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Pediatric Postmarket Adverse Event Review

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Product Name:	Kapvay (Clonidine hydrochloride) Extended-Release
Pediatric Exclusivity Approval Date:	Not Applicable
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EXECUTIVE SUMMARY

In accordance with 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 Kapvay (clonidine hydrochloride) extended-release 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 Kapvay.

Kapvay (clonidine hydrochloride) extended-release is a centrally acting alpha$_2$-adrenergic agonist indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in children and adolescents ages 6 to 17 as monotherapy or as adjunctive therapy to stimulant medications.

The Adverse Event Reporting System (AERS) database was searched for all reports of adverse events (serious and non-serious) up to the "data lock" date of April 9, 2012. AERS contained 20 reports for Kapvay. Pediatric reports represent 45% of the total (9/20).

In addition to reviewing pediatric reports (n=9), we also reviewed all reports with the age unknown (n=11) to determine if the report concerned a pediatric patient. All reports with the age unknown included information to determine that the report described a pediatric patient. After removing duplicates from the case series, we reviewed16 pediatric cases reported with Kapvay use. There were no deaths. The 16 non-fatal cases included psychiatric adverse events (n=7), cardiovascular adverse events (n=5), neurologic adverse events (n=2), anaphylactic reaction (n=1), and medication error (n=1).

The majority of the psychiatric and neurologic cases were confounded by concurrent medical conditions (insomnia, Asperger's disorder, poly-substance abuse, seizure disorder), or concomitant medications (clonidine immediate release [IR], lamotrigine, levetiracetam, lisdexamfetamine, methylphenidate, mixed amphetamine salts, montelukast). The case of anaphylactic reaction was confounded by concomitant medications (alprazolam extended-release [ER], quetiapine ER). The patient in the medication error case experienced adverse events due to inappropriate administration of the extended-release tablet.

One of the cardiovascular adverse event cases reported heart rate increased, which is a labeled event for Kapvay. The second case reported syncope; however, there was insufficient clinical information (outcome unknown) to draw any associations with Kapvay. The two cases of chest discomfort and chest pain reported concomitant medications labeled for serious cardiovascular reactions (dexmethylphenidate, lisdexamfetamine, respectively). The last case reported AV block and noted a positive dechallenge and rechallenge with Kapvay.

DPV recommends harmonizing the Kapvay label with the clonidine IR label for AV block.

1 INTRODUCTION

1.1 PRODUCT FORMULATIONS AND INDICATIONS

Kapvay (clonidine hydrochloride) extended-release tablet received FDA approval on September 29, 2009 for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in children and adolescents ages 6 to 17 as monotherapy or as adjunctive therapy to stimulant medications. (See Appendix A for a summary of clonidine formulations.)

1.2 PEDIATRIC FILING HISTORY[1]

This PREA review was triggered by three studies: CLON-301, CLON-302, and CLON-303. CLON-301 and CLON-302 were phase III evaluations of the efficacy and safety of Kapvay in the treatment of children and adolescents with ADHD as mono- and adjunctive therapy. CLON-303 was an open-label, chronic exposure evaluation of the safety of Kapvay in the treatment of children and adolescents with ADHD.

CLON-301 and CLON-302 were 5-week (8-week total, including taper down period), multi-center, parallel-group, randomized, double-blind, placebo-controlled studies. Both studies included children and adolescents aged 6 to 17 years who met the DSM-IV criteria for ADHD with a minimum score of 26 on the ADHDRS-IV questionnaire at baseline. The primary efficacy variable for both studies was the mean change from baseline in the Investigator-completed ADHDRS-IV scale total score at Week 5, or discontinuation measure if earlier than Week 5.

In CLON-301, 236 subjects were randomly assigned to three treatment groups: clonidine 0.2 mg/day (n=78), clonidine 0.4 mg/day (n=80), or placebo (n=78). The mean change from baseline to Week 5 in ADHDRS-IV in the clonidine 0.2 mg/day (-15.6) and clonidine 0.4 mg/day (-16.6) treatment groups was statistically significantly greater than in the placebo group (-7.5; $p<0.0001$). There were no deaths or nonfatal serious adverse events reported in this study. The most common treatment-emergent adverse events (TEAEs) leading to discontinuation were somnolence (n=8) and fatigue (n=6). These adverse events were reported in the clonidine 0.2 mg/day or the clonidine 0.4 mg/day treatment groups.

In CLON-302, 198 subjects were randomly assigned to two treatment groups: clonidine as an add-on to a psychostimulant (n=102) or placebo as an add-on to a psychostimulant (n=96). The mean change from baseline to Week 5 in ADHDRS-IV in the clonidine as add-on group (-15.7) was statistical significantly greater than the placebo as add-on group (-11.5; $p=0.0091$). There were no deaths reported in this study. There were three serious adverse events reported, but none of these events were attributed to the effects of the study medication.

