Pediatric Focused Safety Review Kapvay™(clonidine hydrochloride) Pediatric Advisory Committee Meeting September 11, 2012

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Food and Drug Administration

Outline

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

Background Drug Information Kapvay™ (clonidine hydrochloride)

- **Drug:** Kapvay™ (clonidine hydrochloride)
- **Therapeutic Category:** Alpha 2 adrenergic agonist
- **Indication**: Treatment of attention deficit hyperactivity disorder (ADHD)
  - Monotherapy
  - Adjunctive therapy to stimulant medications
  - Children 6 to 17 years of age

Background Drug Information
Kapvay™ (clonidine hydrochloride)

Other formulations

- Jenloga™ extended release tablet (Treatment of hypertension)

  Note: product has been never been marketed

- Catapres® oral and transdermal (Treatment of hypertension)
- Duraclon® injection (Severe pain in cancer patients)

Background Drug Information
Kapvay™ (clonidine hydrochloride)

- **Sponsor:** Shionogi Inc.
- **Formulation:** Extended-Release tablets, 0.1 and 0.2 mg
- **Dose:**
  - Starting dose: 0.1 mg tablet at bedtime
  - Maximum dose: 0.4 mg/day
  - Must be swallowed whole and never crushed, chewed or cut.
  - Not interchangeable with immediate release

*Effectiveness > 5 weeks has not been evaluated

Background Drug Information (continued)
Kapvay™ (clonidine hydrochloride)

- **Original market approval**
  - Clonidine September 3,1974
  - Kapvay™/Jenloga™ September 29, 2009
- **Pediatric labeling changes**
  - September 28, 2010: approval of Kapvay™ ER for the treatment of ADHD in children and adolescents 6 to 17 years
- **PREA Post Marketing Studies (PMR)**
  - Juvenile animal study of clonidine in combination with a stimulant (Final Report Submission: April 2013)
  - Randomized withdrawal, long-term maintenance of efficacy (Final Report Submission: December 2013)

Pediatric Efficacy Studies
Kapvay™ (clonidine hydrochloride)

Two Randomized, Double Blind, Placebo Controlled, 8 weeks Efficacy Studies in pediatric patients aged 6 to 17 years:

- Fixed Dose Monotherapy (n= 236)
  Dose: 0.2 mg/day (n=78), 0.4 mg/day (n=80) or placebo (n=78)
- Flexible Dose Adjunctive to psycho-stimulants (n= 198)
  Dose: 0.1- 0.4 mg/day

Results

Treatment groups in both studies demonstrated significant improvement over placebo in ADHD Rating Scale total score at end of 5 week

Pediatric Safety Study
Kapvay™® (clonidine hydrochloride)

- Multi center, open-label, flexible dose, chronic exposure evaluation of safety
- Children and adolescents aged 6 to 17 years (n=301)
- Duration: 12 months
- No deaths
- One case of suicidal behavior (no additional information)

Relevant Safety Labeling
Kapvay™ (clonidine hydrochloride)

