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 Postmarket Adverse Event Review

Date:	14-June-2012
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Product Name:	Vyvanse (lisdexamfetamine dimesylate)
Pediatric Exclusivity Approval Date:	Not Applicable
Application Type/Number:	NDA #21977
Applicant/Sponsor:	Shire
OSE RCM #:	2012-961

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EXECUTIVE SUMMARY

In accordance with the Pediatric Research Equity Act (PREA), the Division of Pharmacovigilance (DPV) was asked to summarize post-marketing reports of adverse events associated with the use of Vyvanse® (lisdexamfetamine dimesylate) in pediatric patients (0-16 years of age). The main focus of this review is pediatric deaths and pediatric reports of serious unlabeled adverse events with lisdexamfetamine.

Vyvanse® (lisdexamfetamine dimesylate) capsule is a central nervous system stimulant indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in patients ages 6 and older.

The Adverse Event Reporting System (AERS) database was searched for all reports of adverse events (serious and non-serious) from the pediatric labeling change date of November 10, 2010 up to the "data lock" date of April 9, 2012. AERS contained 363 reports for lisdexamfetamine for this time period. Non-serious and serious pediatric reports represent approximately 47% of the total (172/363).

In addition to reviewing serious pediatric reports from November 10, 2010 to April 9, 2012 (n=163), we also reviewed all fatal pediatric reports from approval to April 9, 2012 (n=28). Additionally, we reviewed all fatal reports with an unknown age from approval to April 9, 2012 to determine if the report concerned a pediatric patient (n=12). Two fatal reports with the age unknown included information to determine that the report described a pediatric patient. After removing duplicates and excluded reports, we reviewed 135 pediatric cases reported with lisdexamfetamine use.

We identified 12 fatal pediatric cases reported with the use of lisdexamfetamine from approval to April 9, 2012. The majority of the cases (n=9) reported a cause of death related to self-harm or drug misuse. Two of the remaining cases were confounded by underlying cardiac or respiratory problems. The last case reported an unknown event that resulted in death.

Additionally, we identified 123 non-fatal serious cases from November 10, 2010 to April 9, 2012. More than half of the non-fatal serious cases reported psychiatric adverse events (n=45) or cardiac adverse events (n =21). The majority of the psychiatric adverse events (n=27) were homicidal or suicidal ideation, self-injurious behavior or ideation, or suicide attempt, which are not labeled events for lisdexamfetamine. Based on the high prevalence rates of suicidality seen in the U.S. High School population and the absence of increased suicidality rates in patients taking stimulant medications when compared to placebo administration in clinical trials, the extremely small number of suicidality cases noted from this review does not warrant a change in labeling to the lisdexamfetamine label at this time. Over half of the cardiac adverse event cases (n=12) were either labeled events, confounded, or reported the events persisted after treatment with lisdexamfetamine discontinued. All of the neurologic adverse events, and all but one neuromuscular adverse event, were labeled events. Approximately half (n=18) of the remaining 39 cases reported labeled events, accidental exposure, or product quality issues; and there was no pattern for specific adverse events in the remaining 21 reports.

Based on the data summarized in this review, DPV recommends no labeling changes at this time. DPV will continue to monitor adverse events associated with the use of lisdexamfetamine.

1 INTRODUCTION

1.1 PRODUCT FORMULATIONS AND INDICATIONS

Vyvanse® (lisdexamfetamine dimesylate) capsule, a central nervous system stimulant, received FDA approval on February 23, 2007 for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in patients ages 6 and older.

1.2 PEDIATRIC FILING HISTORY[1]

This PREA review was triggered by Study SPD489-305, a 4-week, phase 3, multi-center, randomized, double-blind, placebo-controlled, parallel-group, fixed-dose with titration trial designed to assess the efficacy and safety of lisdexamfetamine compared to placebo for the treatment of ADHD in adolescents aged 13 to 17 years. The primary efficacy outcome measure was the mean change from baseline to endpoint in the clinician completed ADHD-RS-IV total score. The study included adolescents 13 to 17 years of age who met the DSM-IV criteria for ADHD with a minimum baseline ADHD-RS-IV score of 28. A total of 314 adolescents were randomized 1:1:1:1 to receive lisdexamfetamine 30, 50, 70 mg or placebo with the titration schedule shown in Table 1. The baseline demographics and disease characteristics were generally comparable among the treatment groups.

Table 1. Forced-dose titration schedule

Treatment Group	N	Week 1	Week 2	Week 3	Week 4
lisdexamfetamine 30 mg	78	30 mg	30 mg	30 mg	30 mg
lisdexamfetamine 50 mg	77	30 mg	50 mg	50 mg	50 mg
lisdexamfetamine 70 mg	78	30 mg	50 mg	70 mg	70 mg
Placebo	77	Placebo	Placebo	Placebo	Placebo

The efficacy assessment included 299 subjects who took at least one dose of the study medication during this trial and had a valid baseline and at least one post-baseline follow-up assessment of the primary outcome measure (full analysis set). There was a statistically significant reduction in the ADHD-RS-IV total score for the three lisdexamfetamine treatment groups (30, 50, and 70 mg) compared to placebo throughout the study and at endpoint.

The safety population consisted of 310 subjects who received at least one dose of lisdexamfetamine or placebo. There were no deaths or serious adverse events reported during this study. The most common treatment-emergent adverse events that led to discontinuation were irritability, insomnia, decreased appetite, and electrocardiogram (EKG) abnormal. The most common treatment-emergent adverse events that occurred at least 5% in the lisdexamfetamine treatment groups and at a rate at least twice the placebo group) were decreased appetite, insomnia, and weight decreased.

1.3 SUMMARY OF PREVIOUS OFFICE OF SURVEILLANCE AND EPIDEMIOLOGY REVIEW[2]

When looking at the levels of evidence to determine whether or not the use of a medication is associated with particular adverse events, data obtained from randomized, clinical trials provides

the highest level of evidence to infer causality of drug-induced adverse events when compared to post-marketing reports and analysis of the AERS database. To that end, the Agency performed an analysis of psychiatric adverse events that were reported in clinical trials for the stimulant and non-stimulant products available at the time (atomoxetine [Strattera®], dexmethylphenidate [Focalin®], dexmethylphenidate extended-release capsules [Focalin XR®], methylphenidate extended-release capsules [Metadate CD®, Ritalin LA®], methylphenidate extended-release tablets [Concerta®], methylphenidate transdermal system [Daytrana®], mixed amphetamine salts extended-release capsules [Adderall XR®], and modafinil [Provigil®]). The analysis showed no evidence of increased rates of suicidal thoughts, behaviors or suicide in medication-treated patients when compared to control, with the exception of patients taking atomoxetine and modafanil. Consequently labeling for atomoxetine was changed to include language of an association between suicidality and atomoxetine use.

1.4 SUMMARY OF SHIRE REVIEWS OF SUICIDE-RELATED EVENTS FOR LISDEXAMFETAMINE[3,4]

In 2008, Shire completed a review evaluating the suicide-related events for its product portfolio of ADHD stimulants: the extended-release formulation of the mixed amphetamine salts (Adderall XR), methylphenidate transdermal system (Daytrana), and lisdexamfetamine dimesylate (Vyvanse). Using pre-specified database search algorithm for "possibly suicidal" events, 151 cases (spontaneous and serious clinical trial cases) for lisdexamfetamine were retrieved from the Shire Global Safety System (SGSS) database through May 31, 2008. Of the 151 cases, 22 cases met the criteria for the Columbia Classification Algorithm of Suicide Assessment (C-CASA) rating and were deemed suicide-related events. Thirteen of the 22 cases of suicide-related events were pediatric patients, ranging from 6 to 16 years old, including one "adolescent" (age not reported) female patient. Of the pediatric suicide-related events, there were no cases of completed suicide; one case of "preparatory acts toward imminent suicidal behavior," three cases of suicide attempt, and nine cases of suicidal ideation were identified. The majority of the cases were either confounded by concurrent medical histories of conditions that increased the occurrence of suicidal events or concomitant medications labeled for suicidality, or contained insufficient information for a causality assessment. Furthermore, the incidence of suicide-related events in clinical trials was low. In the clinical trial databases, two pediatric subjects who received lisdexamfetamine were categorized as suicidal in one open-label trial (NRP104-302) and one double-blind trial (SPD489-311) across six trials for lisdexamfetamine.

In 2009, Shire completed an addendum report of suicide-related events reported for lisdexamfetamine from 1 June 2008 through 31 January 2009. The same search strategy as the 2008 review was implemented to search the SGSS database, and Shire identified 116 cases with "possibly suicidal" events reported for lisdexamfetamine from 1 June 2008 through 31 January 2009. After applying the C-CASA rating, 15 of the 116 cases retrieved were deemed suicide-related events. All 15 cases of suicide-related events were spontaneous reports; there were no clinical trial reports. Ten of the 15 cases were pediatric patients, ranging from 9 to 14 years old. Of the pediatric suicide-related events, there were no cases of completed suicide; two cases of "preparatory acts toward imminent suicidal behavior," and eight cases of suicidal ideation were identified. Similar to the 2008 review, the majority of the cases were either confounded or contained insufficient information for a causality assessment. Thus, Shire concluded that 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, and will continue to monitor cases of suicide-related events.

Table 2 presents a comparison and cumulative number of spontaneous postmarketing pediatric cases of suicide-related events for lisdexamfetamine from both Shire reviews.

Table 2. Spontaneous Postmarketing Pediatric Reports of Suicide-Related Events for Lisdexamfetamine from the SGSS database

Suicide-related events	Completed suicide	Suicide attempt	Preparatory acts toward imminent suicide behavior	Suicidal ideation	Total
Number of cases through 31 May 2008	0	3	1	9	13
Number of cases 1 June 2008 through 31 January 2009	0	0	2	8	10
Cumulative number of cases through 31 January 2009	0	2	3	17	23

1.5 PREVALENCE OF SUICIDALITY IN U.S. YOUTHS[5]

According to the 2011 Centers for Disease Control's Youth Risk Behavior Surveillance report, 15.8% of U.S. High School students have seriously considered attempting suicide in 2011, with 12.8% of 9th through 12th graders making a plan about how they would attempt suicide. In addition, 7.8% of 9th through 12th graders attempted suicide one or more times in the preceding year before the survey with 2.4% of U.S. High School students' having a suicide attempt resulting in treatment being provided by a doctor or nurse.

1.6 PEDIATRIC LABELING[6]

The following sections of the dexmethylphenidate labels pertain to the pediatric population and this review:

- Contraindications
- Warnings and Precautions
- Adverse Reactions
- Postmarketing Experience
- Drug Interactions
- Drug Abuse and Dependence
- Overdosage
- Use in Specific Populations
- Patient Counseling Information
- Medication Guide

See Appendix A for a complete listing of the relevant pediatric labeling.

2 METHODS AND MATERIALS

2.1 AERS SEARCH STRATEGY

The Adverse Event Reporting System (AERS) was searched with the strategy described in Table 3.

Table 3. AERS Search Strategy*		
Date of search	April 9, 2012	
Time period of search	November 10, 2010† to April 9, 2012 (see Table 4)	All Fatal Reports from approval to April 9, 2012§ (see Table 5)
Product Terms	Lisdexamfetamine, Vyvanse, and all associated active ingredients and trade names.	
Additional criteria	Refer to Appendix B	

* See Appendix C for description of the AERS database
† Pediatric labeling change date
§ Initial FDA approval of Lisdexamfetamine (Vyvanse) (February 23, 2007)

3 RESULTS

3.1 AERS REPORTS

Table 4 represents the results of AERS searches for reports with lisdexamfetamine from November 10, 2010 to April 9, 2012.

Table 4. Total number of AERS reports* (November 10, 2010† to April 9, 2012)			
	All reports (US)	**Serious§ (US)**	**Death (US)¶**
Adults (≥17 years)	121 (115)	115 (109)	3 (3)
Pediatrics (0-16 years)	172 (151)	163 (142) [includes 141** non-fatal serious pediatric reports]	22 (17)
Age unknown (null values)	69 (64)	67 (62)	3 (3) ††
Total	363 (331)	344 (313)	28 (23)

* May include duplicates and have not been assessed for causality
† Pediatric Labeling Change Date
§ 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.
¶ Included within Table 5 below
** See Figure 2
†† Insufficient clinical information to determine age; also see Table 5

The adult reports and all pediatric reports retrieved in Table 4 did not receive a hands-on analysis. See Appendix D for a comparison of the top 25 preferred terms reported and the system organ classes associated with adverse events in pediatrics and adults from November 10, 2010 to April 9, 2012.

Table 5 represents the results of an AERS search for all fatal reports with lisdexamfetamine from FDA approval to April 9, 2012. Thus, the numbers of fatal reports reported in Table 4 are included in Table 5.