CLON-303 was a 12-month, multi-center, open-label study of the safety of a flexible dosing regimen of clonidine in children and adolescents aged 6 to 17 years who met DSM-IV criteria for ADHD. Subjects in this study completed Study CLON-301 or CLON-302 who were good candidates for continued treatment with clonidine in the opinion of the Principal Investigator, and expressed the desire to do so. A total of 301 subjects were included in the CLON-303 Safety Population. There were no deaths reported in this study. Two subjects experienced one or more serious adverse events, such as cellulitis or suicidal behavior. The subject in the case with cellulitis was involved in a motor bike accident and

was unlikely due to a relationship with the study drug. The case with suicidal behavior was not associated with clinical signs or symptoms of a 'large overdose.' The most common TEAEs leading to discontinuation were somnolence (n=3) and headache (n=2). The five most common TEAEs reported were somnolence (n=96), headache (n=49), upper respiratory tract infection (n=39), abdominal pain upper (n=37), and fatigue (n=37).

1.3 PEDIATRIC LABELING [2]

Kapvay is currently approved for the use in children and adolescents 6 to 17 years; therefore, the entire label is relevant in the pediatric population.

2 METHODS AND MATERIALS

2.1 AERS SEARCH STRATEGY

The Adverse Event Reporting System (AERS) was searched with the strategy described in Table 1.

Table 1. AERS Search Strategy*	
Date of search	April 9, 2012
Time period of search	From approval† to April 9, 2012
Product Terms	Trade Names: Clonidine Hydrochloride (Kapvay), Kapvay Verbatim Names: Kapvay, Kapvay (Clonidine) Prolonged-Release Tablet
Additional criteria	Refer to Appendix B

* See Appendix C for description of the AERS database.
† The FDA approved Kapvay on September 29, 2009

Additionally, we searched AERS for all adverse event reports with the use of generic clonidine tablets for the indication of Attention Deficit and Disruptive Behaviour Disorders (High Level Term) from September 29, 2009 to April 9, 2012. See Appendix D for the AERS search strategy, results, and graphical representations of the top 25 preferred terms and adverse events by system organ class.

3 RESULTS

3.1 AERS REPORTS

Table 2. Total number of AERS reports* (From approval† to April 9, 2012)			
	All reports (US)	**Serious§ (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) [includes 11¶ pediatric patients]	0 (0)
Total	20 (20)	20 (20)	0 (0)

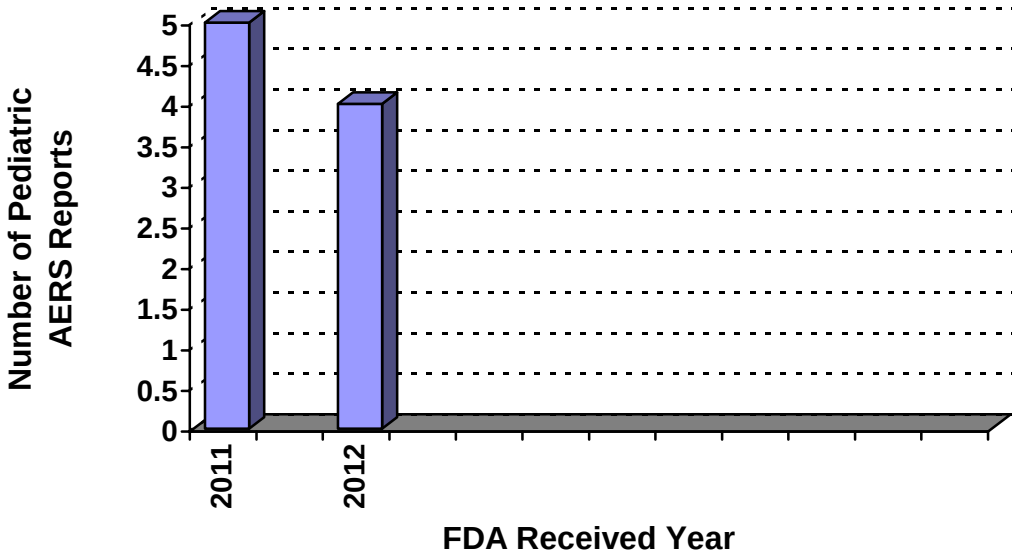
* May include duplicates and have not been assessed for causality
† The FDA approved Kapvay on September 29, 2009
§ Serious adverse drug experiences per regulatory definition (CFR 314.80) include outcomes of death, life-

threatening, hospitalization (initial or prolonged), disability, congenital anomaly, and other serious important m
events.

¶ See Figure 2

Figure 1. Total Number of Pediatric Reports (including serious and non-serious) for Kapvay, by year of FDA receipt (Reports received up to April 9, 2012) (n=9)