4 **Contraindications**: known hypersensitivity to clonidine

5 **Warnings and Precautions**

5.1 Hypotension and Bradycardia

5.2 Sedation and Somnolence

5.3 Abrupt discontinuation may lead to withdrawal effects

5.4 Allergic reactions (rash, urticaria or angioedema)

5.5 Use with caution in patients with vascular disease, cardiac conduction disease, or renal failure

5.6 (Do not use with) Other clonidine-containing products

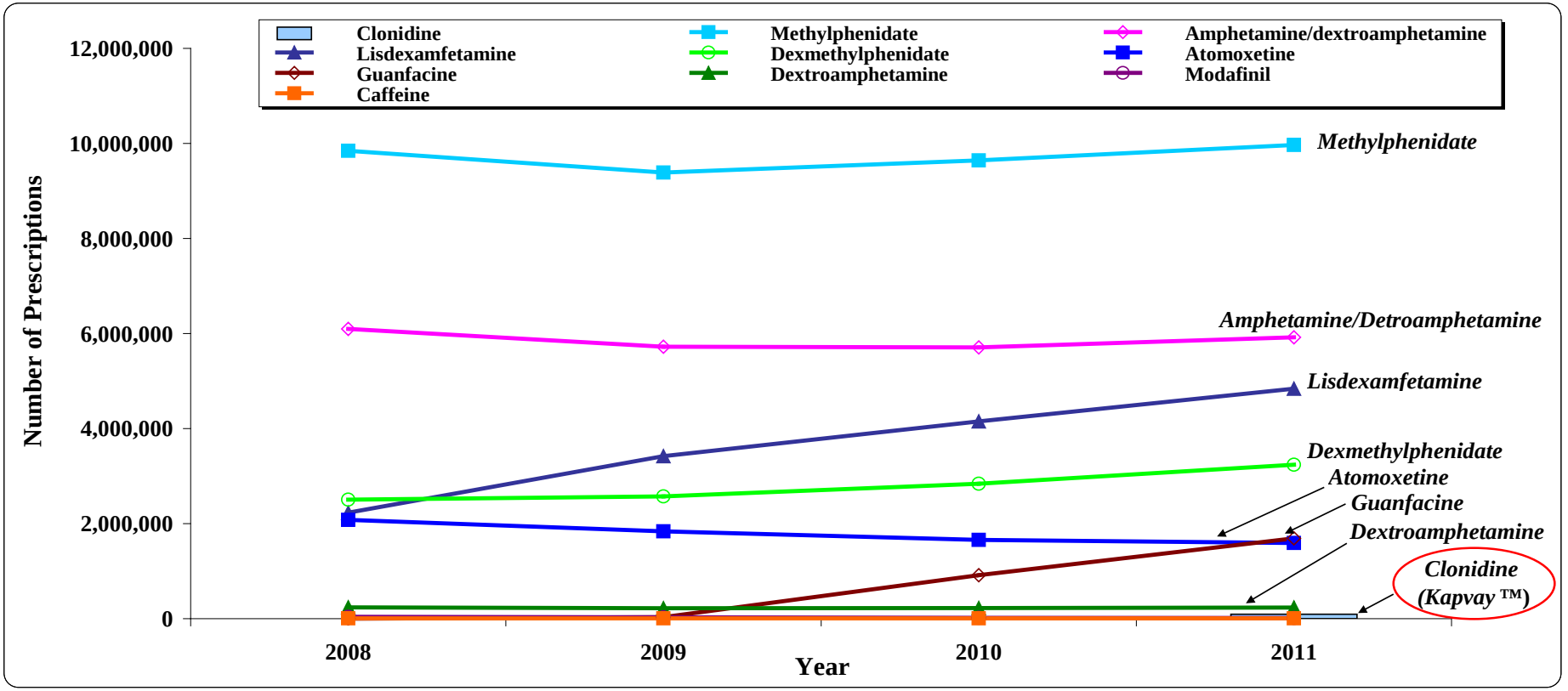
Relevant Safety Labeling
Kapvay™ (clonidine hydrochloride)

6.1 Adverse Reactions: Clinical Trial Experience

Most common	Less common (< 3%)	Leading to discontinuation
Somnolence 30-38%	Emotional disorder and rash	Somnolence/sedation (5%)
Headache (19-29%)	Constipation, and abdominal pain	Fatigue (4%)
Fatigue (13-16%)	Nasal congestion	Tactile hallucinations, vomiting, prolonged QT, increased heart rate and rash (1%)
Irritability (6-9%)	Bradycardia and tachycardia	
Sleep terror, disturbance or, nightmares (3-9%)	Tremors	
Insomnia (4-6%)	Enuresis	

ADHD Market: Kapvay™ Pediatric Utilization

Nationally Estimated Number of Prescriptions for Top ADHD Molecules (USC Classes 64500 and 64700) Dispensed to Patients Aged 0-17 years from U.S. Outpatient Retail Pharmacies, Y2008-Y2011



- Methylphenidate products were the most commonly dispensed medication among patients aged 0-17 years in the ADHD market
- During year 2011, Clonidine (Kapvay™) accounted for less than 1% of the ADHD market

[1]IMS, Vector One®: National (VONA). Year 2008 to Year 2011. Data Extracted May 2012.