Table 5. Total number of Fatal AERS reports* (All Fatal Reports from approval† to April 9, 2012)	
	Death (US)
Adults (≥17 years)	4 (4)
Pediatrics (0-16 years)	28§ (23)
Age unknown (null values)	12 (12) [includes 2§ pediatric patients]
Total	44

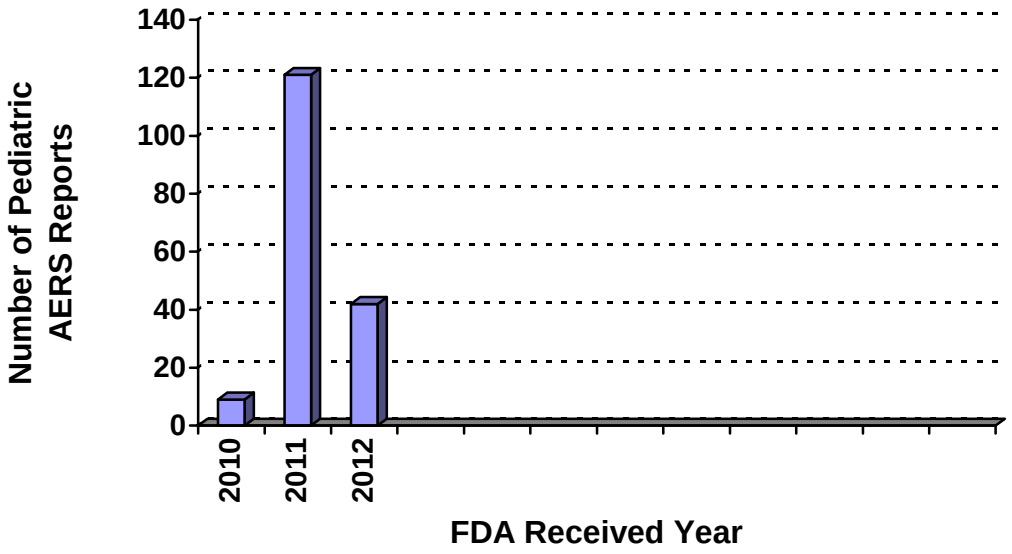
* May include duplicates and have not been assessed for causality

† Initial FDA approval of Lisdexamfetamine (Vyvanse) (February 23, 2007)

§ Also, see Figure 2

Figure 1. Total Number of Pediatric Reports (including serious and non-serious) for lisdexamfetamine, by year of FDA receipt (November 10, 2010 to April 9, 2012) (n=172)

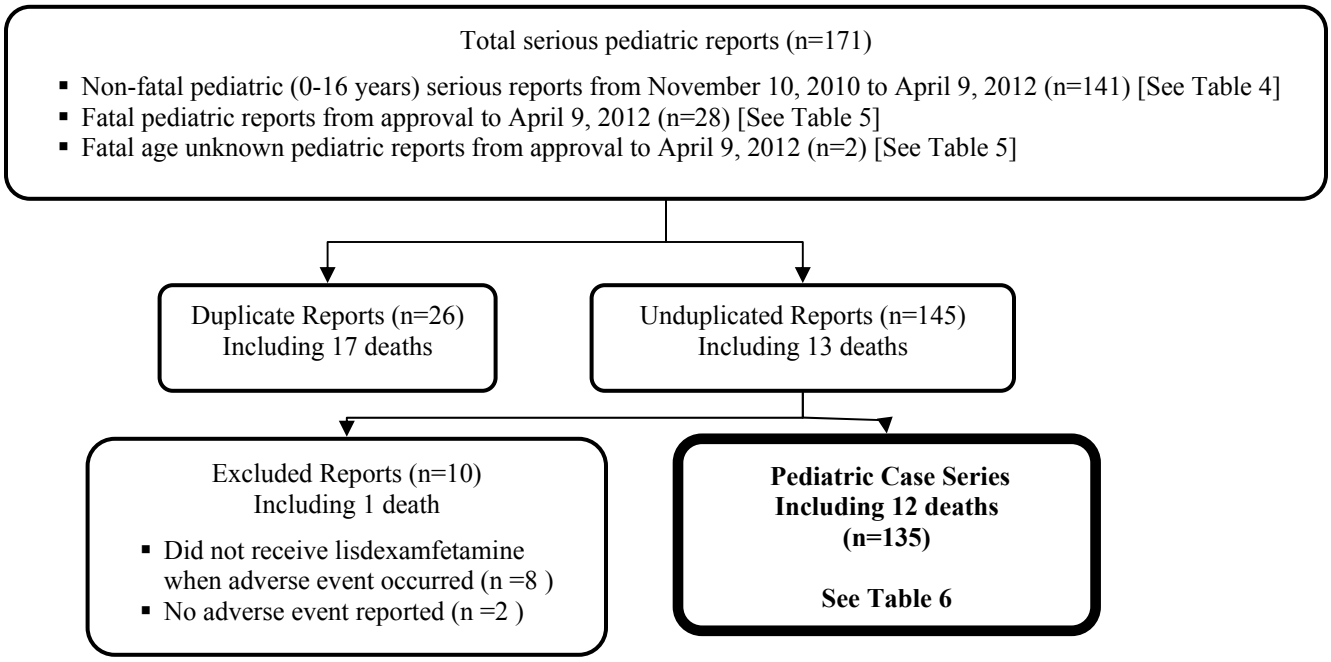
These numbers include data where age (0-16 years) is known and may contain duplicate reports.



In addition to reviewing pediatric reports with serious outcomes, including reports with an outcome of death from November 10, 2010 to April 9, 2012 (n=163), we also reviewed all pediatric reports with an outcome of death from approval to April 9, 2012 (n=28). Additionally, we reviewed all reports with the age unknown reporting an outcome of death from approval to April 9, 2012 to determine if the report concerned a pediatric patient (n=12). Two reports with the age unknown reporting an outcome of death included information to determine that the report described a pediatric patient.

Figure 2 below summarizes the specific selection of cases to be reviewed in **Section 4**.

3.2 FIGURE 2. SELECTION OF SERIOUS PEDIATRIC AERS CASES



3.3 DESCRIPTIVE CHARACTERISTICS FROM PEDIATRIC CASE SERIES

Table 6 summarizes the 135 AERS cases from the Pediatric Case Series with lisdexamfetamine.

Appendix E lists all the AERS case numbers, AERS ISR numbers and Manufacturer Control numbers for the Pediatric Case Series."

Table 6. Descriptive characteristics of Pediatric Case Series (N=135)		
Age	1 month - <2 years	4
	2-5 years	10
	6-11 years	76
	12-16 years	45
Sex	Male	91
	Female	42
	Unknown	2
Country of reporter	United States	121
	Foreign	14
Report type	Expedited	93
	Direct	30
	Periodic	12
Event date	2008	2
	2009	3
	2010	17
	2011	88
	2012	25
Indications	ADD/ADHD	96
	Accidental exposure	5
	Autism	1
	Impulsive behavior	1
	"Keep patient focus"	1
	Unspecified	31
Primary Serious* Outcomes	Death	12
	Hospitalized	20
	Life-threatening	5
	Disability	3
	Other serious	95

* 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.

4 DISCUSSION OF SERIOUS PEDIATRIC CASE SERIES

4.1 SUMMARY OF PEDIATRIC DEATHS (N=12)

The AERS database contained 12 fatal pediatric cases reported with the use of lisdexamfetamine through April 9, 2012. All cases were U.S. reports of males (n=8) and females (n=4) with a median age of 10 years, ranging from 7 to 16 years. The indications for lisdexamfetamine were ADHD (n=6) or unspecified (n=6). The median daily dose of lisdexamfetamine was 50 mg, ranging from 30 mg to 100 mg (n=7). The median time to death following initiating treatment with lisdexamfetamine was 8 months, ranging from 4 months to 20 months (n=5). Reported causes of death were suicide (n=6), accidental (n=1), overdose (n=1), toxicity to various agents (n=1), "cardiac problems" (n=1), aspiration (n=1), and unknown (n=1).

Of the six completed suicide cases, five reported suicide by hanging. Three of these five cases were confounded by a history of being bullied[7,8], the fourth case was confounded by concomitant medications labeled for suicidality (e.g., escitalopram, olanzapine/fluoxetine), and the last case provided insufficient clinical information to assess. The patient in the sixth case of completed suicide experienced "prehospital cardiac and/or respiratory arrest" due to ingesting lisdexamfetamine, morphine solution, and an unspecified stimulant laxative.

The patient who died from toxicity to various agents experienced "prehospital cardiac and/or respiratory arrest" due to "acute/chronic" exposure to multiple medications (codeine, sennoside, quetiapine, aripiprazole, valproic acid, diphenhydramine, clonidine, meloxicam, penicillin); however, the case did not specify if the ingestion was intentional or accidental. The patient in the overdose case "died some time after" a dose increase of lisdexamfetamine from 70 mg daily to 100 mg daily; however, no additional clinical information was provided. The case of accidental death was a 14-year-old male who was "discovered hanging from a low tree branch;" however, his death was determined "impulsive/accidental" by his physician because the patient had no medical, psychiatric or psychosocial history that would predispose him to commit suicide. Additionally, he was not taking any concomitant medications.

Causes of death in the remaining three fatal cases included "cardiac problems" (n=1), aspiration (n=1), and unknown (n=1). A coroner determined that the patient who died from (or with) "cardiac problems," had a structurally abnormal heart; additional clinical information was unavailable. The patient who died from (or with) aspiration had a history of unspecified respiratory problems. The last patient experienced trouble breathing and then experienced an unknown event that resulted in death; additional clinical information was not available.

A detailed summary of the fatal cases can be found in Appendix F.

4.2 SUMMARY OF SELECTED PEDIATRIC ADVERSE EVENTS (N=84)

4.2.1 Psychiatric Adverse Events (n=45)

We identified 45 cases of psychiatric adverse events including homicidal ideation, self-injurious behavior or ideation, suicidal ideation, or suicide attempt (n=27); agitation, anger, or violence-related symptom (n=7); hallucination or paranoia (n=6); and other psychiatric adverse events (n=5), such as depressed mood, dermatillomania, mania, middle insomnia, or obsessive thoughts.

- **Homicidal ideation, Self-injurious behavior or ideation, Suicidal ideation, Suicide attempt (n=27)**

The cases were U.S. (n=20) and foreign (n=7) reports of males (n=19), females (n=7), and one patient of unknown gender. The median age was 10 years, ranging from 6 to 16 years. The indications for lisdexamfetamine were ADD or ADHD (n=18) or unspecified (n=9). The median daily dose of lisdexamfetamine was 30 mg, ranging from 20 mg to 70 mg (n=22). The median time to onset of event following initiating treatment with lisdexamfetamine was 30 days, ranging from 1 day to 6 months (n=13). The median duration of treatment with lisdexamfetamine was 30 days, ranging from 1 day to 2 years (n=14).

Ten cases reported events abated after lisdexamfetamine use stopped or dose reduced. All of these cases reported discontinuation of lisdexamfetamine on recognition of suspected adverse events; no case reported subsequent re-exposure to lisdexamfetamine. Three of these 10 cases were confounded by concomitant medications labeled for suicidal ideation (atomoxetine, cetirizine), concurrent depression or anxiety, or a family history of bipolar disorder and depression. The remaining seven cases did not report confounding factors; these seven cases are summarized below.

- A 10-year-old male experienced aggression, delusion, depression, "feeling abnormal," homicidal ideation, irritability, suicidal ideation, and "thinking abnormal" an unknown time after initiating treatment with lisdexamfetamine 30 mg daily for an unspecified indication. Treatment with lisdexamfetamine discontinued after 31 days and the events resolved.
- An 8-year-old female "wanted to hurt or kill her mother" two days after initiating treatment with lisdexamfetamine 30 mg daily for ADHD. Treatment with lisdexamfetamine discontinued after two days of use and the events resolved.
- A 7-year-old male developed symptoms of depression and suicidal ideation nine days after a dose increase of lisdexamfetamine to 30 mg daily, and 10 days after initiating treatment with lisdexamfetamine 20 mg daily for ADHD. The events resolved after decreasing the dose of lisdexamfetamine to 20 mg daily.
- A 9-year-old male became emotional, described as crying everyday, was depressed, had a lack of appetite, "blacked out" due to low blood glucose, and developed a feeling that he "ought to kill himself" an unknown time after initiating treatment with lisdexamfetamine 30 mg daily for ADHD. Treatment with lisdexamfetamine discontinued and all events resolved.
- An 11-year-old male experienced "drugged out," burst of outrage, suicidality, "seeing things," and psychotic reaction described as extremely fearful, angry, disoriented, and was not able to identify his parents. The events occurred on the same day as initiating treatment with lisdexamfetamine 30 mg daily for ADHD. Treatment with lisdexamfetamine discontinued the next day and all events resolved.
- A 12-year-old male who experienced "feeling spacey and zombie-like," and had suicidal thoughts an unknown time after initiating treatment with lisdexamfetamine 70 mg daily for ADHD. Treatment with lisdexamfetamine discontinued and the events resolved.
- A 6-year-old female required psychiatric hospitalization for suicidal thoughts described as drawing pictures of hanging by a rope, and was "uncontrollable and harming others." The events occurred an unknown time after initiating treatment with lisdexamfetamine 20 mg daily and guanfacine 2 mg daily for ADHD. Treatments included paliperidone, decreased guanfacine to 1 mg, and discontinued lisdexamfetamine after five months of use. The events resolved on an unspecified date after discontinuing lisdexamfetamine.