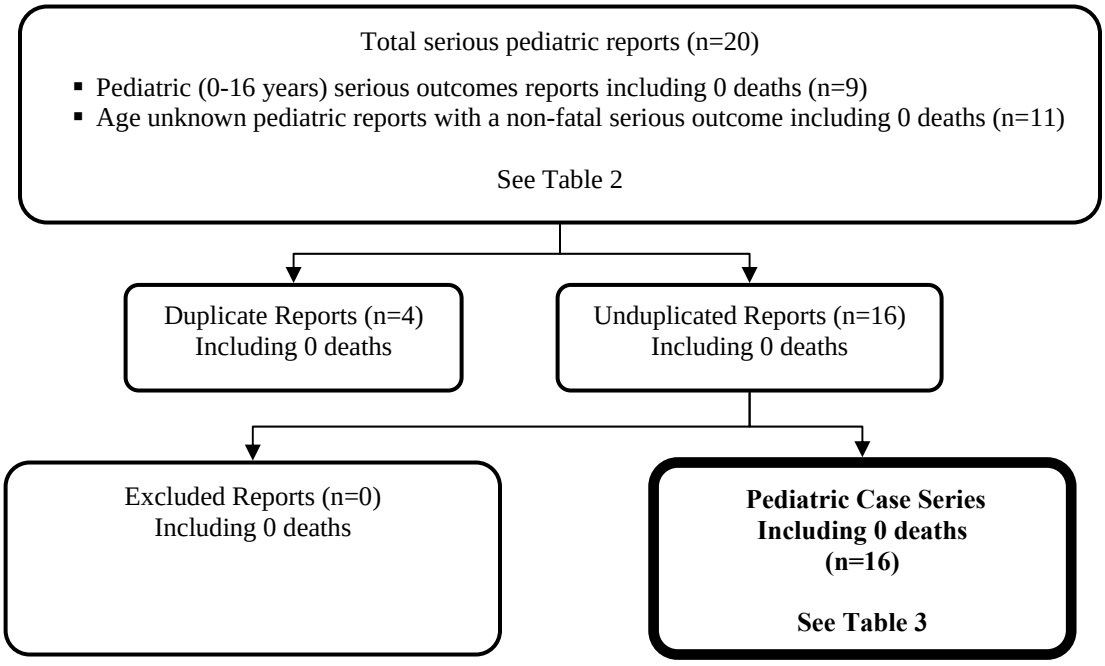
These numbers include data where age (0-16 years) is known and may contain duplicate reports.



In addition to reviewing pediatric reports with serious outcomes, we also reviewed all reports with the age unknown to determine if any reports concerned a pediatric patient. All reports with the age unknown included sufficient information to determine age, and no pediatric reports were identified.

Figure 2 below summarizes the specific selection of cases discussed in **Section 4**.

3.2 FIGURE 2. SELECTION OF SERIOUS PEDIATRIC AERS CASES



3.3 DESCRIPTIVE CHARACTERISTICS FROM PEDIATRIC CASE SERIES

Table 3 summarizes the 16 AERS cases from the Pediatric Case Series with Kapvay.

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

Table 3. Descriptive characteristics of Pediatric Case Series (Reports received up to April 9, 2012) (N=16)		
Age	0 - 1 month	0
	1 month - <2 years	0
	2-5 years	2
	6-11 years	12
	12-16 years	2
Sex	Male	15
	Female	1
Country of reporter	United States	16
Report type	Expedited	14
	Periodic	2
Event date	2011	11
	2012	1
	Unknown	4
Daily dose (n=12)	Mean dose	0.2 mg
	Median dose	0.2 mg
	Range	0.1 - 0.3 mg
Duration of therapy (n=10)	Mean	23 days
	Median	14 days
	Range	1 – 86 days
Indications	ADHD	10
	Unspecified	6
Primary Serious Outcomes*	Life-threatening	1
	Hospitalized	5
	Other serious	10

* 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=0)

There were no reports of death in any age group, or in cases where age was unknown.

4.2 SUMMARY OF ALL PEDIATRIC ADVERSE EVENTS (N=16)

4.2.1 Psychiatric Adverse Events (n=7)

We identified seven cases of psychiatric adverse events reported with Kapvay use. The psychiatric adverse events were hallucination (n=4), self-injurious behaviour (n=1), substance abuse (n=1), and multiple adverse events (n=1).

Hallucination (n=4)

- ISR #7811781: A 9-year-old male received treatment with Kapvay 0.1 mg at bedtime for ADHD and insomnia (he had not slept for 24 hours prior to initiating treatment with Kapvay). Concomitant medications included clonidine and methylphenidate. Three hours after the first dose of Kapvay, he experienced visual hallucinations of "spiders crawling all over the room and on him." Treatment with Kapvay discontinued after the first dose and the events resolved.
- ISR #7812757: An 11-year-old male with a medical history of "absence seizure sedation", autism spectrum disorder, abnormal behavior, anxiety, blunted affect, constipation, developmental delay, hyperlipidemia, increasing enuresis, increased QTc, mania, mood altered, obsessive-compulsive disorder, petit mal epilepsy, sleep disorder, and weight increased, received treatment with albuterol, cetirizine, clonidine immediate-release (IR), fluoxetine, fluticasone/salmeterol inhaler, lansoprazole, levetiracetam, melatonin, methylphenidate, montelukast, and trazodone. Approximately two months after initiating treatment with Kapvay 0.1 mg twice daily and after dose increase to 0.1 mg in the morning and 0.2 mg at bedtime, he experienced visual hallucination and "irregular sleep" described as short duration, over sedation, falls asleep for four hours followed by excess activity. He was hospitalized for visual hallucination; however, his physician noted that these events were possibly present prior to initiating treatment with Kapvay, and does not believe that the visual hallucinations were caused by Kapvay use. Treatment with Kapvay discontinued after three months of use and the sleep problem was resolving, but the outcome of other events was unknown.
- ISR #8080578: A 6-year-old female experienced hallucinations of "bugs crawling over her" and crying inconsolably nine days after initiating treatment with Kapvay 0.1 mg every morning for daytime moodiness, nervousness, "not acting her normal," and "lots of fear." The last dose of Kapvay was approximately 24 hours prior to the event. Her concomitant medication was clonidine IR 0.1 mg every evening for anxiety, sleep problems, and mood swings, which she had been taking for three months prior to initiating treatment with Kapvay. She was admitted to the hospital for observation, during which time she had no hallucinations. Treatment with Kapvay and clonidine discontinued, and the events resolved.
- ISR #8214863: A 6-year-old male experienced hallucinations, nightmares, and somnambulism six days after initiating treatment with Kapvay 0.1 mg daily for ADHD. His concomitant medication included lisdexamfetamine, which he has been taking for 15 months prior to initiating treatment with Kapvay without adverse events. The events were described as "waking up screaming about monsters and spiders." His physician discontinued Kapvay after six days of use and the events resolved.