Kapvay™ Drug Utilization

Prescriptions and Patients

U.S. Outpatient Retail Pharmacy Setting

September 2009 – March 2012, cumulative[1]

	Prescriptions N	Share %		Patients N	Share %
KAPVAY™ TOTAL MARKET	**158,118**	**100.0%**		**49,378**	**100.0%**
0-17 years	**147,967**	**93.6%**		**45,475**	**92.1%**
0-5 years	9,991	6.8%		3,744	8.2%
6-17 years	137,976	93.2%		42,197	92.8%
18 years and older	**10,150**	**6.4%**		**4,095**	**8.3%**
Unspecified Age	**2**	**0.0%**		**2**	**0.0%**

*** Patient age subtotals** may not sum exactly due to patients aging during the study ("the cohort effect"), and may be counted more than once in the individual age categories. For this reason, summing across time periods or patient age bands is not advisable and will result in overestimates of patient counts.

[1]IMS, Vector One®: National VONA and Total Patient Tracker. September 2009 through March 2012. Data Extracted May 2012.

Kapvay™ Drug Utilization

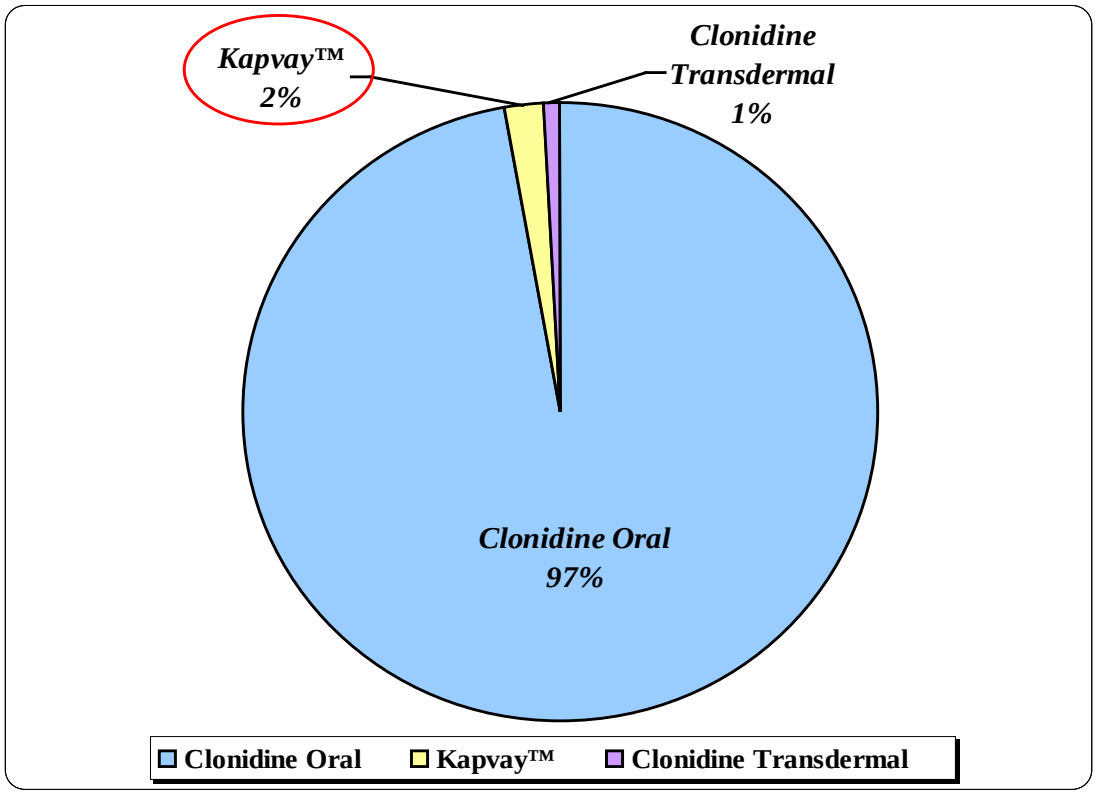
Prescribing Specialty and Diagnosis

September 2009 – March 2012, cumulative[1]

- Top prescribing specialty for Kapvay™ prescriptions:
  - Psychiatry accounting for 49% of prescriptions
  - Pediatrics accounted for 26% of prescriptions
- Top diagnosis code associated with the use of Kapvay™ in pediatric patients aged 0-17 years was “Attention Deficit Disorder” (ICD-9 code 314.0)

[1]IMS, Vector One®: National (VONA) and Encuity, Physician Drug and Diagnosis with Pain Panel. September 2009 through March 2012. Data Extracted May 2012.