Six cases were confounded by concurrent or prior medical disorders (e.g. suicidal ideation, bipolar disorder, mood swings, oppositional defiant disorder, schizophrenia, sleep disorder, or social and psychological stressors), or concomitant exposure to medications labeled for

reported suicidal ideation (e.g. armodafinil, atomoxetine, escitalopram, imipramine, risperidone, or sertraline), or both.

Two cases required hospitalization; however, both cases did not report the action taken with lisdexamfetamine, one case reported the event resolved, and the other case did not report on the outcome of the event.

The nine remaining cases provided insufficient information, such as the action taken with lisdexamfetamine or the outcome of the events, to make causality assessments.

- **Agitation, Anger, Violence-related symptom (n=7)**

Two cases reported irritability and agitation, or "personality became volatile and hostile" while on treatment with lisdexamfetamine. Both patients discontinued lisdexamfetamine after one month and nine months of use, respectively, and the events resolved.

Four of the five remaining cases were confounded by past medical history, medication labeled for neuropsychiatric adverse events, or both. One case was confounded by mixed amphetamine salts (for anger). One case was confounded by Asperger's disorder. One case was confounded by bipolar disorder. One case was confounded by concomitant exposure to escitalopram (labeled for agitation). In the final case, reports of frustration, anger, aggression, and biting persisted after discontinuation of lisdexamfetamine.

- **Hallucination, Paranoia (n=6)**

One case experienced "sudden onset of bizarre episodes and hallucinations" resulted in an ER visit after two months of treatment with lisdexamfetamine. The second case described the hallucinations as "someone was in the house, because she heard voices that a bug was talking to her... room looked as if there was an earthquake..." Both cases discontinued treatment with lisdexamfetamine and the events resolved.

Three cases were confounded by concomitant medication labeled for hallucinations (mirtazapine), past medical history of concussions that prompted "neuropsychological evaluation" that ruled out developmental disorder and psychosis disorder, or concurrent medical condition of high fevers. The events described were "green bugs crawling all over my body," "objects... get really large then small then come at him," or made comment "why is there a fish in your ear?" Two of the cases discontinued treatment with lisdexamfetamine, but the outcome of events was unknown. The third case did not report on the action taken with lisdexamfetamine or the outcome of the event.

The last case reported insomnia, auditory hallucinations, and paranoia, described as hearing voices, thinking people were after them, "found him on the couch holding a baseball bat." Treatment with lisdexamfetamine discontinued, but the outcome of events was unknown.

- **Other psychiatric adverse events (n=5)**

A 7-year-old male experienced depressed mood described as "feelings of dread and deep sadness," crying, and that his brain was "negative" three hours after the first dose of lisdexamfetamine 20 mg for the treatment of ADHD. Treatment with lisdexamfetamine discontinued after one dose and the events resolved.

The events of the remaining four cases were dermatillomania ("picking at his fingers... ripped his skin off to the point he was bleeding... started picking at... other body parts"),

mania ("left the house in the middle of the night, stole a vehicle and robbed a house"), middle insomnia ("awoke at night"), or obsessive thoughts ("obsessed with knives"). In the cases of dermatillomania and mania, treatment with lisdexamfetamine discontinued, but the outcome of events was unknown. The case of insomnia did not report on the action taken with lisdexamfetamine or the outcome of the event. In the case of obsessive thoughts, the patient continued treatment with lisdexamfetamine and the event persisted.

Neuropsychiatric adverse events labeling status for lisdexamfetamine

Adverse Event	*Warnings & Precautions*	*Adverse Reactions*	*Postmarketing Experience*	*Drug Abuse & Dependence*	*Overdosage*
Hallucination*	✓				
Mania*	✓				
Aggression	✓				
Agitation		✓*Adults only*			
Insomnia		✓		✓	
Depression			✓	✓	✓
Dermatillomania			✓		

Treatment emergent psychotic or manic symptoms, e.g., hallucinations, delusional thinking, or mania in children and adolescents without a prior history of psychotic illness or mania can be caused by stimulants at usual doses. If such symptoms occur, consideration should be given to a possible causal role of the stimulant, and discontinuation of treatment may be appropriate.

Unlabeled events: Suicidal ideation, Homicidal ideation, Suicide attempt, Self-injurious behavior, Self-injurious ideation, Obsessive thoughts

4.2.2 Cardiac Adverse Events (n=21)

We identified 21 cases of cardiac adverse events including syncope or loss of consciousness (n=6); arrhythmia, electrocardiogram (EKG) QT shortened, or ventricular extrasystoles (n=4); blood pressure increased or hypertensive crisis (n=3); tachycardia (n=3); cardiac arrest (n=2); chest pain (n=2); and cardiac murmur (n=1). Seventeen cases were U.S. reports. The cases involved males (n=16) and females (n=5) with a median age of 10 years, ranging from 1 to 15 years. The indications for lisdexamfetamine were ADHD (n=14), "keep patient focus" (n=1), or unspecified (n=6). The median daily dose of lisdexamfetamine was 30 mg, ranging from 20 mg to 70 mg (n=20). The median time to onset of events following initiating treatment with lisdexamfetamine was 14 days, ranging from 1 day to 2.5 years (n=15). The median duration of treatment with lisdexamfetamine was 26 days, ranging from 1 day to 2.5 years (n=12).

- **Syncope or Loss of consciousness (n=6)**

One case was a 9-year-old male who "passed out" following the first dose of lisdexamfetamine 20 mg. He was not taking concomitant medications and does not have a relevant medical history. His physician diagnosed him with an "allergic reaction to Vyvanse." Treatment with lisdexamfetamine discontinued and the event resolved.

Three cases were confounded by a past medical history of "near syncopal spell," a family medical history of maternal benign partial epilepsy and "poor breakfast" described as only milk with chocolate then had gym class, or concomitant exposure to guanfacine ER (labeled for syncope) with recent dose increase of guanfacine. One case continued treatment with lisdexamfetamine and the event resolved. The second case discontinued treatment with lisdexamfetamine, but the outcome of the event was unknown. The third case discontinued treatment with lisdexamfetamine and the event resolved with treatment during hospitalization.

One of the two remaining cases was an 8-year-old male who experienced decreased appetite, upper abdominal pain, irritability, insomnia, emotional lability, heart palpitations, and fainted after an unknown time following initiating treatment with lisdexamfetamine 50 mg. The action taken on lisdexamfetamine and the outcome of the events were unknown. The last case was a 15-year-old female who received no concomitant medications and had no medical history experienced headache, chest pain, and a "forceful and bounding pulse" described as "almost like atrial fibrillation" approximately one year after initiating treatment with lisdexamfetamine 70 mg daily for ADHD. She was taken to the ER and the events persisted. During the same month, she "passed out" and was taken to the ER again. Treatment with lisdexamfetamine continued and the event of "passed out" resolved.

- **Arrhythmia, EKG QT shortened, or Ventricular extrasystoles (n=4)**

One case was a 7-year-old male who experienced EKG QT shortened and heart rate increased (160 bpm) approximately 1.5 years following initiating treatment with lisdexamfetamine. The dose and indication for lisdexamfetamine were unknown. Treatment with lisdexamfetamine discontinued and the events resolved within three days of discontinuation.

The second case was a 13-year-old male who complained that his "chest was hurting" three days following initiating treatment with lisdexamfetamine 60 mg every morning prescribed for helping "keep patient focus." The event persisted for approximately two weeks until he was taken to the hospital, where the physician determined the patient had an "irregular heart beat." No additional information was provided.

The remaining two cases were 14-year-old males who received lisdexamfetamine 30 mg daily and 40 mg daily, respectively, for the treatment of ADHD. In one case, the patient experienced shortness of breath, chest pain, lightheadedness, palpitations, and "passing out" one week following initiating treatment with lisdexamfetamine. At the urgent care facility, his EKG revealed premature ventricular contractions (PVCs; coded as ventricular extrasystoles) and "skipping heart beats." Treatment with lisdexamfetamine was discontinued, but the PVCs continued. In the second case, the patient experienced two episodes of "heart pounding out of chest" described as "fluttering, throat gets tight and had a fast and thready pulse." The first episode occurred one week following initiating treatment with lisdexamfetamine, and the second episode occurred approximately one month following the first episode. For both episodes, the event lasted for a minute and resolved on the same day. His physician performed an EKG, which revealed "abnormal arrhythmia." Treatment with lisdexamfetamine discontinued, but the event persisted.

- **Blood pressure increased, Hypertensive crisis (n=3)**

The first case was confounded by inappropriate schedule of lisdexamfetamine 20 mg twice daily for the treatment of ADHD, and the use of concomitant medications labeled for hypertension (clonidine, sertraline). The second case was a 13-year-old male who developed "hypertensive crisis BP=140x80 mmHg," sudoresis, hypotonia, and headache five days after initiating treatment with lisdexamfetamine 30 mg daily for ADHD. He was not receiving concomitant medications. As treatment, he received an unspecified antihypertensive, discontinued lisdexamfetamine, and the events resolved. The last case experienced blood pressure increased, heart rate increased, and cyanosis on the same day as initiating treatment with lisdexamfetamine 50 mg for an unspecified indication. He was taken to the ER for unspecified tests and treatments, treatment with lisdexamfetamine discontinued, and the events resolved.

- **Tachycardia (n=3)**

Two cases of tachycardia required an ER visit or hospitalization. The first case also was a 15-month-old female who was agitated and crying half an hour after receiving lisdexamfetamine 60 mg. At the ER, her vital signs were "BP 117/66, HR 125, RR32, 99.7, 99%." She received treatments with an unspecified benzodiazepine 1 mg, an intravenous (IV) bolus of normal saline (NS) 20 ml/kg, and IV Dextrose 5% NS with 20 meQ KCL. Her laboratory findings were normal "CMP" and blood creatine phosphokinase of 170. Approximately 16 hours after presenting to the ER, her vital signs were "BP 97/43 and HR was within normal limits." The second case was a 10-year-old male who experienced tachycardia and subsequently hospitalized an unknown time following initiating treatment with lisdexamfetamine. The event resolved when lisdexamfetamine "wore off;" however, the action taken on lisdexamfetamine was unknown.

The last case experienced "foaming at mouth, talking gibberish," dry mouth, and tachycardia an unknown time after initiating treatment with lisdexamfetamine 20 mg (unknown frequency) for an unspecified indication. Action taken with lisdexamfetamine and the outcome of events were unknown.

- **Cardiac arrest (n=2)**

One case was an 8-year-old female with a past and concurrent medical history significant for "abnormal" EKG results who experienced cardiac arrest while playing basketball. The event occurred an unknown time after a dose increase of lisdexamfetamine to 30 mg daily. Treatment with lisdexamfetamine discontinued, she was hospitalized, and the event resolved.

The second case was a 15-year-old male who experienced "cardiovascular issues" and cardiac arrest which resulted in an ER visit an unknown time following initiating treatment with lisdexamfetamine 60 mg daily for ADHD. On an unknown date, treatment with lisdexamfetamine discontinued, and event resolved; however, it is unknown if the event resolved prior to or after discontinuing treatment with lisdexamfetamine. The outcome of "cardiovascular issues" was unknown.

- **Chest pain (n=2)**

The first case was a 6-year-old male who experienced itchy skin, constant headaches, and chest pain two weeks after initiating treatment with lisdexamfetamine 20 mg daily for

ADHD. He was taken to the ER, but the details of the visit were not provided. Treatment with lisdexamfetamine discontinued after one month of use and the events resolved.

The second case was a 15-year-old male experienced chest pain, left arm pain, chest and back pain when breathing, sore jaw, pain on the roof of his mouth two months after initiating treatment with lisdexamfetamine 50 mg daily for ADD. No additional clinical information including medical work up was provided. Treatment with lisdexamfetamine discontinued after three months of use and the events resolved.

- **Cardiac murmur (n=1)**

An 11-year-old male whose physician diagnosed him with a heart murmur upon physical examination approximately two years following initiating treatment with lisdexamfetamine 70 mg daily for ADHD. He was not receiving concomitant medications. Prior to the heart murmur diagnosis, he also experienced dysphemia, aphonia, and recurrent tumors and polyps in his throat. As treatment, he received speech therapy and underwent surgery to remove the tumors and polyps; however, the events persisted. Information regarding treatment for the heart murmur, if any, was not provided. Treatment with lisdexamfetamine continued and the event persisted.