None of the above cases of hallucinations reported re-introduction with lisdexamfetamine after discontinuation.

Self-injurious behavior (n=1)

- ISR #7762016: An 11-year-old male with a history of ADHD and Asperger's disorder received treatment with Kapvay 0.1 mg every morning. His concomitant medications included clonidine 0.2 mg at bedtime and lisdexamfetamine 70 mg every morning. Since initiating treatment with Kapvay, he has been trying to "hurt himself", described as "tried to staple his lap and wrapped the

strap of his lunch box around his hand to cut off his circulation." The action taken with Kapvay and the outcome of the event are unknown.

Substance abuse (n=1)

- ISR #7502827: A 14-year-old male with a history of ADHD, conduct disorder, oppositional defiant disorder, and poly-substance abuse initiated treatment with Kapvay 0.1 mg every night. His concomitant medications included lisdexamfetamine and risperidone. One month following initiating treatment with Kapvay, he was admitted to an "inpatient drug rehab" for substance abuse. Treatment with Kapvay, lisdexamfetamine and risperidone discontinued during admission and the event resolved. The patient's physician felt "in no way" did Kapvay contribute to patient's inpatient drug rehabilitation admission.

Multiple adverse events (n=1)

- ISR #7755361: A 4-year-old male experienced abnormal behavior ("acting like a zombie), Attention deficit/hyperactivity disorder ("worsening of ADHD symptoms"), decreased or no eye contact, dysarthria ("slurred speech"), psychotic behavior ("acting crazy and carrying on"), and social avoidant behavior ("became withdrawn") an unknown time after initiating treatment with Kapvay 0.1 mg twice daily for ADHD. His concomitant medications included dexmethylphenidate extended-release and clonidine immediate-release. Treatment with Kapvay discontinued after six weeks of use and the events resolved.

Psychiatric adverse events labeling status for Kapvay (K) and Clonidine IR (IR)[2,3]

Adverse Event	*Warnings & Precautions*	*Adverse Reactions*	*Medication Guide*
Somnolence or sedation	***K***	***K***	***K***
Insomnia		***K/IR***	***K***
Nightmare		***K/IR***	
Abnormal sleep-related event		***K***	
Sleep terror		***K***	
Sleep disorder		***IR***	
Vivid dreams		***IR***	
Hallucination		***IR***	
Other behavioral changes		***IR***	

Unlabeled Events: Decreased or no eye contact, Dysarthria, Worsening ADHD

Drug Abuse and Dependence section: Kapvay is not a controlled substance and has no known potential for abuse or dependence.

Reviewer's comments:
Three of the four hallucination cases were confounded by concomitant medications labeled for hallucination (e.g., clonidine IR, levetiracetam, lisdexamfetamine, methylphenidate, montelukast). The multiple adverse events case was also confounded by concomitant use of clonidine IR and dexmethylphenidate extended-release, which are labeled for "other behavioral changes" and "treatment emergent psychotic or manic symptoms", respectively. The self-injurious behavior and

substance abuse cases were confounded by concurrent medical conditions, such as Asperger's disorder or poly-substance abuse, respectively.

4.2.2 Cardiovascular Adverse Events (n=5)

We identified five cases of cardiovascular adverse events reported with Kapvay use. The cardiovascular adverse events were atrioventricular (AV) block first degree (n=1), syncope (n=1), chest discomfort (n=1), chest pain (n=1), and heart rate increased (n=1).

AV Block (n=1)

- ISR #8193826: A 9-year-old male with a medical history of pre-natal exposure to cocaine and cigarettes, premature birth at 29-weeks gestation, low birth weight of 3 pounds, adopted, learning disability, and ADHD, received dexmethylphenidate extended-release 20 mg twice daily and dexmethylphenidate immediate-release 5 mg every 4PM. Seven months later, his physician performed a pre-Kapvay electrocardiogram (EKG) which was 'normal' ('negative EKG'). Three months later, he initiated treatment with Kapvay 0.1 mg at bedtime and slowly titrated up to 0.2 mg twice daily in four months. Another EKG performed at 4 months of Kapvay treatment showed first-degree heart block ('positive EKG'). The physician tapered the patient off Kapvay and consulted a cardiologist, who confirmed the positive EKG, but cleared the patient for Kapvay rechallenge. One month after the positive EKG, but prior to Kapvay rechallenge,, a follow-up EKG was performed and was negative. Approximately one month following reinitiating Kapvay, another EKG was performed, which was positive for first-degree heart block. Treatment with Kapvay discontinued, and he initiated treatment with guanfacine extended-release. The physician plans to perform a follow-up EKG.

