9182336	1	(blank)
9186789	1	US-SHIRE-ALL1-2013-01745
9187749	2	BE-SHIRE-ALL1-2013-01617
9503601*	2	BE-SHIRE-ALL1-2013-05948
9188404	1	CA-SHIRE-ALL1-2013-01630
9205734	1	US-SHIRE-ALL1-2013-02016
9232650	1	US-SHIRE-ALL1-2013-00634
9237836	1	US-SHIRE-ALL1-2013-02368
9245174	2	US-SHIRE-ALL1-2013-02446
9260465	1	CA-SHIRE-ALL1-2013-02546
9262623	2	CA-SHIRE-ALL1-2013-02579
9271784	2	US-SHIRE-ALL1-2013-02838
9276314	1	(blank)
9277471	1	(blank)
9284683	1	PHHY2013BR045122
9287067	1	US-SHIRE-ALL1-2013-02971
9291367	1	US-SHIRE-ALL1-2013-02157
9291441	1	US-SHIRE-ALL1-2013-03045
9291450	1	US-SHIRE-ALL1-2013-03085
9310806	1	US-SHIRE-ALL1-2013-03273
9313962	1	US-SHIRE-ALL1-2013-03333
9316621	2	US-SHIRE-ALL1-2013-03413
9316622	1	US-SHIRE-ALL1-2013-03409
9338809	1	US-SHIRE-ALL1-2013-03536
9345580	1	CA-SHIRE-ALL1-2013-03856

FAERS Case #	Version Number	Manufacturer Control #
9350290	2	US-SHIRE-ALL1-2013-03880
9357344	1	GB-SHIRE-ALL1-2013-03990
9360563	1	US-SHIRE-ALL1-2013-04029
9417498	1	(blank)
9434194	1	(blank)
9441886*	1	US-SHIRE-ALL1-2013-05248
9441882	2	US-SHIRE-ALL1-2013-05218
9444583	1	(blank)
9461420	1	(blank)
9510299	1	US-BRISTOL-MYERS SQUIBB COMPANY-18736876
9519479	1	GB-SHIRE-ALL1-2013-06112
9519481	1	US-SHIRE-ALL1-2013-06169
9519485	1	US-SHIRE-ALL1-2013-06214
9522258	1	US-SHIRE-ALL1-2013-06233
9527631	3	DE-SHIRE-ALL1-2013-06151
9539087	2	US-SHIRE-ALL1-2013-06291
9571008	2	CA-SHIRE-ALL1-2013-06622
9625080	1	US-SHIRE-ALL1-2013-06943
9630532	3	US-SHIRE-ALL1-2013-07024
9633680	3	DE-SHIRE-ALL1-2013-06976
9648533	1	DE-SHIRE-ALL1-2013-07155
9666637	1	US-SHIRE-ALL1-2013-07451
9675780	1	US-SHIRE-ALL1-2013-07493
9675781	1	US-SHIRE-ALL1-2013-07485
9675789	2	US-SHIRE-ALL1-2013-07484
9680634	1	US-SHIRE-ALL1-2013-07633
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9692305	3	US-SHIRE-ALL1-2013-07627
9693026	1	BR-SHIRE-ALL1-2013-07740
9706607	1	US-SHIRE-ALL1-2013-07945
9717326	1	US-SHIRE-ALL1-2013-08147
9739133	1	US-SHIRE-ALL1-2013-08301
9742294	1	GB-SHIRE-ALL1-2013-08331
9742296	1	US-SHIRE-ALL1-2013-08414
9758352	1	US-SHIRE-ALL1-2013-08560
9769174	1	(blank)
9774215	1	US-SHIRE-ALL1-2013-08744
9774220	1	US-SHIRE-ALL1-2013-08774
9807667	1	US-SHIRE-ALL1-2014-00055

FAERS Case #	Version Number	Manufacturer Control #
9820110	1	ALL1-2013-01989
9820209	1	ALL1-2013-04813
9820205	1	ALL1-2013-04811
9840251	1	ALL1-2012-04214
9840284	1	ALL1-2012-05033
9840350	1	ALL1-2013-01125
9840754	1	SPV1-2012-01198
9840778	1	ALL1-2013-00137
9125819*	1	US-SHIRE-ALL1-2013-00137
9841613	1	ALL1-2012-01333
8526934*	1	US-SHIRE-ALL1-2012-01333
9841676	1	ALL1-2012-01769
9841676*	1	US-SHIRE-ALL1-2012-01769
9848200	1	DE-SHIRE-ALL1-2014-00431
9854819	3	DE-SHIRE-ALL1-2013-08316
9858041	1	US-SHIRE-ALL1-2014-00580
9862901	1	GB-SHIRE-ALL1-2014-00576
9869271	2	US-SHIRE-ALL1-2014-00714
9880367	2	DE-SHIRE-ALL1-2014-00848
9897211	3	US-SHIRE-ALL1-2014-00892
9902087	1	CA-SHIRE-ALL1-2014-01096
9902098	1	CA-SHIRE-ALL1-2014-01085
9902103	1	CA-SHIRE-ALL1-2014-01089
9912480	1	BR-SHIRE-ALL1-2014-01191
9924422	1	US-SHIRE-ALL1-2014-01284
9938148	1	US-SHIRE-ALL1-2014-01283
10014795	2	US-SHIRE-US201400514
10023725	1	(blank)
10037205	2	US-SHIRE-US201400057
10049484	2	US-SHIRE-US201400836
10098898	2	US-SHIRE-US201401373
10137061	1	(blank)
10139678	1	BR-SHIRE-BR201401503
10141240	2	US-SHIRE-US201401460
10152612	1	US-SHIRE-US201401547
10153920	2	US-SHIRE-US201401344
10153972	1	US-SHIRE-US201401643
10153977	2	US-SHIRE-US201401707
10154002	1	US-SHIRE-US201401911
10154033	1	US-SHIRE-US201401907