Clonidine Prescriptions Dispensed to Patients Aged 0-17 Years for All Indications by Product and Formulation U.S. Outpatient Retail Pharmacy Setting September 2009 – March 2012, cumulative[1]



[1]IMS, Vector One®: National VONA. September 2009 through March 2012. Data Extracted June 2012.

Top 5 Diagnoses Associated With the Use of Clonidine (excluding Kapvay™) U.S. Office-Based Physician Survey Data February 2007 – March 2012[1]

- **Patients 0-5 years**
  - Sleep Disturbances
  - ADHD
  - Conduct Disturbances
  - Manic Depressive
  - Medical Exam Not Elsewhere Classified
- **Patients 6-17 years**
  - ADHD
  - Sleep Disturbances
  - Bipolar Disorders
  - Tics
  - Other Adjustment Reactions

[1]Encuity Research, LLC., Physician Drug and Diagnosis with Pain Panel. September 2009 through March 2012. Data Extracted May 2012.

Total Number[1] of Kapvay™ Adverse Event Reports Since Approval Reports received up to April 9, 2012

Table 2. Total number of AERS reports[1] (reports received up to April 9, 2012)[2]			
	All reports (US)3	Serious[4] (US)	Death (US)
Adults (≥17 years)	0 (0)	0 (0)	0 (0)
Pediatrics (0-16 years)	9 (9)	9 (9)	0 (0)
Age unknown (null values)	11 (11)	11 (11)	0 (0)
Total	20 (20)	20 (20)	0 (0)

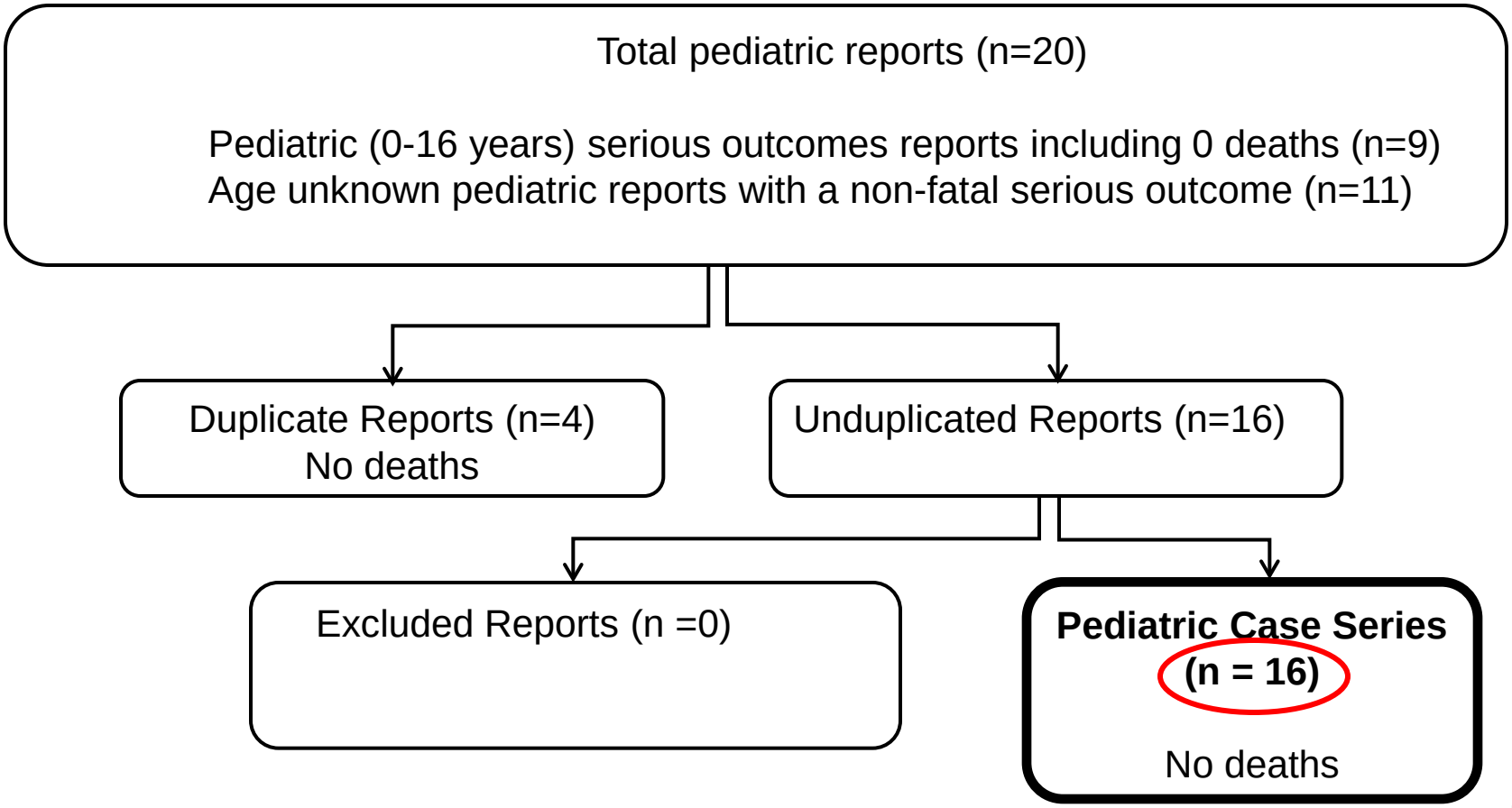
[1] May include duplicates and have not been assessed for causality