Syncope (n=1)

- ISR #8211559: A 10-year-old male received Kapvay 0.1 mg twice daily for ADHD. His past medical history was significant for anxiety, and concomitant medications were two different formulations of methylphenidate. Approximately two to three weeks following initiating treatment with Kapvay, he experienced headache, falling asleep, and micturition syncope, described as "the patient urinated, passed out, fell on the ground and experienced loss of consciousness for 60 seconds. When the patient woke up, he was tired and out of it." Treatment with Kapvay discontinued, but the outcome of events was unknown.

Chest discomfort (n=1)

- ISR #8222647: A 9-year-old male experienced sleeping in school, "could not be woken up," chest and stomach "feeling tight," and uncontrollable urination one week after initiating treatment with Kapvay 0.1 mg daily and two days after dose increase of Kapvay to 0.2 mg daily for an unspecified indication. His concomitant medications were dexmethylphenidate and risperidone. His physician examined him on the day of the event, discontinued treatment with Kapvay, and the events resolved.

Chest pain (n=1)

- ISR #7845594: A 9-year-old male received unknown doses of Kapvay for an unspecified indication. His concomitant medication included lisdexamfetamine. On an unknown date, he experienced three or four sleepless nights, chest pain for two days, and hemoptysis. The patient's father transported him to the emergency room, treatment with Kapvay discontinued, and the events resolved.

Heart rate increased (n=1)

- ISR #7895462: A 4-year-old male received Kapvay 0.1 mg at bedtime for an unspecified indication, concomitantly with clonidine IR 0.1 mg three times a day. In one day, he received two doses of clonidine IR and Kapvay 0.1 mg at bedtime. The next day, he received only Kapvay 0.1 mg at bedtime. Subsequently, he was extremely hyperactive and agitated. At the emergency room, his heart rate was 178 (units not provided). Treatment with Kapvay discontinued, but the outcome of events was unknown.

Cardiovascular adverse event labeling status for Kapvay (K) and Clonidine IR (IR)[2,3]

Adverse Event	***Adverse Reactions***
Heart rate increased or tachycardia	***K/IR***
AV block	***IR***
Syncope	***IR***
Chest pain	***IR***

Unlabeled Events: Chest discomfort

Reviewer's comments:
The AV block case noted a positive dechallenge (adverse event abated after use stopped or dose reduced) and a positive rechallenge (adverse event reappeared after reintroduction) with Kapvay. The syncope case lacked sufficient clinical information (outcome of events unknown). The chest discomfort and chest pain cases were confounded by concomitant medications labeled for serious cardiovascular reactions (dexmethylphenidate and lisdexamfetamine, respectively).

4.2.3 Neurologic Adverse Events (n=2)

We identified two cases of convulsion reported with Kapvay use.

Convulsion (n=2)

- ISR #8018275: A 6-year-old male with a medical history of ADHD, mood disorder, seizure disorder, chromosomal disorder, asthma, gastric reflux, cataracts, sleep apnea, "PE" tubes in ear and feeding tube, received treatment with clonidine, lamotrigine, and risperidone. He initiated treatment with Kapvay 0.1 mg every morning and 0.2 mg at bedtime via G-tube for ADHD. Approximately two months following initiating treatment with Kapvay, his mother decreased his lamotrigine dose and he experienced an "increased seizure activity." Subsequently, he was hospitalized for three days. His neurologist increased the lamotrigine dose, continued treatment with Kapvay, and the event resolved.
- ISR #8098766: A 13-year-old male with a medical history of ADHD and moderate mental retardation received treatment with mixed amphetamine salts. He initiated treatment with Kapvay 0.1 mg at bedtime for ADHD, and increased to 0.1 mg twice daily one month later. He experienced a seizure approximately one week following the Kapvay dose increase. The patient's father witnessed the seizure, who described the event as "[he] fell to the floor and was having convulsions which lasted 3-4 minutes." The patient was transported to the hospital via emergency services, CAT scan and "blood work-up" were performed, and both were "negative." Of note, the patient's physician also stated that the patient was playing a lot of video games which might have triggered the seizure.

Kapvay is not labeled for convulsion or seizure in therapeutic doses.

Reviewer's comments:
One of the two convulsion cases was confounded by a concurrent medical condition of seizure disorders, as well as concomitant use of lamotrigine, which is labeled for withdrawal seizures, status epilepticus, and seizure exacerbation. The second convulsion case was also confounded by concomitant use of mixed amphetamine salts, which is labeled for seizures.

4.2.4 Other Adverse Events (n=3)

The remaining three cases reported anaphylactic reaction (n=1), overdose (n=1), or urinary incontinence (n=1) with Kapvay use.

