Pediatric Focused Safety Review:

Vyvanse (lisdexamfetamine dimesylate)

Pediatric Advisory Committee Meeting
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Outline

- Background Information
- Relevant Safety Labeling
- Pediatric Studies
- Pediatric Labeling Changes
- Drug Use Trends
- Adverse Events
- Summary

Background Information: Vyvanse (lisdexamfetamine dimesylate)

- **Drug:** Vyvanse (lisdexamfetamine dimesylate)
- **Drug Category:** Central nervous system (CNS) stimulant
- **Indications**:
  - Attention deficit hyperactivity disorder (ADHD), 6 years and older
  - Moderate to severe binge eating disorder (BED), 18 years and older
- **Dose:** 30 mg daily (maximum dose 70 mg daily)
- **Formulation:** 10, 20, 30, 40, 50, 60, 70 mg capsules
- **Sponsor: Shire Development, Inc.**

Background Information: Vyvanse (lisdexamfetamine dimesylate)

February 23, 2007: Original market approval

April 23, 2008: Approval in adults

November 10, 2010: Approval in adolescents

- Prompted PREA mandated safety review

April 26, 2013: Approval for ADHD maintenance

- PREA requirements fulfilled for all age groups; impetus for today's PAC review and presentation

January 30, 2015 Approval for BED in adults

Relevant Safety Labeling: Vyvanse (lisdexamfetamine dimesylate)

WARNING: ABUSE AND DEPENDENCE

CNS stimulants (amphetamines and methylphenidate-containing products), including VYVANSE, have a high potential for abuse and dependence. Assess the risk of abuse prior to prescribing and monitor for signs of abuse and dependence while on therapy *[see Warnings and Precautions (5.1, 5.2), and Drug Abuse and Dependence (9.2, 9.3)]*.

Section 4 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 inhibitors (MAOI) or administration of VYVANSE within 14 days of the last MAOI dose. Hypertensive crisis can occur *[see Drug Interactions (7.2)]*.

Relevant Safety Labeling: Vyvanse (lisdexamfetamine dimesylate)

Section 5 Warnings and Precautions

5.1 Potential for Abuse and Dependence

5.2 Serious Cardiovascular Reactions

5.3 Blood Pressure and Heart Rate Increases

5.4 Psychiatric Adverse Reactions

5.5 Suppression of Growth

5.6 Peripheral Vasculopathy, including Raynaud's Phenomenon

Pediatric Studies: Vyvanse (lisdexamfetamine dimesylate)

- Short-term multicenter, randomized, double-blind, placebo- and active-controlled safety and efficacy study (6 years to 17 years; n= 336)
  - 80.7% male and mean age 10.9 years
  - Significantly greater baseline improvement in ADHD-Rating Scale-IV Total Score after 7 weeks in Vyvanse-vs. placebo-treated patients (-24.7 vs. -6.3; $p<0.001$)
  - Safety profile similar to overall safety profile

Pediatric Studies: Vyvanse (lisdexamfetamine dimesylate)

- 26-week, multicenter, double-blind, placebo-controlled, randomized withdrawal study (6 years to 17 years of age; n=276)
  - 76.8% male and mean age 10.9 years
  - Significantly lower proportion of treatment failures in Vyvanse- vs. placebo-treated patients (15.8% vs. 67.5%;$p<0.001$)
  - Reported adverse events consistent with known safety profile

Pediatric Labeling Changes: Vyvanse (lisdexamfetamine dimesylate)