Cardiac adverse events labeling status for lisdexamfetamine

Adverse Event	*Warnings & Precautions*	*Adverse Reactions*	*Overdosage*	*Patient Counseling Information*	*Medication Guide*
Hypertension, Increased blood pressure	***✓***	***✓Adults only***	***✓***	***✓***	***✓***
Myocardial infarction, Heart attack	***✓Adults only***			***✓***	***✓Adults only***
Tachycardia, Increased heart rate	***✓***	***✓Adults only***			***✓***
Arrhythmia			***✓***		
Hypertensive crisis	***labeled under Contraindications and Drug Interactions for concomitant use of lisdexamfetamine with monoamine oxidase inhibitor (MAOI) antidepressants or use of lisdexamfetamine within 14 days of discontinued use of MAOI antidepressants***				

Unlabeled events: Electrocardiogram QT shortened, Ventricular extrasystoles, Syncope, Loss of consciousness, Chest pain, Cardiac murmur

4.2.3 Neurologic Adverse Events (n=9)

We identified nine cases of neurologic adverse events including convulsions (n=5), benign rolandic seizures or epilepsy (n=2), and grand mal seizure or convulsion (n=2) reported with the use of lisdexamfetamine. All cases were U.S. reports. The cases involved males (n=5) and females (n=4) with a median age of 7 years, ranging from 6 to 12 years. In all of the cases, the patients received lisdexamfetamine for the treatment of ADHD. The daily median dose of lisdexamfetamine was 30 mg, and ranged from 20 mg to 50 mg daily. The

median time to onset of event following initiating treatment with lisdexamfetamine was 8 months, ranging from one day to 1.5 years (n=6). The median duration of treatment of lisdexamfetamine was 6 days, ranging from one day to 1.5 years (n=5).

Five cases were confounded by a past or concurrent medical history of primary central nervous system pathology (subependymal nodules), convulsion, or concomitant medication labeled for convulsions (levetiracetam and mixed amphetamine salts).

There was limited clinical information in three cases. One case described seizures as "second degree twitching... twitching eye brows, leg spasms, and sleepiness" that resolved with discontinuation of lisdexamfetamine. The second case described an ill-characterize seizure that resolved after discontinuation of lisdexamfetamine, however other interventions are not specified. The third case was a 7-year-old female with 'no relevant medical history" and no concomitant medication exposure who experienced a seizure on the same day as initiating treatment with lisdexamfetamine 30 mg daily. Treatment with lisdexamfetamine discontinued, but the outcome of the event was unknown.

The last case was a 9-year-old female with no significant past or concurrent medical history or taking any medication concomitantly who experienced a seizure while on treatment with lisdexamfetamine. She was diagnosed with benign rolandic epilepsy. Treatment with lisdexamfetamine discontinued, but the event was unresolved.

Labeled events: Seizures (Warnings and Precautions, Adverse Reactions, Medication Guide), Convulsions (Drug Interactions with propoxyphene overdosage, Overdosage).

4.2.4 Neuromuscular Adverse Events (n=9)

We identified nine cases of neuromuscular adverse events including dyskinesia (n=5), "nervous tic" of the eye or tic (n=3), and muscle contractions involuntary (n=1) reported with the use of lisdexamfetamine. Seven cases were U.S. reports. The cases involved males (n=6) and females (n=3) with a median age of 8 years, ranging from 6 to 14 years. The indications for lisdexamfetamine were ADD or ADHD (n=7) or unspecified (n=2). The median daily dose of lisdexamfetamine was 30 mg, ranging from 20 mg to 70 mg. The median time to onset of event following initiating treatment with lisdexamfetamine was 1.5 days, ranging from 2 hours to 1 month (n=4). The median duration of treatment with lisdexamfetamine was 6 days, ranging from 1 day to 10 months (n=6).

- **Dyskinesia (n=5)**

One case reported a 6-year-old female who experienced dyskinesia described as "mouth puckering... continuous tongue chewing... tongue began to involuntarily move in and out of the mouth in rapid speed" within two to six hours of taking the first dose of lisdexamfetamine 20 mg. Treatment with lisdexamfetamine discontinued after one dose, and the events resolved.

The remaining four cases reported dyskinesia, with two cases described as "tongue rolling and lips smacking," and "dyskinesia, muscle twitching." Two cases did not report on the action taken with lisdexamfetamine or the outcome of events. One case also did not report on the action of lisdexamfetamine, but the event resolved. The last case discontinued

treatment with lisdexamfetamine after ten days of use, but the outcome of event was unknown.

- **"Nervous tic" of the eye, Tic (n=3)**

The first case reported facial tics, described as "opening/stretching his jaw" that resulted in raw upper lip. The second case reported a tic, described as a constant cough. Both cases discontinued treatment with lisdexamfetamine and the events resolved or lessened in severity. The third case reported a "nervous tic - eye" approximately four months following initiating treatment with lisdexamfetamine 20 mg and within the same month of the dose increase to 30 mg. Subsequently, he saw a neurologist who determined the event was due to lisdexamfetamine. Treatment with lisdexamfetamine discontinued, but the outcome of the event was unknown.

- **Muscle contractions involuntary (n=1)**

A 14-year-old female experienced lethargy, dizziness, difficulty breathing, "eyes were rolling back in her head," confusion, hallucinations, panic attack, "muscle tensing in her jaw and tongue," stomach cramps, tingling in her hands and feet, and vomiting on the same day as initiating treatment with lisdexamfetamine 40 mg daily for the treatment of ADHD. At the emergency room, she was treated with lorazepam intravenously and unspecified blood work performed, which were normal. Treatment with lisdexamfetamine discontinued and all events resolved.

Labeled events: Dyskinesia (Postmarketing experience), Tic (Warnings and Precautions, Adverse Reactions).

Unlabeled events: Muscle contractions involuntary

4.3 SUMMARY OF REMAINING PEDIATRIC ADVERSE EVENTS (N=39)

The remaining 39 cases not categorized in the above sections, are summarized in Appendix G.

5 CONCLUSION

We reviewed 135 serious pediatric cases reported with lisdexamfetamine use. There were 12 fatal cases from approval to April 9, 2012. The majority of the cases (n=9) reported a cause of death related to self-harm or drug misuse. Two of the remaining cases were confounded by underlying cardiac or respiratory problems. The last case reported an unknown event that resulted in death.

We identified 123 non-fatal serious cases from November 10, 2010 to April 9, 2012. More than half of the non-fatal cases reported psychiatric adverse events (n=45) or cardiac adverse events (n =21). The majority of the psychiatric adverse events (n=27) were homicidal or suicidal ideation, self-injurious behavior or ideation, or suicide attempt, which are not labeled events for lisdexamfetamine. When looking at the levels of evidence to determine whether or not the use of a medication is associated with particular adverse events, data obtained from randomized, clinical trials provides the highest level of evidence to infer causality of drug-induced adverse events when compared to post-marketing reports and analysis of the AERS database. Based on the high prevalence rates of suicidality seen in the U.S. High School population and the absence of increased suicidality rates in patients taking stimulant medications when compared to placebo

administration in clinical trials, the extremely small number of suicidality cases noted from this review does not warrant a change in labeling to the lisdexamfetamine label at this time.

As with all ADHD stimulants, lisdexamfetamine carries the same class warnings and precautions for serious cardiovascular reactions in its label. Over half of the cardiac adverse event cases (n=12) were either labeled events, confounded, or reported the events persisted after treatment with lisdexamfetamine discontinued. All of the neurologic adverse events, and all but one neuromuscular adverse event, were labeled events. Approximately half (n=18) of the remaining 39 cases reported labeled events, accidental exposure, or product quality issues; and there was no pattern for specific adverse events in the remaining 21 reports.

6 RECOMMENDATIONS

Based on the data summarized in this review, DPV recommends no labeling changes at this time. DPV will continue to monitor adverse events associated with the use of lisdexamfetamine.

7 REFERENCES

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8 APPENDICES

8.1 APPENDIX A. PEDIATRIC PRODUCT LABELING[2]

CONTRAINDICATIONS

- Known hypersensitivity to amphetamine products or other ingredients of Vyvanse. Anaphylactic reactions, Stevens-Johnson Syndrome, angioedema, and urticaria have been observed in postmarketing reports *[see Adverse Reactions (6.2)]*.
- Concurrent administration of monoamine oxidase (MAO) inhibitors because MAOIs potentially can result in hypertensive crisis. Vyvanse should not be given for at least 14 days after discontinuation of an MAO inhibitor *[see Drug Interactions (7.3)]*

WARNINGS AND PRECAUTIONS

SERIOUS CARDIOVASCULAR REACTIONS

Sudden Death and Pre-existing Structural Cardiac Abnormalities or Other Serious Heart Problems

Children and Adolescents

Sudden death has been reported in association with CNS stimulant treatment at usual doses in children and adolescents with structural cardiac abnormalities or other serious heart problems. Although some serious heart problems alone carry an increased risk of sudden death, stimulant products generally should not be used in children or adolescents with known serious structural cardiac abnormalities, cardiomyopathy, serious heart rhythm abnormalities, or other serious cardiac problems that may place them at increased vulnerability to the sympathomimetic effects of a stimulant drug.

Assessing Cardiovascular Status in Patients Being Treated with Stimulant Medications

Children, adolescents, or adults who are being considered for treatment with stimulant medications should have a careful history (including assessment for a family history of sudden death or ventricular arrhythmia) and physical exam to assess for the presence of cardiac disease, and should receive further cardiac evaluation if findings suggest such disease (e.g. electrocardiogram and echocardiogram). Patients who develop symptoms such as exertional chest pain, unexplained syncope, or other symptoms suggestive of cardiac disease during stimulant treatment should undergo a prompt cardiac evaluation.

INCREASED BLOOD PRESSURE

Stimulant medications cause a modest increase in average blood pressure (about 2-4 mm Hg) and average heart rate (about 3-6 bpm) and individuals may have larger increases. While the mean changes alone would not be expected to have short-term consequences, all patients should be monitored for larger changes in heart rate and blood pressure. Caution is indicated in treating patients whose underlying medical conditions might be compromised by increases in blood pressure or heart rate, e.g. those with pre-existing hypertension, heart failure, recent myocardial infarction, or ventricular arrhythmia.

PSYCHIATRIC ADVERSE REACTIONS

Pre-existing Psychosis

Administration of stimulants may exacerbate symptoms of behavior disturbance and thought disorder in patients with a pre-existing psychotic disorder.

Bipolar Illness

Particular care should be taken in using stimulants to treat ADHD in patients with comorbid bipolar disorder because of concern for possible induction of a mixed/manic episode in such patients. Prior to initiating treatment with a stimulant, patients with comorbid depressive symptoms should be adequately screened to determine if they are at risk for bipolar disorder. Such screening should include a detailed psychiatric history, including a family history of suicide, bipolar disorder, and depression.

Emergence of New Psychotic or Manic Symptoms

Treatment-emergent psychotic or manic symptoms, e.g. hallucinations, delusional thinking, or mania in children and adolescents without a prior history of psychotic illness or mania, can be caused by stimulants at usual doses. If such symptoms occur, consideration should be given to a possible causal role of the stimulant, and discontinuation of treatment may be appropriate. In a pooled analysis of multiple short-term, placebo-controlled studies, such symptoms occurred in about 0.1% (4 patients with events out of 3482 exposed to methylphenidate or amphetamine for several weeks at usual doses) of stimulant-treated patients compared to 0 in placebo-treated patients.

Aggression

Aggressive behavior or hostility is often observed in children and adolescents with ADHD, and has been reported in clinical trials and the postmarketing experience of some medications indicated for the treatment of ADHD. Although there is no systematic evidence that stimulants cause aggressive behavior or hostility, patients beginning treatment of ADHD should be monitored for the appearance of, or worsening of, aggressive behavior or hostility.

LONG-TERM SUPPRESSION OF GROWTH

In pediatric patients, growth (weight and height) 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 Adverse Reactions (6.1)]*.

SEIZURES

Stimulants may lower the convulsive threshold in patients with prior history of seizures, in patients with prior EEG abnormalities in absence of seizures, and, very rarely, in patients without a history of seizures and no prior EEG evidence of seizures. In the presence of seizures, Vyvanse should be discontinued.

TICS

Amphetamines have been reported to exacerbate motor and phonic tics and Tourette's syndrome. Therefore, clinical evaluation for tics and Tourette's syndrome should precede use of Vyvanse.

ADVERSE REACTIONS

The premarketing development program for Vyvanse included exposures in a total of 995 participants in clinical trials (348 pediatric patients aged 6 to 12 years, 233 adolescent patients aged 13 to 17 years, 358 adult patients and 56 healthy adult subjects). Of these, 348 pediatric (aged 6 to 12) patients were evaluated in two controlled clinical studies (one parallel-group and one crossover), one open-label extension study, and one single-dose clinical pharmacology study, 233 adolescent (aged 13 to 17) patients were evaluated in one controlled clinical study, and 358 adult patients were evaluated in one controlled clinical study and one open-label extension study. The information included in this section is based on data from the 4-week parallel-group controlled clinical studies in pediatric and adult patients with ADHD *[see Clinical Studies (14)]*. Adverse reactions were assessed by collecting adverse events, results of physical examinations, vital signs, weights, laboratory analyses, and ECGs.

Adverse reactions during exposure were obtained primarily by general inquiry and recorded by clinical investigators using terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse reactions without first grouping similar types of reactions into a smaller number of standardized reactions categories.

The stated frequencies of adverse reactions represent the proportion of individuals who experienced an adverse reaction of the type listed at least once.

Adverse Reactions Associated with Discontinuation of Treatment in Clinical Trials

In the controlled pediatric (ages 6 to 12 years) trial, 9% (20/218) of Vyvanse-treated patients discontinued due to adverse reactions compared to 1% (1/72) who received placebo. The most frequent adverse reactions leading to discontinuation and considered to be drug-related (i.e. leading to discontinuation in at least 1% of Vyvanse-treated patients and at a rate at least twice that of placebo) were ECG voltage criteria for ventricular hypertrophy, tic, vomiting, psychomotor hyperactivity, insomnia, and rash (2/218 each; 1%).