Anaphylactic Reaction (n=1)

ISR # 8042510: A 7-year-old male experienced two episodes of tongue swelling following the change from the immediate-release formulations to the extended-release formulations of alprazolam, clonidine, and quetiapine. The first episode occurred 18 days following the change in formulations and after he consumed a Lipton Black Iced Tea with lemon flavoring. Treatment included diphenhydramine and the patient recovered. The second episode occurred the day after the first episode when he was found drooling in the school bus. The school nurse reported the patient's tongue was enlarged and blue, and he was wheezing and tachycardic by the time the emergency medical services arrived. He was admitted to the hospital for anaphylaxis and aggressive behavior. Treatments included methylprednisolone, diphenhydramine, ranitidine, and discontinued all psychiatric medications. Throughout admission, he had stable vital signs, no wheezing, and no difficulty with secretions. His exam was significant for intermittent flushing and scant macular rash. The clinical impression included angioedema in addition to pre-existing autism and behavioral issues. The Allergy and Immunology consult service advised it would be safe to restart clonidine and quetiapine since the patient tolerated these medications previously. Treatment with diazepam was initiated to prevent benzodiazepine withdrawal. He was discharged with clonidine, diphenhydramine, prednisolone, epinephrine, quetiapine, and diazepam (taper off over a week). He recovered from anaphylaxis, but the outcome of aggression was unknown.

Kapvay is not labeled for anaphylactic reaction.

Contraindications section: "clonidine hydrochloride tablets should not be used in patients with known hypersensitivity to clonidine."

Warnings and Precautions: "in patients who have developed localized contact sensitization or other allergic reaction to clonidine in a transdermal system, substitution of oral clonidine hydrochloride therapy may be associated with the development of a generalized skin rash, urticaria, or angioedema."

Reviewer's comments:
This case was confounded by concomitant medications labeled for angioedema or anaphylaxis, such as alprazolam extended-release and quetiapine extended-release, respectively.

Medication Error (n=1)

ISR #8183114: A 10-year-old male received Kapvay 0.2 mg at 7 AM and an unknown dose of clonidine IR at 1 AM for unspecified indications. Subsequently, he experienced extreme sleepiness,

responsiveness only to movement, low blood pressure of 84/30 (units not provided), and pinpoint pupils. The school nurse sent him to the hospital for a possible overdose of clonidine. Upon follow up, the physician reported that pre-hospital Kapvay administration included cutting tablets in half, crushing them, for administration to the patient. Thus, the patient appeared over-sedated following inappropriate administration of the extended-release tablet.

***Dosage and Administration section*: Kapvay is an extended-release tablet and, therefore, must be swallowed whole and never crushed, cut or chewed.**

Reviewer's comments:
The case was originally coded as an overdose; however, upon follow up with the treating physician, he reported that the patient experienced adverse events due to inappropriate administration (cutting and crushing) of the extended-release tablet.

5 CONCLUSION

We reviewed 16 pediatric cases reported with Kapvay use. There were no deaths. The 16 non-fatal cases included psychiatric adverse events (n=7), cardiovascular adverse events (n=5), neurologic adverse events (n=2), anaphylactic reaction (n=1), and medication error (n=1).

The majority of the psychiatric and neurologic cases were confounded by concurrent medical conditions (insomnia, Asperger's disorder, poly-substance abuse, seizure disorder) or concomitant medications (clonidine immediate release [IR], lamotrigine, levetiracetam, lisdexamfetamine, methylphenidate, mixed amphetamine salts, montelukast). The anaphylactic reaction case was also confounded by concomitant medications (alprazolam extended-release [ER], quetiapine ER). The patient in the medication error case experienced adverse events due to inappropriate administration of the extended-release tablet.

One of the cardiovascular adverse event cases reported heart rate increased, which is a labeled event for Kapvay. The second case reported syncope; however, there was insufficient clinical information (outcome unknown) to draw any associations with Kapvay. The two cases of chest discomfort and chest pain reported concomitant medications labeled for serious cardiovascular reactions (dexmethylphenidate, lisdexamfetamine, respectively). The last case reported AV block and noted a positive dechallenge and rechallenge with Kapvay.

6 RECOMMENDATIONS

DPV recommends harmonizing the Kapvay label with the clonidine IR label for AV block.

7 REFERENCES

1. Mathews M. Clonidine hydrochloride clinical review for Attention deficit hyperactivity disorder in children and adolescents. July 15, 2010.
2. Kapvay® (Clonidine hydrochloride) tablet, extended release Prescribing Information. Shionogi Pharma, Inc. Atlanta, GA. September 2010.
3. Catapres® (Clonidine hydrochloride) tablet Prescribing Information. Boehringer Ingelheim Pharmaceuticals, Inc. Ridgefield, CT. April 2010.

8 APPENDICES

8.1 APPENDIX A. SUMMARY OF CLONIDINE FORMULATIONS

Brand Name	Formulation	NDA Number	Indication	Approval Date	Marketing Status
Kapvay	Tablet, Extended release; Oral	022331	ADHD for patients aged 6 – 17 years old	September 29, 2009	Prescription
Jenloga	Tablet, Extended release; Oral	022331	Hypertension	September 29, 2009	*Discontinued*
Catapres	Tablet; Oral	017407	Hypertension	September 3, 1974	Prescription
Catapres-TTS	Film, Extended release; Transdermal	018891	Hypertension	October 10, 1984	Prescription
Clonidine	Suspension, Extended release; Oral	022499	Hypertension	December 3, 2009	*Discontinued*
Clonidine	Tablet, Extended release; Oral	022500	Hypertension	December 3, 2009	*Discontinued*
Duraclon	Injectable; Injection	020615	In combination with opiates for the treatment of severe pain in cancer patients that is not adequately relieved by opioid analgesics alone.	October 2, 1996	Prescription