- **8.4 Pediatric Use**

  ADHD

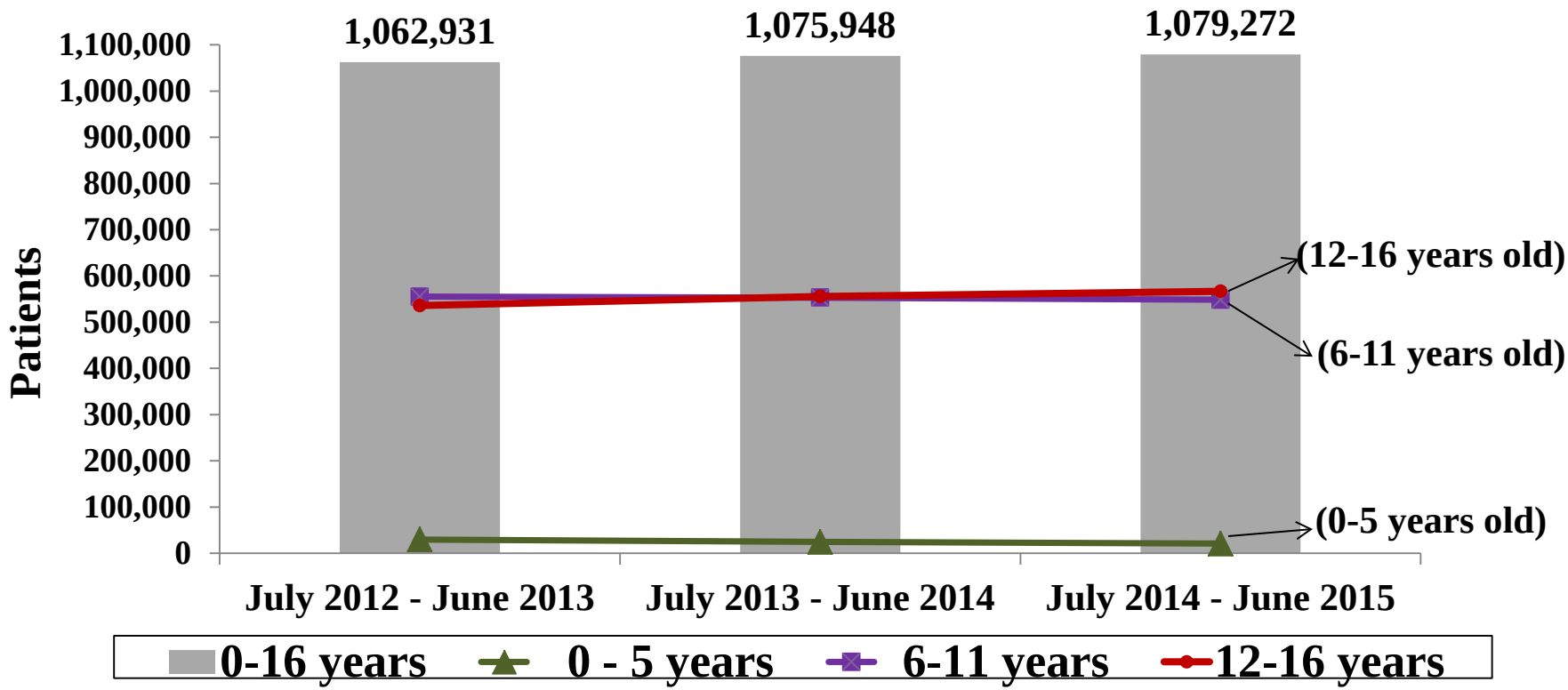
  Safety and effectiveness have been established in pediatric patients with ADHD ages 6 to 17 years *[see Adverse Reactions (6.1), Clinical Pharmacology (12.3), and Clinical Studies (14.1)].* Safety and efficacy in pediatric patients below the age of 6 years have not been established.

  BED

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

Pediatric Drug Utilization: Vyvanse

Nationally estimated number of pediatric patients (0-16 years) who received a dispensed prescription for lisdexamfetamine dimesylate from U.S. outpatient retail pharmacies, from July 2012 - June 2015, yearly



Source: IMS Total Patient Tracker (TPT), Extracted FEB2016

Drug Utilization: Vyvanse

Top Prescribing Specialties and Diagnosis Data: July 2012- June 2015

- Top Prescribing Specialties Data [1]
  - Psychiatry (31% of prescriptions)
  - Pediatricians (26% of prescriptions)
  - General Practice/Family Practice/Doctor of Osteopathy (22% of prescriptions)
- Diagnosis Data (0-5 years, 6-11years and 12-16 years)[2]
  - Attention Deficit Disorder (ICD-9 314.0)
    - 96.4% (< 6 years), 99.0% (6-11 years), 99.0% (12-16 years)

[1]Source: IMS Health, National Prescription Audit (NPA). Extracted Oct 2015.

[2]Source: Encuity Research, LLC., TreatmentAnswers™. Extracted Oct 2015.

Adverse Events: Vyvanse (lisdexamfetamine dimesylate)

(April 10, 2012‡ - June 30, 2015)

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

** May include duplicates and transplacental exposures, and have not been assessed for causality*

† Serious adverse drug experiences per regulatory definition (CFR 314.80) include outcomes of death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, and other serious important medical events.

§ One additional report of pediatric death was identified among reports not providing an age.

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

Adverse Events:
Vyvanse (lisdexamfetamine dimesylate)
Selection of Pediatric FAERS Cases

Total Pediatric Reports Reviewed (n=429)

Age 0 to < 6 years (n=40)
Age 6 years to < 17 years (n=389)

Excluded Reports (n=214)*

Fatal
Duplicate reports (n=15)
No lisdexamfetamine use at time of death (n=1)
Received before April 10, 2012 (n=1)
Non-Fatal
Labeled events in 6 years to < 17 years (n=141)
Duplicate reports (n=32)
Did not receive lisdexamfetamine when adverse event occurred (n=11)
Duplicate of a case received before April 10, 2012 (n=4)
No adverse event reported with lisdexamfetamine (n=8)
More than 1 case in report (n=1)

Pediatric Case Series (n=215)

Age 0 to < 6 years
(n=30; 1 fatal report)

Age 6 years to < 17 years
(n=185; 7 fatal reports)

* Reviewed and excluded for the reasons listed

Adverse Events: Vyvanse (lisdexamfetamine dimesylate)

Summary of Fatal Cases (n=8)

Median age 14 years (3 months to 16 years)

Suicide (n=4)

Homicide (n=1)

Vascular disorder (n=1)

Unknown (n=2)

September 11, 2012 PAC Presentation

Summary of Shire Reviews of Spontaneous Postmarketing Pediatric Suicide-Related Events for Vyvanse