FAERS Case #	Version Number	Manufacturer Control #
10155344	1	US-SHIRE-US201401659
10159223	2	DE-SHIRE-DE201401841
10162581	1	US-SHIRE-US201402002
10172967	1	ALL1-2013-08177
10172969	1	ALL1-2013-08182
10173387	1	ALL1-2014-01100
10174364	2	US-SHIRE-US201402038
10182385	2	US-SHIRE-US201402159
10183470	1	GB-SHIRE-GB201402307
10209899	1	US-SHIRE-US201402528
10213468	1	US-SHIRE-US201402527
10213469*	1	US-SHIRE-US201402539
10220525	2	CA-SHIRE-CA201402373
10229813	2	CA-SHIRE-CA201402832
10261076	1	US-SHIRE-US201403202
10289464	1	US-SHIRE-US201403646
10304517	1	DK-SHIRE-DK201403783
10310767	1	US-SHIRE-US201403877
10334063	2	BR-SHIRE-BR201404167
10334989	1	(blank)
10342260	1	US-SHIRE-US201404066
10349487	1	CA-SHIRE-CA201404278
10356992	1	US-SHIRE-US201404298
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10375173	1	US-SHIRE-US201404582
10384445	1	(blank)
10426209	1	(blank)
10443673	1	GB-SHIRE-GB201405552
10443674	1	DE-SHIRE-DE201405525
10453366	1	US-PFIZER INC-2014255022
10456503	1	US-SHIRE-US201405956
10456509	1	US-SHIRE-US201405928
10477204	2	DE-SHIRE-DE201406087
10477207	1	DE-SHIRE-DE201406092
10480307	1	DE-SHIRE-DE201406158
10497915	2	BR-SHIRE-BR201406334
10501655	1	(blank)
10537553	2	CA-SHIRE-CA201407159
10540101	2	ES-SHIRE-ES201407016

FAERS Case #	Version Number	Manufacturer Control #
10543001	1	SE-SHIRE-SE201407074
10543019	1	SE-SHIRE-SE201407125
10549444	1	US-SHIRE-US201407239
10551966	2	US-SHIRE-US201407296
10570455	1	BR-SHIRE-BR201407508
10589914	3	US-JNJFOC-20141100601
10607345	1	US-SHIRE-US201408068
10611569	2	DE-SHIRE-DE201408130
10655521	1	(blank)
10661561	1	DE-SHIRE-DE201408867
10662369	1	CA-SHIRE-CA201408854
10668438	1	US-SHIRE-US201408947
10674360	1	US201401171
10677057	2	US-BRISTOL-MYERS SQUIBB COMPANY-21374004
10680113	1	US-SHIRE-US201409242
10685313	1	SE-SHIRE-SE201409218
10685558	1	US-SHIRE-US201409339

*Duplicate case

8.4 Appendix D. Ten Leading Causes of Death in 2014 for Ages 0-24 Years Old[9]

2014, All Races, Both Sexes

	Age Groups				
Rank	<1	1-4	5-9	10-14	15-24
1	Congenital Anomalies 4,746	Unintentional Injury 1,216	Unintentional Injury 730	Unintentional Injury 750	Unintentional Injury 11,836
2	Short Gestation 4,173	Congenital Anomalies 399	Malignant Neoplasms 436	Suicide 425	Suicide 5,079
3	Maternal Pregnancy Comp. 1,574	Homicide 364	Congenital Anomalies 192	Malignant Neoplasms 416	Homicide 4,144
4	SIDS 1,545	Malignant Neoplasms 321	Homicide 123	Congenital Anomalies 156	Malignant Neoplasms 1,569
5	Unintentional Injury 1,161	Heart Disease 149	Heart Disease 69	Homicide 156	Heart Disease 953
6	Placenta Cord Membranes 965	Influenza & Pneumonia 109	Chronic Low. Respiratory Disease 68	Heart Disease 122	Congenital Anomalies 377
7	Bacterial Sepsis 544	Chronic Low. Respiratory Disease 53	Influenza & Pneumonia 57	Chronic Low. Respiratory Disease 71	Influenza & Pneumonia 199
8	Respiratory Distress 460	Septicemia 53	Cerebro-vascular 45	Cerebro-vascular 43	Diabetes Mellitus 181
9	Circulatory System Disease 444	Benign Neoplasms 38	Benign Neoplasms 36	Influenza & Pneumonia 41	Chronic Low. Respiratory Disease 178
10	Neonatal Hemorrhage 441	Perinatal Period 38	Septicemia 33	Benign Neoplasms 38	Cerebro-vascular 177

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Data Source: National Center for Health Statistics (NCHS), National Vital Statistics System

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/s/

CARMEN CHENG
02/17/2016

JENNIE Z WONG
02/17/2016

RAJDEEP K GILL
02/18/2016
drug use data cleared by data vendors

IDA-LINA DIAK
02/18/2016

GRACE CHAI
02/18/2016

CINDY M KORTEPETER
02/18/2016

ROBERT L LEVIN
02/18/2016