In the controlled adolescent (ages 13 to 17 years) trial, 4% (10/233) of Vyvanse-treated patients discontinued due to adverse reactions compared to 1% (1/77) who received placebo. The most frequent adverse reactions leading to discontinuation and considered to be drug-related were irritability (3/233; 1%), decreased appetite (2/233; 1%), and insomnia (2/233; 1%).

Adverse Reactions Occurring at an Incidence of 2% or More Among Vyvanse Treated Patients in Clinical Trials

Adverse reactions reported in the controlled trials in pediatric patients ages 6 to 12 years, adolescent patients ages 13 to 17 years, and adult patients treated with Vyvanse or placebo are presented in Tables 1, 2, and 3 below.

Pediatric

Table 1 Adverse Reactions Reported by 2% or More of Children (Ages 6 to 12 Years) Taking Vyvanse in a 4-Week Clinical Trial

Body System	Preferred Term	Vyvanse (n=218)	Placebo (n=72)
Gastrointestinal Disorders	Abdominal Pain Upper	12%	6%
	Vomiting	9%	4%
	Nausea	6%	3%
	Dry Mouth	5%	0%
General Disorder and Administration Site Conditions	Pyrexia	2%	1%
Investigations	Weight Decreased	9%	1%
Metabolism and Nutrition	Decreased Appetite	39%	4%
Nervous System Disorders	Dizziness	5%	0%
	Somnolence	2%	1%
Psychiatric Disorders	Insomnia[a]	23%	3%
	Irritability	10%	0%
	Affect lability	3%	0%
	Tic	2%	0%
Skin and Subcutaneous Tissue Disorders	Rash	3%	0%

[a] Insomnia includes the following preferred terms reported in the study: Initial Insomnia, Insomnia.

Note: This table includes those reactions for which the incidence in patients taking Vyvanse is at least twice the incidence in patients taking placebo.

Table 2 Adverse Reactions Reported by 2% or More of Adolescent (Ages 13 to 17 Years) Patients Taking Vyvanse in a 4-Week Clinical Trial

Body System	Preferred Term	Vyvanse (n=233)	Placebo (n=77)
Gastrointestinal Disorders	Dry Mouth	4%	1%
Investigations	Weight Decreased	9%	0%
Metabolism and Nutrition	Decreased Appetite	34%	3%
Psychiatric Disorders	Insomnia[b]	13%	4%

[b] Insomnia includes the following preferred terms reported in the study: Initial Insomnia, Insomnia.
Note: This table includes those reactions for which the incidence in patients taking Vyvanse is at least twice the incidence in patients taking placebo

Weight Loss and Slowing Growth Rate in Pediatric Patients
In a controlled trial of Vyvanse in children ages 6 to 12 years, mean weight loss from baseline after 4 weeks of therapy was -0.9, -1.9, and -2.5 pounds, respectively, for patients receiving 30 mg, 50 mg, and 70 mg of Vyvanse, compared to a 1 pound weight gain for patients receiving placebo. Higher doses were associated with greater weight loss with 4 weeks of treatment. Careful follow-up for weight in children ages 6 to 12 years who received Vyvanse over 12 months suggests that consistently medicated children (i.e. treatment for 7 days per week throughout the year) have a slowing in growth rate, measured by body weight as demonstrated by an age- and sex-normalized mean change from baseline in percentile, of -13.4 over 1 year (average percentiles at baseline and 12 months were 60.6 and 47.2, respectively). In a 4-week controlled trial of Vyvanse in adolescents ages 13 to 17 years, mean weight loss from baseline to endpoint was -2.7, -4.3, and -4.8 lbs., respectively, for patients receiving 30 mg, 50 mg, and 70 mg of Vyvanse, compared to a 2.0 pound weight gain for patients receiving placebo.

Careful follow-up of weight and height in children ages 7 to 10 years who were randomized to either methylphenidate or non-medication treatment groups over 14 months, as well as in naturalistic subgroups of newly methylphenidate-treated and non-medication treated children over 36 months (to the ages of 10 to 13 years), suggests that consistently medicated children (i.e. treatment for 7 days per week throughout the year) have a temporary slowing in growth rate (on average, a total of about 2 cm less growth in height and 2.7 kg less growth in weight over 3 years), without evidence of growth rebound during this period of development. In a controlled trial of amphetamine (d- to l-enantiomer ratio of 3:1) in adolescents, mean weight change from baseline within the initial 4 weeks of therapy was -1.1 pounds and –2.8 pounds, respectively, for patients receiving 10 mg and 20 mg of amphetamine. Higher doses were associated with greater weight loss within the initial 4 weeks of treatment.

POSTMARKETING EXPERIENCE
The following adverse reactions have been identified during post approval use of Vyvanse. Because these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency or establish a causal relationship to drug exposure.
Cardiac Disorders - Palpitations, cardiomyopathy
Eye Disorders - Mydriasis, diplopia
Hepatobiliary Disorders - Eosinophilic hepatitis
Immune System Disorders - Anaphylactic reaction, hypersensitivity
Nervous System Disorders - Dyskinesia
Psychiatric Disorder - Depression, dysphoria, euphoria, logorrhea, dermatillomania
Skin and Subcutaneous Tissue Disorder - Stevens-Johnson Syndrome, angioedema, urticaria

DRUG INTERACTIONS
MONOAMINE OXIDASE INHIBITORS
Dextroamphetamine is known to inhibit monoamine oxidase.
MAOI antidepressants, as well as a metabolite of furazolidone, slow amphetamine metabolism. This slowing potentiates amphetamines, increasing their effect on the release of norepinephrine and other monoamines from adrenergic nerve endings; this can cause headaches and other signs of hypertensive crisis. A variety of toxic neurological effects and malignant hyperpyrexia can occur, sometimes with fatal results. Do not administer Vyvanse during or within 14 days following the administration of monoamine oxidase inhibitors [*see Contraindications (4)*].

AGENTS THAT MAY POTENTIATE THE EFFECTS OF AMPHETAMINES
Propoxyphene Overdosage

In cases of propoxyphene overdosage, amphetamine CNS stimulation is potentiated and fatal convulsions can occur.

PEDIATRIC USE
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)]*. The long-term efficacy of amphetamines, including Vyvanse, in pediatric patients have not been established. Safety and efficacy in pediatric patients below the age of 6 years have not been established.

Long Term 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 (5.4)*, *Adverse Reactions (6.1)*].

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

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

DEPENDENCE
Tolerance, extreme psychological dependence, and severe social disability have occurred. There are reports of patients who have increased the dosage to levels many times higher than recommended. Abrupt cessation following prolonged high-dosage administration results in extreme fatigue and mental depression; changes are also noted on the sleep EEG. Manifestations of chronic intoxication with amphetamines may include severe dermatoses, marked insomnia, irritability, hyperactivity, and personality changes. The most severe manifestation of chronic intoxication is psychosis, often clinically indistinguishable from schizophrenia.

OVERDOSAGE
Consult with a Certified Poison Control Center for up-to-date guidance and advice for treatment of overdosage. Individual patient response to amphetamines varies widely. Toxic symptoms may occur idiosyncratically at low doses.

Manifestations of acute overdosage with amphetamines include restlessness, tremor, hyperreflexia, rapid respiration, confusion, assaultiveness, hallucinations, panic states, hyperpyrexia, and rhabdomyolysis. Fatigue and depression usually follow the central nervous system stimulation. Cardiovascular effects include arrhythmias, hypertension or hypotension, and circulatory collapse. Gastrointestinal symptoms include nausea, vomiting, diarrhea, and abdominal cramps. Fatal poisoning is usually preceded by convulsions and coma.

PATIENT COUNSELING INFORMATION
See FDA-approved patient labeling (Medication Guide).

SERIOUS CARDIOVASCULAR RISKS

There is a potential serious cardiovascular risk including sudden death, myocardial infarction, stroke, and hypertension with Vyvanse use. Contact the doctors immediately if patients develop symptoms such as exertional chest pain, unexplained syncope, or other symptoms suggestive of cardiac disease [*see Warnings and Precautions(5.1)*].

PSYCHIATRIC RISKS

Prior to initiating treatment with Vyvanse, patients with comorbid depressive symptoms should be adequately screened to determine if they are at risk for bipolar disorder. Such screening should include a detailed psychiatric history, including a family history of suicide, bipolar disorder, and/or depression. Additionally, Vyvanse therapy at usual doses may cause treatment-emergent psychotic or manic symptoms in patients without prior history of psychotic symptoms or mania [*see Warnings and Precautions (5.3)*].

LONG-TERM SUPPRESSION OF GROWTH

Growth should be monitored during treatment with Vyvanse, and children who are not growing or gaining weight as expected may need to have their treatment interrupted *[see Warnings and Precautions(5.4) and Use in Specific Populations (8.4)]*.

MEDICATION GUIDE

Some people have had the following problems when taking stimulant medicines such as Vyvanse:

1. Heart-related problems including:

- **sudden death in people who have heart problems or heart defects**
- **stroke and heart attack in adults**
- **increased blood pressure and heart rate**

2. Mental (psychiatric) problems including:

In Children, Teenagers, and Adults:

- **new or worse behavior and thought problems**
- **new or worse bipolar illness**
- **new or worse aggressive behavior or hostility**

In Children and Teenagers

- **new psychotic symptoms such as:**
  - **hearing voices**
  - **believing things that are not true**
  - **being suspicious**
- **new manic symptoms**

Do not take Vyvanse if you or your child:

- is taking or has taken within the past 14 days an anti-depression medicine called a monoamine oxidase inhibitor or MAOI.
- is sensitive to, allergic to, or had a reaction to other stimulant medicines.

Before you or your child takes Vyvanse, tell your doctor if you or your child has or if there is a family history of:

- heart problems, heart defects, high blood pressure
- mental problems including psychosis, mania, bipolar illness, or depression
- tics or Tourette's syndrome
- seizures or have had an abnormal brain wave test (EEG)

Tell your doctor if:

- you or your child is pregnant or plan to become pregnant. It is not known if Vyvanse will harm your unborn baby.
- you or your child is breastfeeding or plan to breastfeed. Vyvanse passes into breast milk. Discuss with your doctor before you breastfeed while you are taking Vyvanse.

Tell your doctor about all of the medicines that you or your child takes, including prescription and non-prescription medicines, vitamins, and herbal supplements.

Vyvanse can affect the way other medicines work, and other medicines may affect how Vyvanse works. Using Vyvanse with other medicines can cause serious side effects.

Especially tell your doctor if you or your child takes:

- anti-depression medicines including MAOIs
- anti-psychotic medicines
- lithium
- blood pressure medicines
- seizure medicines
- narcotic pain medicines

Know the medicines that you or your child takes. Keep a list of them to show your doctor and pharmacist when you get a new medicine.

How should I take Vyvanse?

- Take Vyvanse exactly as your doctor tells you to take it.
- Your doctor may change your dose until it is right for you or your child.
- Take Vyvanse once a day in the morning.
- Vyvanse can be taken with or without food.
- Vyvanse capsules may be taken whole or opened and the powder may be mixed in a glass of water. Use all of the powder from the capsule so you get all of the medicine. Drink the entire glass of water right away after mixing.
- Your doctor may sometimes stop Vyvanse treatment for a while to check your ADHD symptoms.
- Your doctor may do regular checks of your blood, heart, and blood pressure while taking Vyvanse.
- Children should have their height and weight checked often while taking Vyvanse. Vyvanse treatment may be stopped if a problem is found during these check-ups.
- If you or your child takes too much Vyvanse, call your doctor or poison control center right away, or get to the nearest hospital emergency room.

Vyvanse may cause serious side effects, including:

- See **"What is the most important information I should know about Vyvanse?".**
- slowing of growth (height and weight) in children
- seizures, mainly in people with a history of seizures
- eyesight changes or blurred vision
- worsening of sudden, repeated movements or sounds (tics) and Tourette's syndrome in people who already have these problems

Talk to your doctor if you or your child has any side effects that are bothersome or do not go away.

Keep Vyvanse and all medicines out of the reach of children.