8.2 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

8.3 APPENDIX C. ADVERSE EVENT REPORTING SYSTEM (AERS)

Adverse Event Reporting System (AERS)

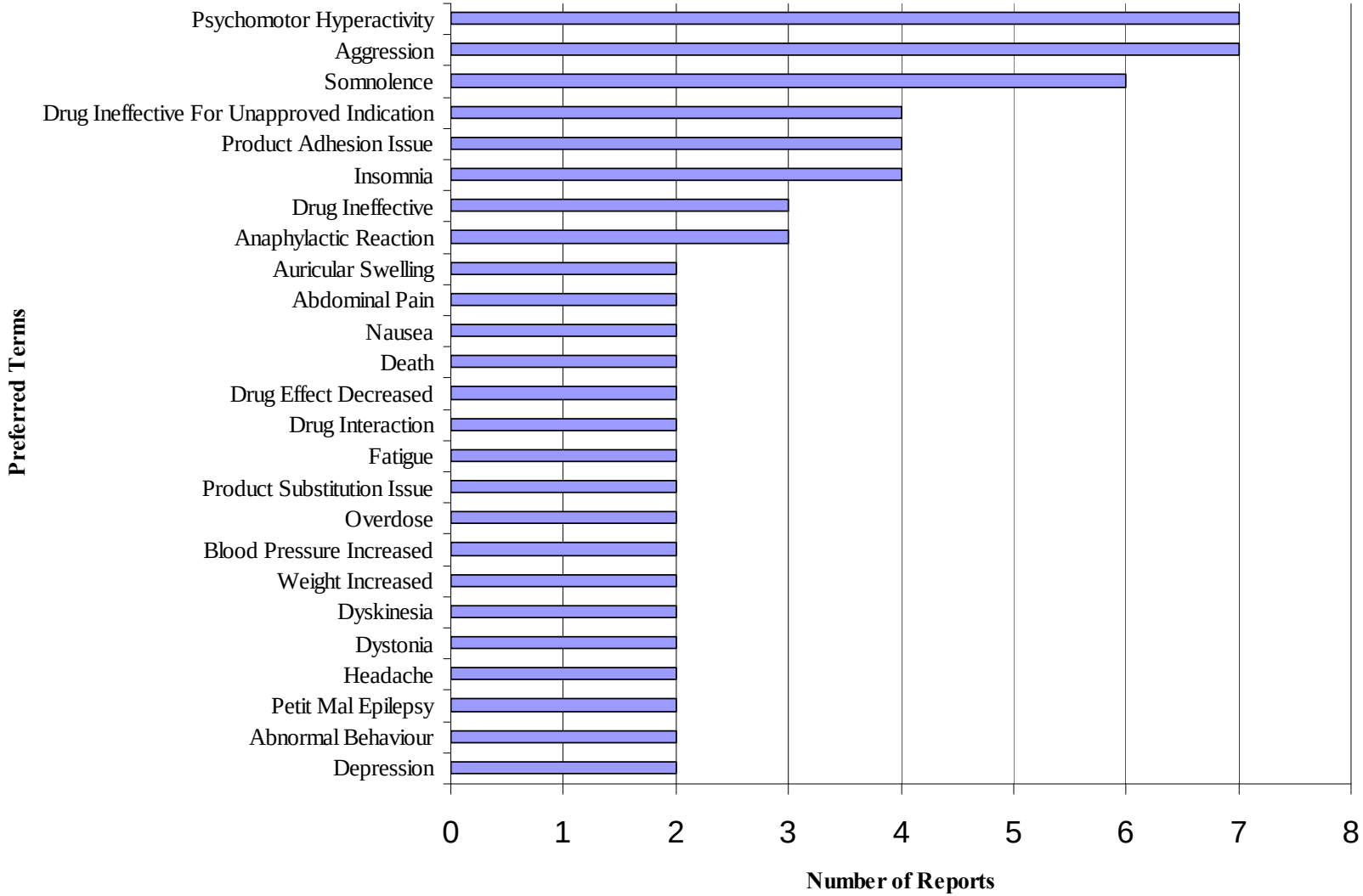
The Adverse Event Reporting System (AERS) is a computerized information database designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. The FDA uses AERS to monitor adverse events and medication errors that might occur with these marketed 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.