[2] The FDA approved Kapvay on September 29, 2009; however, this search captures all reports in the AERS database up to April 9, 2012

[3] US counts in parentheses

[4]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

Kapvay™ (clonidine hydrochloride) Selection of Serious Pediatric AERS Cases



Kapvay™ (clonidine hydrochloride) Non-Fatal Adverse Events

Psychiatric (n=7)

Cardiovascular (n=5)

Neurologic (n=2)

Anaphylactic reaction (n=1)

Medication error (n=1)

Kapvay™ (clonidine hydrochloride) Non-Fatal Psychiatric Adverse Events

Hallucinations (n=4)

9 year-old male experienced visual hallucinations

- Concomitant methylphenidate
- Event resolved after treatment with Kapvay was discontinued

11 year old male experienced visual hallucinations

- Past medical history: autism spectrum disorder, anxiety, developmental delay, and seizures
- Multiple concomitant medications including trazadone
- Kapvay discontinued. No information on outcome.

Both trazodone and methylphenidate are labeled for hallucinations
Unlabeled adverse events are underlined

Kapvay™ (clonidine hydrochloride)
Non-Fatal Psychiatric Adverse Events (continued)

Hallucinations (continued) (n=4)

6 year old female experienced hallucinations nine days after taking Kapvay

- Concomitant clonidine IR
- The event resolved after Kapvay™ and clonidine IR were discontinued

6 year old male experienced nightmares, and "somnambulism" "waking up screaming about monsters and spiders" 6 days after taking Kapvay™

- Concomitant lisdexamfetamine for 15 months
- The events resolved 6 days after Kapvay™ was discontinued

Labeling: Kapvay™ 6.1 Adverse events during clinical trials: nightmares and formication
Clonidine IR 6.2 Adverse Events during Clinical Trials: hallucinations
Lisdexamfetamine 5.3: hallucinations

Kapvay™ (clonidine hydrochloride)
Non-Fatal Psychiatric Adverse Events (continued)

Self injurious behavior (n=1)

11 year-old male with ADHD and Asperger's syndrome

- Concomitant clonidine IR and lisdexamfetamine
- After starting Kapvay™, "tried to staple his lip" and "wrap the strap of his lunch box around his wrists"
- Outcome is unknown

Substance abuse (n=1)

14 year-old male with ADHD, conduct disorder, oppositional defiant disorder, and poly-substance abuse

- Concomitant lisdexamfetamine and risperidone
- One month following treatment with Kapvay™, he was admitted to a drug rehabilitation center

Kapvay™ (clonidine hydrochloride) Non-Fatal Psychiatric Adverse Events (continued)

Multiple adverse events (n=1)

4 year-old male experienced worsening of ADHD symptoms, loss of direct eye contact, dysarthria, and agitation after taking Kapvay™

- Concomitant dexmethylphenidate ER and clonidine IR
- The event resolved after discontinuing Kapvay™

Kapvay™ (clonidine hydrochloride) Non-Fatal Cardiac Adverse Events

Cardiovascular (n=5)