APPENDIX B. STANDARD SEARCHES

A. Adults (17 yrs and above)
   1. All outcomes from approval date (no set criteria)
   2. Serious outcomes from approval date
   3. Death as an outcome from approval date

B. Ages 0-16 yrs ONLY
   1. Same as above 1-3

8.2 APPENDIX C. ADVERSE EVENT REPORTING SYSTEM (AERS)

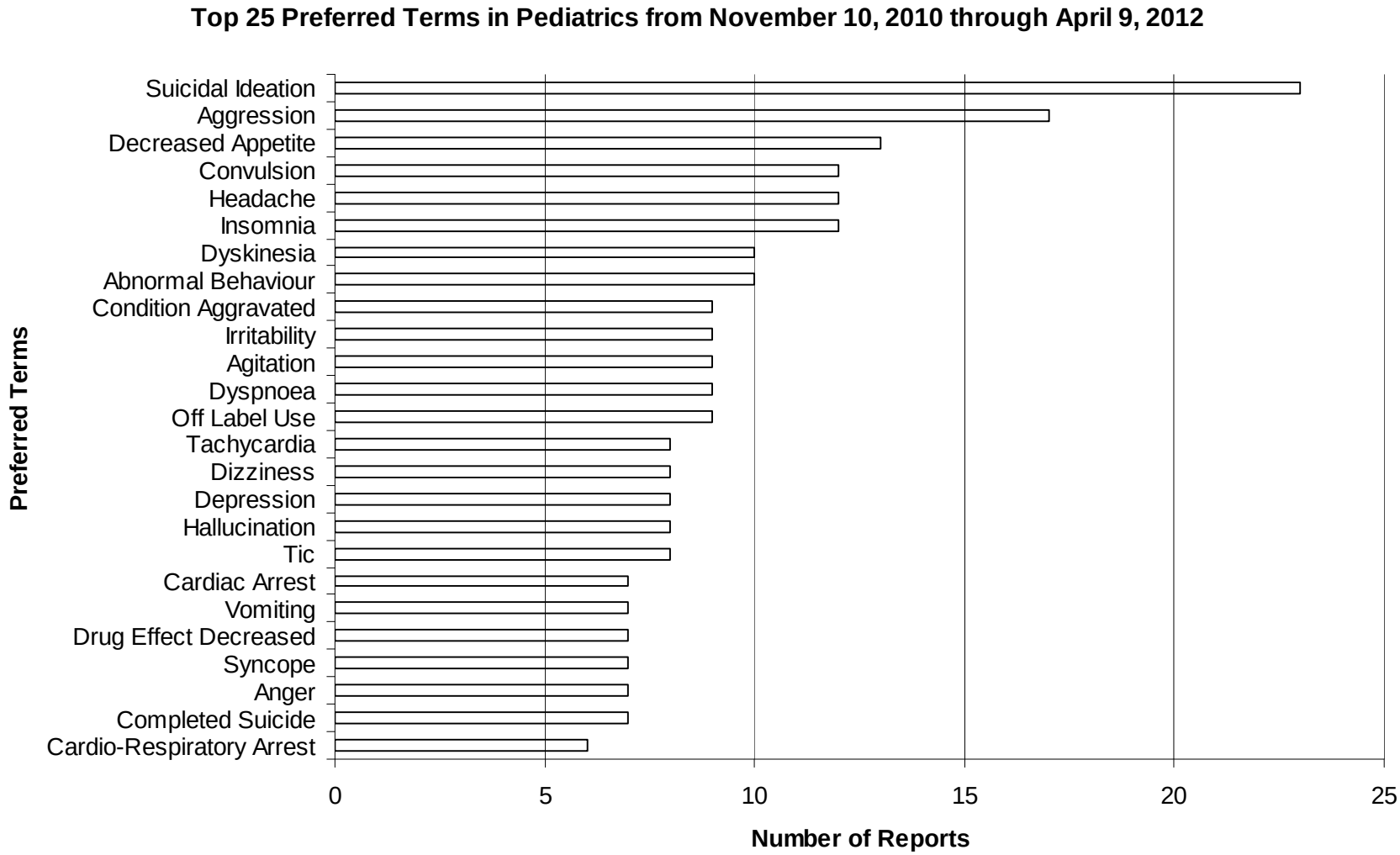
Adverse Event Reporting System (AERS)

The Adverse Event Reporting System (AERS) is a computerized information database designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. The FDA uses AERS to monitor adverse events and medication errors that might occur with these marketed products. The structure of AERS complies with the international safety reporting guidance (ICH E2B) issued by the International Conference on Harmonisation. Adverse events in AERS are coded to terms in the Medical Dictionary for Regulatory Activities terminology (MedDRA).

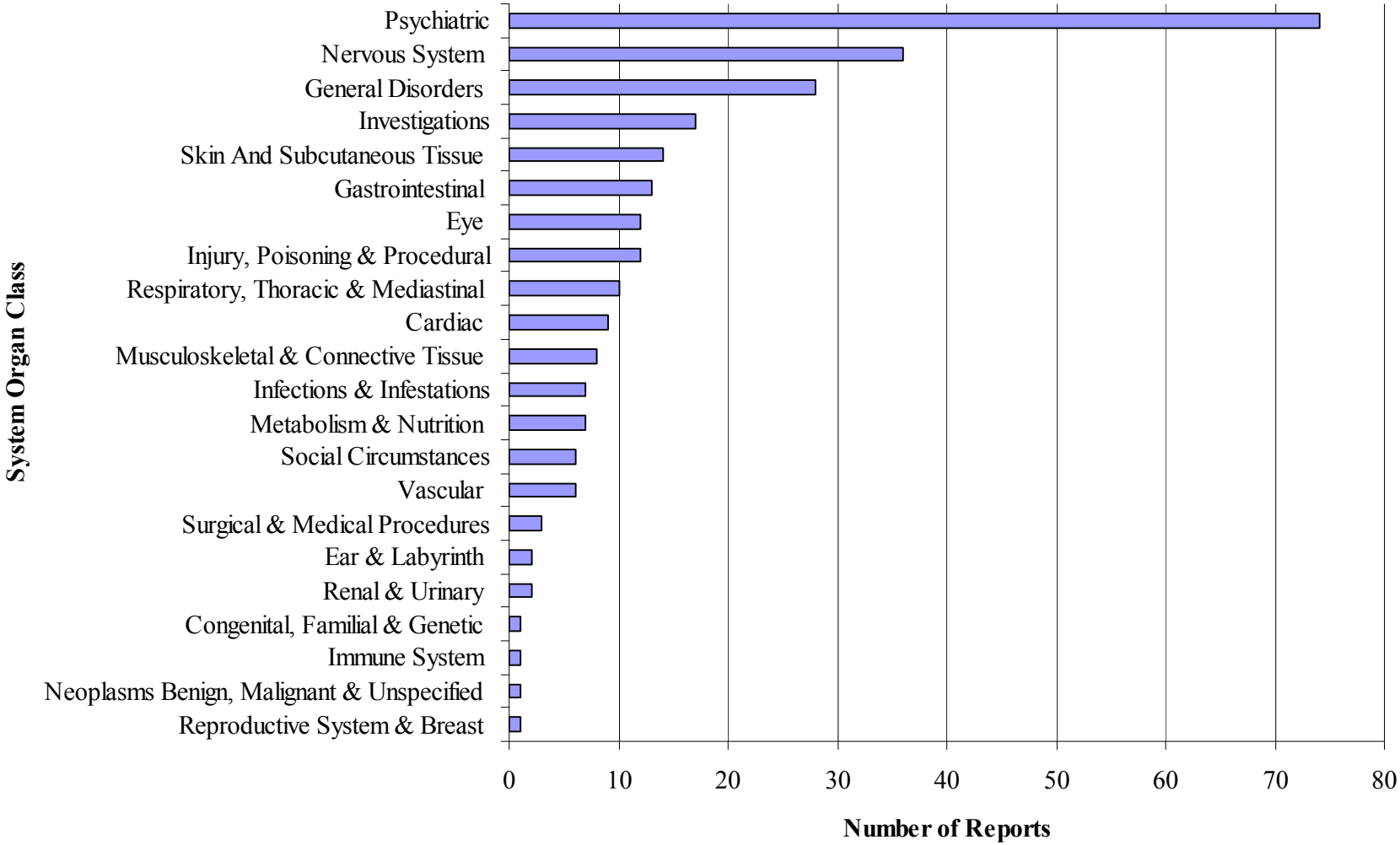
AERS data do have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive all adverse event reports that occur 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, AERS cannot be used to calculate the incidence of an adverse event in the U.S. population.

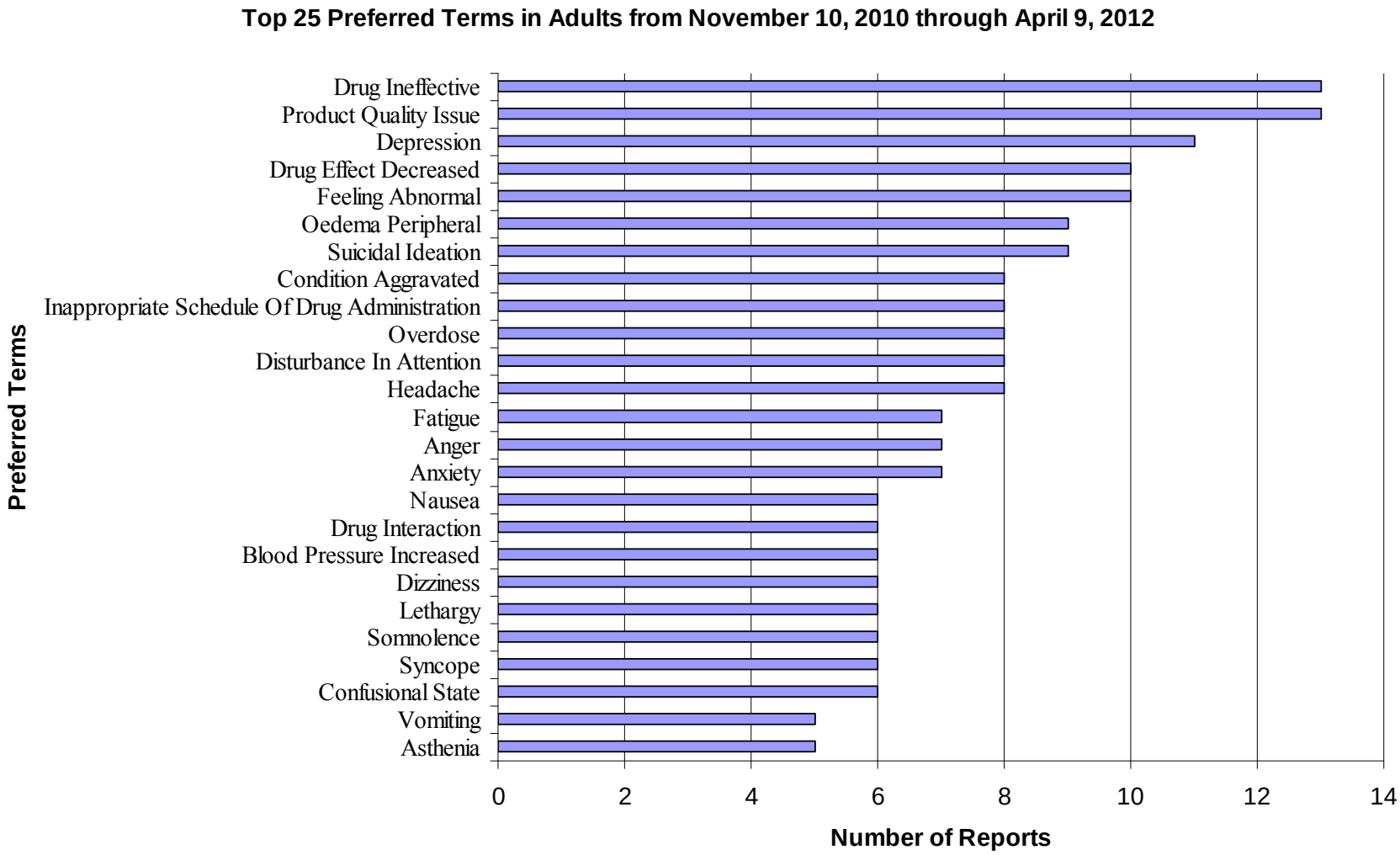
8.3 APPENDIX D. PEDIATRIC VS. ADULT ADVERSE EVENT GRAPHICAL REPRESENTATIONS

The following four charts may contain duplicate reports, in addition to events reporting both serious and non-serious outcomes.