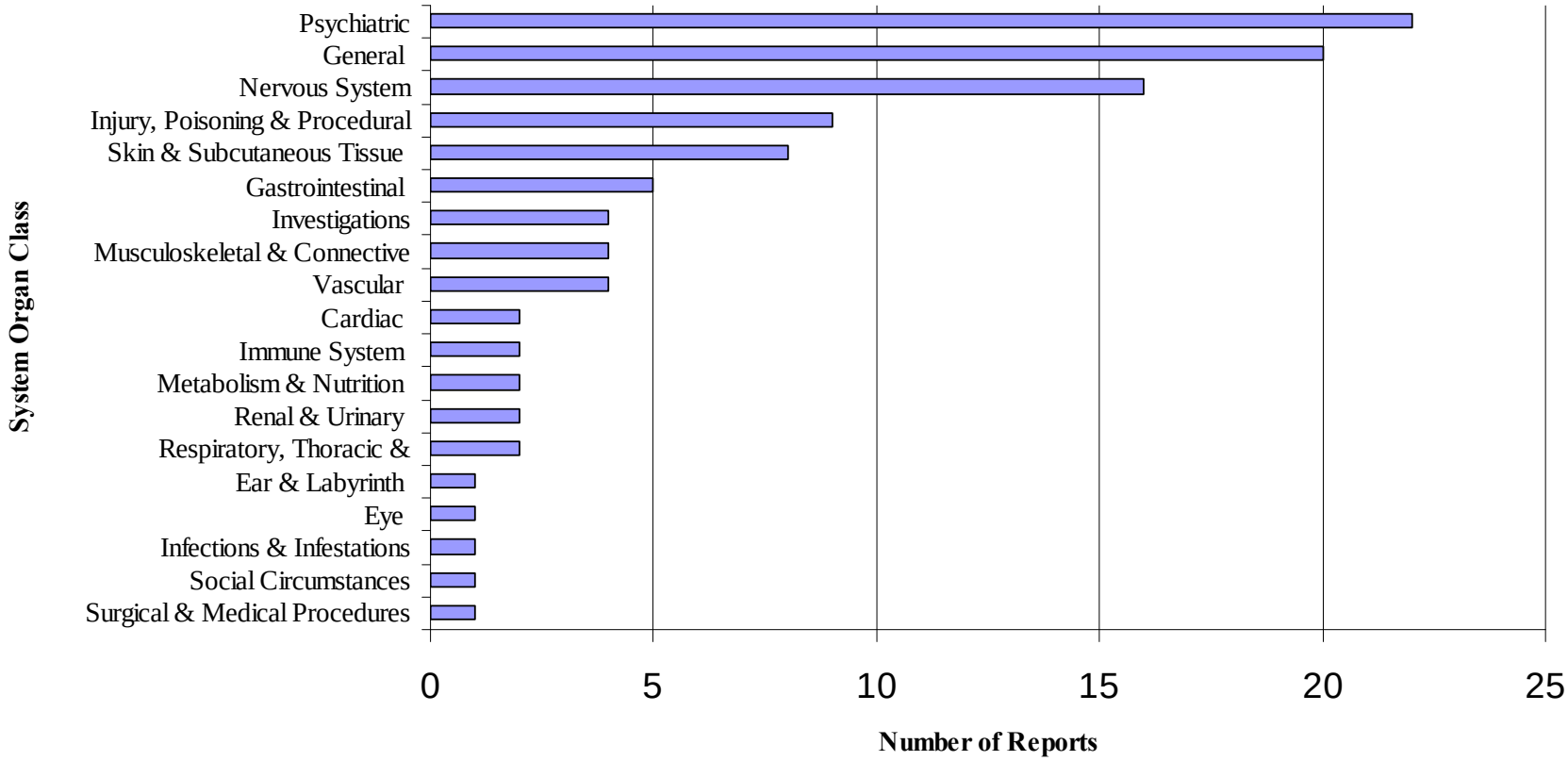
8.4 APPENDIX D. GENERIC CLONIDINE AERS SEARCH STRATEGY, RESULTS, AND GRAPHICAL REPRESENTATIONS

AERS Search Strategy and Results		
Date of search	May 18, 2012	
Time period of search	September 29, 2009 to April 9, 2012	
Product Terms	Clonidine and all associated active ingredients and verbatim names	
Advanced Product Criteria	HLT *Attention Deficit and Disruptive Behaviour Disorders* include PTs *Attention deficit/hyperactivity disorder, Atypical attention deficit syndrome, Conduct disorder, Oppositional defiant disorder*	
Reports retrieved	45	
Age	0 - 1 month	0
	1 month - <2 years	0
	2-5 years	7
	6-11 years	22
	12-16 years	2
	17-20 years	3
	Null age value	11
Sex	Male	30
	Female	10
	Unknown	5

Top 25 Preferred Terms for Generic Clonidine for the indication of ADHD
from September 29, 2009 to April 9, 2012



Adverse Events by MedDRA SOC for Generic Clonidine for All Ages for the indication of ADHD from September 29, 2009 to April 9, 2012



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

CSENUM	ISRNUM	MFRCNTRL
7959851	7502827	US-SHIONOGI, INC-2011000075
8118475	7755361	US-SHIONOGI, INC-2011000152
8143994	7762016	US-SHIONOGI, INC-2011000166
8159866	7811781	US-SHIONOGI, INC-2011000167
8179987	7812757	US-UCBSA-042895
8199268	7845594	US-SHIONOGI, INC-2011000197
8236162	7895462	2011000147
8256475	8042510	US-SHIONOGI, INC-2011000218
8256476	8098766	US-SHIONOGI, INC-2011000217
8293015	8018275	US-SHIONOGI, INC-2011000271
8361824	8080578	US-SHIONOGI, INC-2012000081
8447725	8193826	US-SHIONOGI, INC-2012000099
8452689	8183114	2011000216
8460636	8211559	US-SHIONOGI, INC-2012000101
8462891	8214863	US-SHIONOGI, INC-2012000105
8468445	8222647	US-SHIONOGI, INC-2012000112

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/s/

VICKY C HUANG
06/25/2012

IDA-LINA DIAK
06/25/2012

LINDA J SCARAZZINI
06/27/2012