

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology**

Pediatric Postmarketing Pharmacovigilance and Drug Utilization Review

Date: November 29, 2017

Safety Evaluator: Amy Chen, PharmD
Division of Pharmacovigilance-I (DPV-I)

Drug Use Analyst: Shekhar Mehta, PharmD, MS
Division of Epidemiology II (DEPI II)

Team Leaders: Thao Tran, PharmD, BCPS
Acting Team Leader, DPV-I

Rajdeep Gill, PharmD
Drug Use Analyst Team Leader, DEPI II

Deputy Directors: Monica Muñoz, PharmD, MS, BCPS
DPV-I

Grace P. Chai, PharmD
DEPI II (Drug Utilization)

Product Name: Kapvay® (clonidine extended-release) tablets

Pediatric Labeling Approval Date: November 20, 2014

Application Type/Number: 022331

Applicant/Sponsor: Concordia Pharmaceuticals Inc

OSE RCM #: 2017-820

TABLE OF CONTENTS

1	Introduction	4
1.1	Pediatric Regulatory History.....	4
1.2	Highlights of Labeled Safety Issues.....	4
2	Drug Utilization Data	5
2.1	Methods and Materials.....	5
2.1.1	Data Sources Used	5
2.2	Results.....	5
2.2.1	Determining Settings of Care.....	5
2.2.2	Patient Data.....	6
3	Postmarket Adverse Event Reports.....	7
3.1	Methods and Materials.....	7
3.1.1	FAERS Search Strategy	7
3.2	Results.....	7
3.2.1	Total Number of FAERS Reports by Age	7
3.2.2	Selection of Serious Pediatric Cases in FAERS	7
3.2.3	Characteristics of Pediatric Case Series (N=11)	8
3.3	Summary of Fatal Pediatric Adverse Event Cases (N=1).....	9
3.3.1	Psychiatric Adverse Events (N=1).....	9
3.4	Summary of Non-Fatal Pediatric Serious Adverse Event Cases (N=10).....	9
3.4.1	Lack of Effect (N=7).....	9
3.4.2	Psychiatric Adverse Events (N=2).....	10
3.4.3	Ocular (N=1).....	10
4	Discussion	11
5	Conclusion.....	11
6	Recommendations	11
7	References.....	12
8	Appendices.....	13
8.1	Appendix A. Drug Utilization Database Descriptions/Limitations	13
8.2	Appendix B. FDA Adverse Event Reporting System (FAERS)	14
8.3	Appendix C. FAERS Case Numbers, FAERS Version Numbers And Manufacturer Control Numbers For The Pediatric Case Series With kapvay (N=11)	15
8.4	Appendix D. Ten Leading Causes of Death in 2015 for Ages 0-24 Years Old	16

EXECUTIVE SUMMARY

In accordance with the Food and Drug Administration Amendments Act (FDAAA) Pediatric Research Equity Act (PREA), the Office of Surveillance and Epidemiology (OSE) evaluated postmarketing adverse event reports with a serious outcome and drug utilization data for Kapvay® (clonidine hydrochloride) extended-release (ER) tablets in pediatric patients.

Kapvay® is a centrally acting alpha₂-adrenergic agonist indicated for the treatment of attention deficit hyperactivity disorder (ADHD) as monotherapy or as adjunctive therapy to stimulant medications in pediatric patients 6 to 17 years of age.

To capture pediatric use for Kapvay® and to provide context for the adverse event cases submitted to the FDA Adverse Event Reporting System (FAERS) database, drug utilization patterns were assessed. Approximately 52,000 patients 17 years or younger received prescriptions for clonidine ER from outpatient retail pharmacies in the 12-month period from June 2016 through May 2017. Patients 17 years or younger accounted for between 81%-92% of patients receiving dispensed prescriptions for clonidine ER annually between June 2012 and May 2017. Most pediatric patients who received clonidine ER were 7-17 years old.

The Division of Pharmacovigilance (DPV) evaluated all FAERS reports of adverse events in the pediatric population received between April 10, 2012 to July 5, 2017. Eleven cases describing serious unlabeled events were identified including one death and ten non-fatal post-marketing cases. The fatal case described suicide in a 15-year-old female with multiple comorbidities and exposure to concomitant medications with labeled Warnings for suicidal ideation. Ten non-fatal cases reported drug ineffective (7), confusion (1), suicide attempt (1), and diplopia (1). All non-fatal post-marketing cases were confounded by underlying comorbidities, concurrent medication use, or contained insufficient information for assessment. No pediatric safety signals were identified.

Given the small number of events reported in the FAERS database relative to the significant utilization of Kapvay in the pediatric population, the evidence does not suggest any new safety signals associated with the use of Kapvay at this time. DPV will continue postmarketing surveillance of adverse events associated with Kapvay use in pediatric patients.