Asymptomatic first degree heart block (n=1)

9 year-old male with ADHD, and learning disability developed first degree AV block after starting treatment with Kapvay™

- Pre-natal exposure to cocaine and cigarettes
- Born at 29-weeks with low birth weight
- Concomitant dexmethylphenidate ER and IR
- Kapvay™ re-challenge was positive
- Kapvay™ was discontinued

Labeling 6.2: Experience with Immediate-Release Clonidine electrocardiographic abnormalities (i.e., sinus node arrest, junctional bradycardia, high degree AV block and arrhythmias)

Kapvay™ (clonidine hydrochloride) Non-Fatal Cardiac Adverse Events (continued)

Syncope (n=1)

- 10-year-old male with history of anxiety experienced headache and micturition syncope
- Concomitant methylphenidate
- Treatment with Kapvay™ was discontinued. No report on outcome.

Chest tightness (n=1)

- 9 year-old male experienced chest and stomach tightness and loss of bladder control
- Concomitant dexmethylphenidate and risperidone
- The symptoms resolved after treatment was discontinued.

Labeling 5.3: Chest tightness with abrupt discontinuation.
6.1: Adverse Events during clinical trials: enuresis

Kapvay™ (clonidine hydrochloride)
Non-Fatal Cardiac Adverse Events (continued)

Chest pain (n=1)

- 9 year-old male on Kapvay™ and lisdexamfetamine developed insomnia, chest pain and hemoptysis.
- No information on diagnosis
- Symptoms resolved after Kapvay™ was discontinued

Increased heart rate (n=1)

- 4 year-old male developed agitation and increased heart rate (178/min)
- Concomitant clonidine IR
- Treatment with Kapvay™ was discontinued
- No report on outcome

Labeling 6.1 Clinical Trial Experience: increased heart rate occurred with Kapvay™ 3% vs. 0% with placebo

Kapvay™ (clonidine hydrochloride) Non-fatal Neurologic Adverse Events

Seizures (n=2)

6 year-old male with ADHD, developmental delay, and seizure disorder. Experienced increase in seizures after lamotrigine dose was reduced by the mother

- Concomitant clonidine, lamotrigine, and risperidone.
- History of asthma, and sleep apnea
- Seizures subsequently improved after increasing lamotrigine dose

13 year-old male mentally handicapped, diagnosed with ADHD

- Concomitant amphetamine treatment
- Kapvay™ 0.1 mg. Experienced seizures one week following increasing Kapvay™ (unknown dose).
- Physician believed excessive video games "may have triggered"the patient's seizures

Vyvanse labeling 5.5: Stimulants may lower the convulsive threshold in patients with prior history of seizures, in patients with prior EEG abnormalities in absence of seizures

Kapvay™ (clonidine hydrochloride) Non-Fatal Allergic Adverse Events

Anaphylactic reaction (n=1)

7 year-old male with autism

- Two episodes of angioedema and aggressive behavior, 18 days after changing to an extended release formulations of clonidine, alprazolam and quetiapine
- The patient recovered after receiving treatment
- Clonidine IR was reinstated before his discharge

Labeling
Kapvay™ 5.4: Allergic Reactions including angioedema
Alprazolam Adverse Reactions: angioedema
Quetiapine 6.3 Post Marketing Experience: anaphylactic reaction

Kapvay™ (clonidine hydrochloride) Non-Fatal Miscellaneous Adverse Events

Medication Error (n=1)

10-year-old male experienced decrease level of consciousness, BP 84/30 mmHg, and pinpoint pupils

- Received "crushed" Kapvay™ tablets and clonidine IR
- Possible clonidine overdose

Labeling 10 Overdose: hypertension may develop early and may be followed by hypotension, bradycardia, respiratory depression, hypothermia, drowsiness, decreased or absent reflexes, weakness, irritability and miosis.

Summary Pediatric Focused Safety Review Kapvay™ (clonidine hydrochloride)

- This concludes the pediatric focused safety review.
- Pediatric labeling changes for new ADHD indication in pediatric patients 6-17 years.
- No new pediatric safety signals were identified.
- FDA recommends harmonizing the Kapvay™ label with the clonidine IR label for AV block and hallucinations.
- FDA recommends return to routine monitoring.
- Does the Committee concur?

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