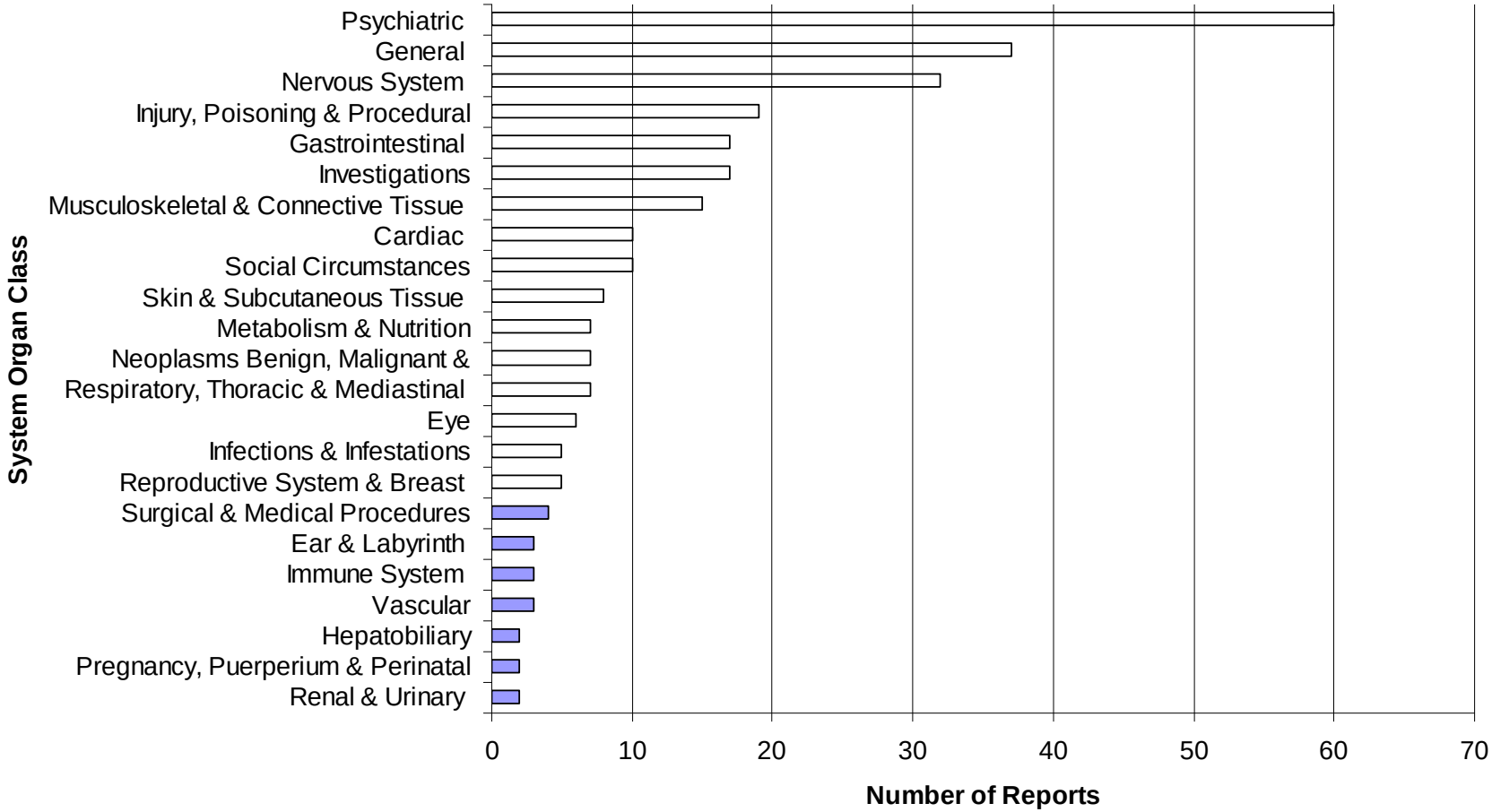


Adverse Events by MedDRA SOC reported in Pediatrics from November 10, 2010 through April 9, 2012




Top 25 Preferred Terms in Adults from November 10, 2010 through April 9, 2012
Drug Ineffective
Product Quality Issue
Depression
Drug Effect Decreased
Feeling Abnormal
Oedema Peripheral
Suicidal Ideation
Condition Aggravated
Inappropriate Schedule Of Drug Administration
Overdose
Disturbance In Attention
Headache
Fatigue
Anger
Anxiety
Nausea
Drug Interaction
Blood Pressure Increased
Dizziness
Lethargy
Somnolence
Syncope
Confusional State
Vomiting
Asthenia
Preferred Terms
0
2
4
6
8
10
12
14
Number of Reports

Adverse Events by MedDRA SOC reported in Adults from November 10, 2010 through April 9, 2012



8.4 APPENDIX E. AERS CASE NUMBERS, AERS ISR NUMBERS AND MANUFACTURER CONTROL NUMBERS

CSE#	ISR#	MFRCNTRL#
6659701	7508461	SPV1-2008-01133
6814376	5947621	SPV1-2008-02387
7048933	6262705	SPV1-2009-01304
7174073	7508491	SPV1-2009-02050
7200055	7508548	ALL1-2009-02978
7261341	7508503	SPV1-2010-00005
7362483	6679980	SPV1-2010-00619
7384264	7508459	SPV1-2010-00060
7391838	7346072	US-SHIRE-SPV1-2010-00909
7410572	6757155	US-SHIRE-SPV1-2009-00850
7490025	6859748	US-SHIRE-SPV1-2010-01263
7555990	6944369	US-SHIRE-SPV1-2010-01462
7669982	7104727	US-SHIRE-SPV1-2010-01972
7673540	7109815	US-SHIRE-SPV1-2010-01936
7677606	7115201	US-SHIRE-SPV1-2010-01934
7679481	7311745	US-SHIRE-SPV1-2010-01979
7684415	7216347	US-SHIRE-SPV1-2010-01996
7701379	7148189	US-SHIRE-SPV1-2010-02093
7706858	7117929	CTU 435959
7739349	7196999	US-SHIRE-SPV1-2010-02207
7739992	7134543	CTU 437152
7743693	7203343	US-SHIRE-ALL1-2010-06130
7746080	7206645	US-SHIRE-SPV1-2010-02224
7759443	7224796	US-SHIRE-ALL1-2011-00010
7773646	7244207	US-SHIRE-SPV1-2011-00103
7774116	7244813	US-SHIRE-SPV1-2011-00104
7774117	7244814	CA-SHIRE-SPV1-2011-00094
7774118	7346073	CA-SHIRE-SPV1-2011-00082
7777260	7248708	US-SHIRE-SPV1-2011-00081
7793685	7266787	US-SHIRE-SPV1-2011-00146
7800610	7227961	CTU 441113
7808444	7244210	CTU 441603
7810050	7270198	CTU 442427
7840456	7330679	US-SHIRE-SPV1-2011-00337
7845079	7315164	CTU 444930
7845190	7337076	US-SHIRE-SPV1-2011-00311
7849002	7355396	US-SHIRE-ALL1-2011-00173
7863583	7363104	US-SHIRE-ALL1-2011-00717
7866379	7344761	CTU 446473
7867621	7461397	US-SHIRE-SPV1-2011-00417
7874976	7578118	US-SHIRE-SPV1-2011-00450
7876490	7381741	US-SHIRE-SPV1-2011-00438
7884601	7393382	US-SHIRE-SPV1-2011-00491
7890992	7402404	US-SHIRE-SPV1-2011-00549
7891195	7402741	US-SHIRE-SPV1-2011-00560
7901891	7419618	US-SHIRE-SPV1-2011-00609
7905992	7425489	US-SHIRE-ALL1-2011-00989
7910644	7412941	CTU 450225
7922280	7554313	US-SHIRE-SPV1-2011-00705
7930098	7495589	US-SHIRE-SPV1-2011-00702
7932171	7442958	CTU 451713
7940462	7472920	US-SHIRE-ALL1-2011-00706
7947451	7570975	US-SHIRE-SPV1-2011-00783
7951726	7475013	CTU 452957
7983200	7508249	SPV1-2010-00438
7983210	7508250	SPV1-2010-00521
7983761	7508320	SPV1-2010-01371
7990215	7525943	CTU 455543
7991638	7508409	SPV1-2011-00080
7991774	7878831	ALL1-2011-00282
7991789	7878832	ALL1-2011-00315
7995308	7553409	US-SHIRE-ALL1-2011-01851
8003780	7570979	US-SHIRE-ALL1-2011-01891
8003781	7703457	CA-SHIRE-ALL1-2011-01886
8010680	7574145	US-SHIRE-ALL1-2011-01882
8010718	7574215	US-SHIRE-ALL1-2011-01972
8017982	7585275	US-SHIRE-ALL1-2011-02011
8018089	7570810	CTU 457427
8027921	7670777	US-SHIRE-ALL1-2011-02070
8036176	7610280	US-SHIRE-ALL1-2011-02132
8049233	7629093	US-FDA-7629093
8064020	7642276	CTU 460219
8070403	7658067	US-SHIRE-SPV1-2011-00802
8081420	7680491	US-SHIRE-ALL1-2011-02531
8081421	7680489	US-SHIRE-ALL1-2011-02539
8081422	7680490	US-SHIRE-ALL1-2011-02534
8084098	7674372	US-SHIRE-ALL1-2011-02628
8089874	7682877	US-SHIRE-ALL1-2011-02670
8090591	7683853	US-SHIRE-ALL1-2011-01811
8092444	7686615	US-FDA-7686615
8097861	7693542	CA-SHIRE-ALL1-2011-02772
8101176	7786119	US-SHIRE-ALL1-2011-02755
8114893	7892351	US-SHIRE-ALL1-2011-02950
8114894	7956772	US-SHIRE-ALL1-2011-02934
8121885	7731102	US-FDA-7731102
8129952	7741670	US-SHIRE-ALL1-2011-03183
8145335	7763748	US-SHIRE-ALL1-2011-03398
8147447	7766821	US-ASTRAZENECA-2010SE58167

CSE#	ISR#	MFRCNTRL#
8157666	7780193	US-FDA-7780193
8169462	7792520	CTU 463422
8173852	7804171	US-SHIRE-ALL1-2011-03762
8184270	7818295	BR-SHIRE-SPV1-2011-01273
8184272	7818297	US-SHIRE-ALL1-2011-03949
8195619	7833984	US-SHIRE-ALL1-2011-03027
8199495	7846399	US-FDA-7846399
8216626	7877730	US-FDA-7877730
8228722	7878958	SPV1-2011-00393
8228727	7878973	SPV1-2011-00543
8228750	7878855	ALL1-2011-02119
8228760	7878858	ALL1-2011-02409
8239196	7906425	US-SHIRE-ALL1-2011-04354
8242436	7911262	CA-SHIRE-ALL1-2011-04356
8254496	7919363	CTU 465934
8256077	7929500	US-SHIRE-ALL1-2011-04519
8266363	7945112	US-FDA-7945112
8286050	7973578	US-SHIRE-ALL1-2011-04713
8286052	8052587	US-SHIRE-ALL1-2011-04763
8297616	7988842	US-SHIRE-ALL1-2011-04919
8313230	8118963	US-SHIRE-ALL1-2011-05040
8316934	8015786	US-SHIRE-ALL1-2011-04308
8325021	8027771	US-FDA-8027771
8333111	8143472	US-SHIRE-ALL1-2012-00070

CSE#	ISR#	MFRCNTRL#
8346311	8163836	PHEH2012US001244
8347911	8061808	US-SHIRE-ALL1-2012-00251
8350358	8065169	US-SHIRE-ALL1-2012-00325
8359917	8066959	AUR-APL-2012-00149
8371612	8091060	CA-SHIRE-ALL1-2012-00439
8371756	8091209	CA-SHIRE-ALL1-2012-00405
8374424	8094145	US-FDA-8094145
8374529	8094271	CA-SHIRE-ALL1-2012-00399
8374530	8094272	CA-SHIRE-ALL1-2012-00412
8374532	8094274	BR-SHIRE-SPV1-2012-00062
8375018	8094949	CA-SHIRE-ALL1-2012-00396
8397042	8103103	2012POI057500026
8405719	8131068	CTU 470118
8419801	8155502	US-SHIRE-ALL1-2012-00803
8422822	8159946	US-SHIRE-ALL1-2012-00866
8429169	8168489	US-FDA-8168489
8437517	8180101	US-FDA-8180101
8439668	8182600	US-SHIRE-ALL1-2012-00214
8443858	8188662	BR-SHIRE-SPV1-2012-00166
8445654	8184742	US-FDA-8184742
8452486	8200084	US-SHIRE-ALL1-2012-01247
8457895	8207626	US-FDA-8207626
8487117	8250582	US-FDA-8250582

8.5 APPENDIX F. DETAILED SUMMARY OF FATAL CASES (N=12)

Suicide

ISR #6679980; US; 2010: A13-year-old male hung himself in the family barn 20 months after initiating treatment with lisdexamfetamine 50 mg "on school days" for ADHD. He did not have a personal or family history of psychiatric illnesses, including suicidal thoughts or attempts, completed suicides, or drug or alcohol abuse. However, he experienced "extreme bullying" by his classmates for "some time" due to his facial scar and small stature. His physician recommended counseling and addressing bullying at school, but his recommendations were not carried out.

ISR #6757155; US; 2010: This is a report from the South Florida Sun-Sentinel and Miami Herald newspaper articles. A 7-year-old male hung himself with a detachable shower hose approximately 2 weeks after a dose increase of lisdexamfetamine to 50 mg daily, and 4 months after initiating treatment with lisdexamfetamine 30 mg daily for ADHD. He received concomitant medications labeled for suicidality; escitalopram 5 mg daily for one month then changed to olanzapine/fluoxetine 3 mg / 25 mg for one month up to the time of death. He has a significant medical and psychosocial history of sexual abuse, living in foster care, impulse-control disorder, aggression, and self-injurious behavior. Additionally, the event occurred following an argument with his foster father's son. The cause of death determined by autopsy was asphyxiation due to hanging.

ISR #6859748; US; 2010: A 9-year-old male hung himself in a school bathroom an unknown time after initiating treatment with an unknown dose of lisdexamfetamine for ADHD. Although he did not receive a diagnosis, his mother believed the patient was "bipolar." Additionally, his family believed the patient was "bullied into suicide." The autopsy reported amphetamines in his blood, but no other clinical information was provided.

ISR #7906425; US; 2011: A 16-year-old male hung himself five months after initiating treatment with an unknown dose of lisdexamfetamine for an unspecified indication. No additional clinical information was provided.