Shire Global Safety System (SGSS) database†

	Number of Patients	C-CASA* Criteria	Pediatric Patients	Suicide Attempt	Completed Suicide
Through May 2008	151	22	13 (6-16 years)	3	0
June 2008 – January 2009	116	15	10 (9-14 years)	0	0

* Columbia Classification Algorithm of Suicide Assessment

† Suicide-Related Events and Treatment with Stimulant Medications Indicated for Attention Deficit Hyperactivity Disorder. Shire Pharmaceutical Development, December 09, 2008

Summary of All Non-Fatal Adverse Events (< 6 years; n=29)

Labeled Events (n=17)

5 Warnings and Precautions

5.4 Psychiatric Adverse Reactions (n=7)

6 Adverse Reactions

Affect lability	(n=2)
Dermatillomania	(n=1)
Agitation	(n=1)
Irritability	(n=1)
Tic	(n=2)
Tachycardia	(n=1)
Palpitations	(n=1)
Psychomotor Hyperactivity	(n=1)

Unlabeled Events (n=7)

Suicidal ideation/self-injurious behavior	(n=2)
Social avoidant behavior	(n=1)
Drug ineffective	(n=2)
Drug effect increased	(n=1)
Dystonia	(n=1)

Other (n=5)

Accidental exposure	(n=4)
Overdose	(n=1)

Adverse Events: Vyvanse (lisdexamfetamine dimesylate)

Summary of Non-Fatal Serious Unlabeled Events

(by System Organ Class)

(6 years to less than 17 years; n=178)

Psychiatric Disorders	(n=73)
Nervous System Disorders	(n=25)
Cardiac Disorders	(n=20)
Skin and Subcutaneous Tissue Disorders	(n=6)
Other System Organ Classes	(n=54)

Adverse Events: Vyvanse (lisdexamfetamine dimesylate)

Psychiatric Disorders: Serious Unlabeled Events

(6 years to less than 17 years; n=73)

Suicidal/Self-Injurious/Behavior/Ideation, Intentional Overdose	(n=52)
Anger	(n=9)
Homicidal Ideation, Violence-Related Symptom	(n=6)
Trichotillomania	(n=1)
Bipolar Disorder	(n=1)
Head Banging	(n=1)
Logorrhea	(n=1)
Memory Impairment	(n=1)
Social Avoidant Behavior	(n=1)

Adverse Events: Vyvanse (lisdexamfetamine dimesylate)

Nervous System Disorders: Serious Unlabeled Events

(6 years to less than 17 years; n=25)

Loss of Consciousness/Syncope (LOC) (n=12)

- 4 cases with inadequate data for assessment
- 5 cases involved concomitant use of drugs labeled for LOC, prior history of anemia/dizziness, or possible alternative cause
- 3 cases without risk factors for LOC had normal cardiac evaluations

Adverse Events: Vyvanse (lisdexamfetamine dimesylate)

Nervous System Disorders: Serious Unlabeled Events

(6 years to less than 17 years; n=25)

Incoherent/Speech Disorder/Unresponsive to Stimuli	(n=4)
No consistent pattern on clinical review	
Hypoaesthesia	(n=2)
Myasthenia Gravis	(n=2)
Neuroleptic Malignant Syndrome	(n=2)
Extrapyramidal Disorder/Dystonia	(n=2)
Hypersomnia	(n=1)

Adverse Events: Vyvanse (lisdexamfetamine dimesylate)

Cardiac Disorders: Serious Unlabeled Events

(6 years to less than 17 years; n=20)

Chest Discomfort, Chest Pain (n=12)

- 4 cases with inadequate data for assessment
- 3 cases reported underlying medical conditions (e.g. history of asthma, reaction consistent with gluten exposure in patient with celiac disorder)
- 5 cases underwent cardiac evaluations
  - 4 cases with normal cardiac evaluation
  - 1 case that showed “heart murmur and one artery of the heart was larger than the others”

Adverse Events: Vyvanse (lisdexamfetamine dimesylate)

Cardiac Disorders: Serious Unlabeled Events

(6 years to less than 17 years; n=20)

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

- 1 case had atrial septal defect and cardiomyopathy of unknown duration
- 1 case with inadequate data for assessment
- 1 case with ongoing right bundle branch block

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

- 3 cases with known cardiovascular disease

Bradycardia (n=1)

Postural Orthostatic Tachycardia Syndrome (n=1)

Adverse Events: Vyvanse (lisdexamfetamine dimesylate)

Skin & Subcutaneous Disorders:

Serious Unlabeled Events

(6 years to less than 17 years; n=6)

Alopecia (n=3)

- 2 cases with diffuse scalp alopecia with apparent dechallenge and no rechallenge information
- 1 case with alopecia areata with unknown outcome

Skin Exfoliation (n=2)

Henoch-Schonlein Purpura (n=1)

Summary:
Vyvanse (lisdexamfetamine dimesylate)

- This concludes the pediatric focused safety review
- Possible signal for alopecia to undergo further FDA review with results to be presented at future PAC meeting
- FDA recommends continuing ongoing surveillance
- Does the Committee concur?

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