1 INTRODUCTION

In accordance with the PREA, the Division of Pharmacovigilance (DPV) was asked to summarize post-marketing reports of adverse events associated with the use of Kapvay® ER tablets in pediatric patients (0-17 years of age). The focus of this review is pediatric deaths and pediatric reports of serious unlabeled adverse events with Kapvay tablets. In addition, the Office of Pediatric and Therapeutics (OPT) requested DPV to summarize post-marketing adverse event reports associated with the use of generic clonidine ER tablets.

1.1 PEDIATRIC REGULATORY HISTORY

Kapvay®, approved by the FDA on September 29, 2009, is a centrally acting alpha₂-adrenergic agonist indicated for the treatment of ADHD in pediatric patients 6 to 17 years of age as monotherapy or as adjunctive therapy to stimulant medications.¹ Kapvay is supplied as an ER tablet in 0.1 mg and 0.2 mg strengths. Kapvay 0.2 mg tablet has been withdrawn from sale for reasons unrelated to safety or effectiveness.²

This PREA review was triggered by study SHN-KAP-401. On November 20, 2014 maintenance monotherapy for ADHD was established based on one long-term randomized monotherapy trial. SHN-KAP-401 was a 40-week, phase 4 double-blind, placebo-controlled, randomized-withdrawal study to evaluate the long-term efficacy and safety of Kapvay in children and adolescents aged 6 to 17 years with DSM-IV-TR diagnosis of ADHD.¹ Adverse events reported in this study were consistent with the known safety profile of Kapvay.³ The findings of the study were updated to include Section Clinical Trials (6.1), Use in Special Populations (8.4), and Clinical Studies (14) of Kapvay labeling.

A previous OSE pediatric postmarketing review was completed on June 25, 2012 and presented to the PAC in September 2012.⁴ This past 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 monotherapy 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. Based on these studies, the safety and efficacy of Kapvay in the treatment of ADHD was established in pediatric patients 6 to 17 years of age. The OSE reviewer recommended to harmonize the Kapvay label with the clonidine IR label for AV block. Subsequently, Kapvay was labeled for AV block under the Warnings and Precautions and Drug Interactions section of labeling. At the September 2012 PAC meeting the committee had agreed with the new labeling and recommended that Kapvay return to ongoing surveillance.

1.2 HIGHLIGHTS OF LABELED SAFETY ISSUES¹

WARNINGS AND PRECAUTIONS

- Hypotension/bradycardia/syncope: Titrate slowly and monitor vital signs frequently in patients at risk for hypotension, heart block, bradycardia, syncope, cardiovascular disease, vascular disease, cerebrovascular disease or chronic renal failure. Measure heart rate and blood pressure prior to initiation of therapy, following dose increases, and periodically while on therapy. Avoid concomitant use of drugs with additive effects unless clinically indicated. Advise patients to avoid becoming dehydrated or overheated. (5.1)
- Somnolence/Sedation: Has been observed with KAPVAY. Consider the potential for additive sedative effects with CNS depressant drugs. Caution patients against operating heavy equipment or driving until they know how they respond to KAPVAY. (5.2)

- Cardiac Conduction Abnormalities: May worsen sinus node dysfunction and atrioventricular (AV) block, especially in patients taking other sympatholytic drugs. Titrate slowly and monitor vital signs frequently. (5.5)

ADVERSE REACTIONS

Most common adverse reactions (incidence at least 5% and twice the rate of placebo) as monotherapy in ADHD: somnolence, fatigue, irritability, nightmare, insomnia, constipation, dry mouth. (6.1)

Most common adverse reactions (incidence at least 5% and twice the rate of placebo) as adjunct therapy to psychostimulant in ADHD: somnolence, fatigue, decreased appetite, dizziness. (6.1)

DRUG INTERACTIONS

- Sedating Drugs: Clonidine may potentiate the CNS-depressive effects of alcohol, barbiturates or other sedating drugs. (7)
- Tricyclic Antidepressants: May reduce the hypotensive effect of clonidine. (7)
- Drugs Known to Affect Sinus Node Function or AV Nodal Conduction: Caution is warranted in patients receiving clonidine concomitantly with agents known to affect sinus node function or AV nodal conduction (e.g., digitalis, calcium channel blockers and beta-blockers) due to a potential for additive effects such as bradycardia and AV block. (7)
- Antihypertensive drugs: Use caution when coadministered with KAPVAY. (7)

2 DRUG UTILIZATION DATA

2.1 METHODS AND MATERIALS

Proprietary drug utilization databases available to the Agency were used to conduct these analyses. Detailed descriptions and limitation of the databases are included in the Appendix A.

2.1.1 Data Sources Used

Sales Distribution Data

The IQVIA, National Sales Perspectives™ database was used to obtain the nationally estimated number of units (packages) sold for clonidine ER from manufacturers to all U.S. channels of distribution for 2016. The sales distribution data represent the amount of product sold from manufacturers to pharmacies and other settings of care; it does not reflect what is dispensed or administered to patients directly.