ISR #8143472; US; 2012: A 10-year-old female hung herself with a cloth belt an unknown time after initiating treatment with an unknown dose of lisdexamfetamine for ADHD; however, it was unknown if she took lisdexamfetamine up to the time of death. Additionally, she was picked on at school, was suspended from school for fighting the month prior to the event, and lost television privileges at home. She also said to her grandmother "I ought to kill myself" three months prior to the event. The cause of death by autopsy was asphyxia due to hanging.

ISR #8103103; US; 2012: This is a case report from the 2010 Annual Report of the American Association of Poison Control Centers' National Poison Data System (NPDS). A 16-year-old female experienced "prehospital cardiac and/or respiratory arrest" after an acute exposure of morphine solution, lisdexamfetamine, and a stimulant laxative for "intentional suicide." No additional clinical information was provided.

Accidental Death

ISR #6262705; US; 2009: A 14-year-old male was discovered hanging from a low tree branch in the backyard by his siblings. The event occurred eight months after he initiated treatment with lisdexamfetamine 50 mg daily for ADHD. He did not have medical, psychiatric or psychosocial histories of suicidal ideation or attempts, self-injurious behaviors, depression, emotional problems, bipolar disorder, substance or alcohol abuse, family concerns, or bullying. Of note, he played with the rope for several days prior to the event. His physician felt the patient was not trying to kill himself; rather the incident was "impulsive/accidental." No autopsy performed.

Toxicity to various agents

ISR #8066959; US; 2012: This is a case report from the 2010 Annual Report of the American Association of Poison Control Centers' National Poison Data System (NPDS). A 14-year-old male experienced "prehospital cardiac and/or respiratory arrest" after an "acute/chronic exposure" of codeine (primary toxic substance), stimulant laxative, quetiapine, aripiprazole, valproic acid, lisdexamfetamine, diphenhydramine, penicillin, meloxicam, and clonidine. The report listed blood or urine levels of all suspected substances or their respective metabolites. Additionally, sertraline and norsertraline levels were detected in the patient's blood during biopsy.

Overdose

ISR #6944369; US; 2010: An 8-year-old female died "some time after" a dose increase of lisdexamfetamine from 70 mg to 100 mg daily. The event occurred an unknown time after she

initiated treatment with lisdexamfetamine 70 mg daily for an unspecified indication. No additional clinical information was provided.

"Cardiac problem"
ISR #5947621; US; 2008: A 7-year-old male died while sleeping during a camping trip with his father. The event occurred 16 months after he initiated treatment with lisdexamfetamine 30 mg daily and methylphenidate 10 mg every evening for ADHD. His physician "thought" he died due to a "cardiac problem" and that the coroner had informed the physician that the patient had a structurally abnormal heart; however, further details were not provided.

Aspiration
ISR #7244207: US; 2011: Emergency medical services personnel arrived to the patient's home, found the 8-year-old male in asystole and with emesis on his bed; thus, they believed he had aspirated. He had a history of unspecified respiratory problems and received treatment with lisdexamfetamine 70 mg and melatonin 3 mg for unspecified indications for an unknown amount of time when the event occurred. He was pronounced dead at the hospital emergency department.

Unknown
ISR # 7553409; US; 2011: A 9-year-old female experienced an unknown event resulting in death the same year she initiated treatment with lisdexamfetamine 30 mg or 40 mg daily for an unspecified indication. Her mother tried to wake her up in the morning, but she was not arousable from sleep.

8.6 APPENDIX G. SUMMARY OF REMAINING PEDIATRIC ADVERSE EVENTS (N=39)

Adverse Event	N	Labeling Status	Comments / Summary of Unlabeled Event
Accidental exposure	5	Procedure related	All five cases were literature reports from the 2010 or 2011 Annual Report of the American Association of Poison Control Centers National Poison Data System (NPDS). The cases were males and females ranging from 4-month to 3-years old, and all required hospitalization. One case detected tetrahydrocannabinol on urine drug screen and another case received concomitant risperidone and unspecified anticonvulsant.
Abnormal loss of weight, Weight gain poor	4	Labeled under Long-term suppression of growth (W&P)	Two cases reported weight loss persisted despite discontinuing treatment with lisdexamfetamine. The remaining two cases continued treatment with lisdexamfetamine; one case reported weight loss resolved after dose increase of lisdexamfetamine, and the other case reported weight loss persisted.
Alopecia	4	Not labeled	Some of the descriptions of alopecia were hair loss on scalp, eyebrows, and eyelashes; or "hair thinning/hair loss." Two cases discontinued treatment with lisdexamfetamine, but the outcomes of events were unknown. The other two cases discontinued treatment with lisdexamfetamine and the events persisted.
Angioedema, Pharyngeal edema	3	Labeled as Angioedema (CI, PM)	One case experienced pitting edema, described as swollen ankles, approximately two months after initiating treatment with lisdexamfetamine 40 mg daily for ADHD. The differential diagnoses in the ER were peripheral edema or angioedema due to lisdexamfetamine. Treatment with lisdexamfetamine discontinued and the events resolved. Both cases of pharyngeal edema were confounded. One case had a history of "hypersensitivity" and concomitant use of Coppertone Kids Continuous Spray SPF 50 to the upper part of the patient's body, which then broke out in a rash, swelling of face, ears, lips, and throat that resulted an ER visit. The second case had concomitant use of risperidone, which is also labeled for a variety of edema including angioedema.
Drug interaction	2	Not labeled	A 9-year-old male received lisdexamfetamine and sertraline concomitantly, and experienced aggressiveness that resulted in admission to an acute facility for seven days. Events resolved after treatment with sertraline discontinued and decreased dose of lisdexamfetamine. A 15-year-old female experienced seizure and tachycardia after ingesting an overdose of chlorpheniramine and dextromethorphan along with lisdexamfetamine, mirtazapine, oxcarbazepine, and sertraline. The action taken on lisdexamfetamine and outcome of events were unknown.
Dyspnea	2	Not labeled for pediatrics; Labeled for adults as Dyspnea (AR)	One case reported dyspnea resolved upon treatment discontinuation with lisdexamfetamine and dyspnea recurred with reintroduction of lisdexamfetamine; however, episodes of dyspnea were accompanied by an upper respiratory infection or cold and sinus type symptoms, unrelieved by unspecified inhalers. The second case was confounded by concomitant use of topiramate, which is labeled for dyspnea, as well as gluten intolerance. The symptoms reported were similar to those experienced with past gluten ingestion.
Fatigue	2	Labeled as fatigue (DA&D, OD)	An 8-year-old male experienced fatigue described as "rapid and extreme period of exhaustion" within 20 minutes of first dose of lisdexamfetamine 20 mg for ADHD. Treatment with lisdexamfetamine discontinued, but the outcome of event was unknown. A 9-year-old male with a history of sleep apnea that resolved after surgery four years prior to the event, experienced fatigue, described as "slept all night... unable to awaken easily... fell asleep at school..." one to two days after initiating treatment with lisdexamfetamine 30 mg daily for ADHD. Treatment with

			lisdexamfetamine discontinued and the events resolved.
Abdominal pain, Vomiting	1	Labeled as Upper abdominal pain, Abdominal cramps, Vomiting (AR, OD)	A 14-year-old male experienced severe acute abdominal pain, which resulted in hospitalization after "recently" initiating lisdexamfetamine 50 mg for an unspecified indication. Additional clinical information were not provided.
Antinuclear antibody positive	1	Not labeled	A 13-year-old male experienced Raynaud's phenomenon approximately one year after initiating treatment with lisdexamfetamine 50 mg daily for ADHD. At an unknown time, he also tested positive for antinuclear antibody. Treatment with lisdexamfetamine continued and the events persisted.
Apnea	1	Not labeled	A 12-year-old female was admitted to the intensive care unit the same day as re-initiating treatment with lisdexamfetamine 30 mg daily for ADHD. Treatment with lisdexamfetamine discontinued and the events resolved.
Blood bilirubin increased	1	Not labeled	A 12-year-old male experienced elevated bilirubin 2.1 (baseline 1.1 almost three years prior, and 1.3 about 1.5 years prior) approximately 3 years after initiating treatment with lisdexamfetamine 30 mg daily for ADHD. Confounders included concomitant use of medication labeled for cholestasis (e.g., cyproheptadine), and ate McDonald's for every meal. Treatment with lisdexamfetamine and cyproheptadine discontinued, but the event persisted.
Chromatopsia	1	Not labeled	A 9-year-old male experienced chromatopsia, described as "seeing colors... they were moving" within two weeks of initiating treatment with lisdexamfetamine 30 mg daily for ADD. Treatment with lisdexamfetamine discontinued, but the events persisted.
Drug withdrawal	1	Labeled under Dependence (DA&D)	A 9-year-old male with a history of affect disorder, Asperger's disorder, and seasonal allergy experienced "acting up when coming down off of Vyvanse" while on treatment with lisdexamfetamine 20 mg daily for impulsive behavior. As treatment, dextroamphetamine initiated and lisdexamfetamine increased to 30 mg daily, but the events persisted, despite another increase of lisdexamfetamine to 40 mg daily.
Headache	1	Not labeled for pediatrics. Labeled as Headache for adults (AR, DI)	A 9-year-ole male experienced "regular headaches" while on lisdexamfetamine 30 mg daily for the treatment of ADHD. for three months. Treatment with lisdexamfetamine discontinued and the events resolved.
Hypoaesthesia	1	Not labeled	A 7-year-old male experienced hyperhidrosis, hypoaesethesia, nausea, palpitations, and toxicity to unspecified various agents an unknown time after initiating treatment with an unknown dose of lisdexamfetamine for an unspecified indication. The events resolved on an unspecified date, but the action taken on lisdexamfetamine was unknown.
Intraocular pressure increased	1	Not labeled	A 13-year-old female experienced increase in intraocular pressure in one of her eyes, "24% to 29%," an unknown time after initiating treatment with an unknown dose of lisdexamfetamine for ADHD. Treatment with lisdexamfetamine discontinued, but the outcome of event was unknown.
Product quality issue	1	Product quality issue	An 11-year-old male experienced "withdrawal symptoms" (not further specified) when received treatment with lisdexamfetamine 70 mg every morning. His grandparents believed the events were due to "medication missing in capsule – sometimes no medication at all in them."
Pruritus	1	Not labeled	A 16-year-old female with a pertinent history of allergies "broke out in hives and a rash and itching on both legs" four days after dose increase of lisdexamfetamine from 20 mg to 30 mg. Treatment with lisdexamfetamine discontinued, but the outcome of events was unknown.

Retinal detachment, Retinal vein occlusion, Scotoma	1	Not labeled	An optometrist diagnosed a 13-year-old male with "central retinal vein occlusion of the right eye" and "exudative retinal detachment of the right eye "approximately two years after the patient initiated treatment with lisdexamfetamine, and one year after dose increase of lisdexamfetamine to 40 mg daily for ADHD. Treatment with lisdexamfetamine continued and the exudative retinal detachment resolved, but the central retinal vein occlusion persisted.
Scleroderma	1	Not labeled	A 13-year-old female experienced worsened underlying Raynaud's syndrome and diagnosed with scleroderma two months after initiating treatment with lisdexamfetamine 40 mg every morning for ADHD. Treatment with lisdexamfetamine discontinued by her rheumatologist, who believed lisdexamfetamine "may have exacerbated her Raynaud's or brought on the scleroderma." The outcome of events was unknown.
Stevens-Johnson Syndrome (SJS)	1	Labeled as SJS (CI, PM)	A 9-year-old male experienced SJS 1.5 years after initiating treatment with lisdexamfetamine 50 mg daily for ADHD. Concurrent to treatment discontinuation of lisdexamfetamine, the patient also developed a viral infection. The even resolved after one week.
Skin exfoliation	1	Not labeled	A 7-year-old male experienced "skin on all fingers/hands and feet began to peel off" an unknown time after initiating treatment with lisdexamfetamine 20 mg for ADHD. Treatment with lisdexamfetamine discontinued after one month, but the outcome of event was unknown.
Type I Diabetes mellitus (DM)	1	Not labeled	A 9-year-old male was diagnosed with DM approximately one year after initiating an unknown dose of lisdexamfetamine for ADHD. His concomitant medication was reported as "Claritin (glicalzide)." In the same year, he received various insulin regimens for the treatment of DM, a dose increase of lisdexamfetamine to 70 mg daily, and experienced unintentional weight gain of 20 pounds (85 pounds to 115 pounds); however, the order of occurrence of events was not reported. Treatment with lisdexamfetamine continued and all events persisted.
Weight increased	1	Not labeled	A 15-year-old male gained 15 pounds (115 to 130 pounds) 15 months after initiating treatment with lisdexamfetamine 30 mg twice daily. His concomitant medications were guanfacine immediate-release for anxiety and sleep issues and buprenorphine/naltrexone for drug addiction to unspecified drug. Treatment with guanfacine IR discontinued, lisdexamfetamine and buprenorphine/naltrexone continued, and weight gain persisted.

CI = Contraindications; W&P = Warnings and Precautions; AR = Adverse Reactions; PM = Postmarketing experience; DI = Drug Interactions; DA&D = Drug Abuse and Dependence; OD = Overdosage

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/s/

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06/22/2012

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06/25/2012

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06/27/2012