Outpatient Retail Setting

The IQVIA, Total Patient Tracker™ (TPT) database was used to provide the nationally estimated number of patients who received a dispensed prescription for clonidine ER oral tablets from the U.S. outpatient retail pharmacy setting from June 2012 through May 2017, and stratified by age groups (0-6 years, 7-17 years, and 18 years of age and older).

2.2 RESULTS

2.2.1 Determining Settings of Care

Sales data for by the number of packages sold from manufacturers to all U.S. settings of distribution indicated that approximately 87% of sales of total clonidine ER were to retail settings of care, 8% to non-

retail, and 5% to mail-order/specialty pharmacies for year 2016. Accordingly, utilization data from U.S. outpatient retail pharmacies were assessed for this review.^a

2.2.2 Patient Data

Table 2.2.3 shows the nationally estimated number of patients who received dispensed prescriptions for clonidine ER from U.S. outpatient retail pharmacies, stratified by patient age from June 2012 through May 2017, annually. Overall, the total number of patients gradually decreased from approximately 81,000 patients in the 12-month period ending May 2013 to approximately 65,000 patients in the 12-month period ending May 2017. Pediatric patients 0-17 years old accounted for the majority of patients, however the number and proportion of pediatric patients decreased over the examined time period. The majority of pediatric patients who received a dispensed prescription for clonidine ER were 7-17 years old for each 12-month period over the examined time.

Table 2.2.3. Nationally estimated number of patients who received a prescription for clonidine ER from U.S. outpatient retail pharmacies, stratified by patient age*, June 2012 through May 2017, annually.

	June 2012 - May 2013		June 2013 - May 2014		June 2014 - May 2015	
	Patients (N)	Share(%)	Patients (N)	Share(%)	Patients (N)	Share(%)
Grand Total	81,220	100%	71,386	100%	65,202	100%
0-17 years	74,662	91.9%	64,526	90.4%	55,728	85.5%
0-6 years	12,364	15.2%	8,398	11.8%	5,981	9.2%
7-17 years	64,593	79.5%	58,017	81.3%	51,049	78.3%
18 years and older	7,053	8.7%	7,470	10.5%	10,079	15.5%
Unknown Age	-	-	169	0.2%	443	0.7%
	June 2015 - May 2016		June 2016 - May 2017			
	Patients (N)	Share(%)	Patients (N)	Share(%)		
Grand Total	62,574	100%	65,170	100%		
0-17 years	51,966	83.0%	52,865	81.1%		
0-6 years	5,209	8.3%	5,485	8.4%		
7-17 years	47,781	76.4%	48,469	74.4%		
18 years and older	10,956	17.5%	12,299	18.9%		
Unknown Age	891	1.4%	1,040	1.6%		

Source: IQVIA Health, Total Patient Tracker™. June 2012 – May 2017. Extracted July 2017. File: TPT L 2017-820 Kapvay 8-2-2017.xlsx; TPT L 2017-820 Kapvay 00-17_8-2-2017.xlsx

*Summing across patient age bands is not advisable because this will result in overestimates of patient counts, patient age subtotals do not sum exactly (>100%) due to patients aging during the study period. Patients may be counted more than once in the individual age categories.

^a Source: IQVIA, National Sales Perspective (NSP) January 2016 – December 2016. Extracted July 2017. File: NSP 217-820 clonidine ER BPCA 08-04-17.xlsx

3 POSTMARKET ADVERSE EVENT REPORTS

3.1 METHODS AND MATERIALS

3.1.1 FAERS Search Strategy

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

Table 3.1.1 FAERS Search Strategy

Date of Search	September 7, 2017
Time Period of Search	April 10, 2012* to July 5, 2017
Search Type	Quick Query
Product Name(s) †	Product name: Kapvay Product verbatim: clonidine ER, clonidine ER 0.1 mg, clonidine ER 0.1 mg - Mfg Par, Clonidine ER 0.1 mg tablets Par, clonidine ER 0.1mg, clonidine ER 0.1mg Par Pharmaceuticals, clonidine ER 0.3 mg, clonidine ER.-generic 0.1mg, clonidine ERO.1mg Par-IS manufacture, generic clonidine ER, Kapvay clonidine ER Par NDC# 1370-0257-02
Search Parameters	NDA 022331, ANDA 202984, ANDA 203320

* End date from previous pediatric review †

† FAERS product search expanded to clonidine ER generic

3.2 RESULTS

3.2.1 Total number of FAERS reports by Age

Table 3.2.1 Total Adult and pediatric FAERS reports* from April 10, 2012 to July 5, 2017 with Kapvay

	All reports (U.S.)	Serious† (U.S.)	Death (U.S.)
Adults (> 17 years)	3(3)	2(2)	0(0)
Pediatrics (0 - ≤17 years)	66(66)	34‡(34)	1(1)

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

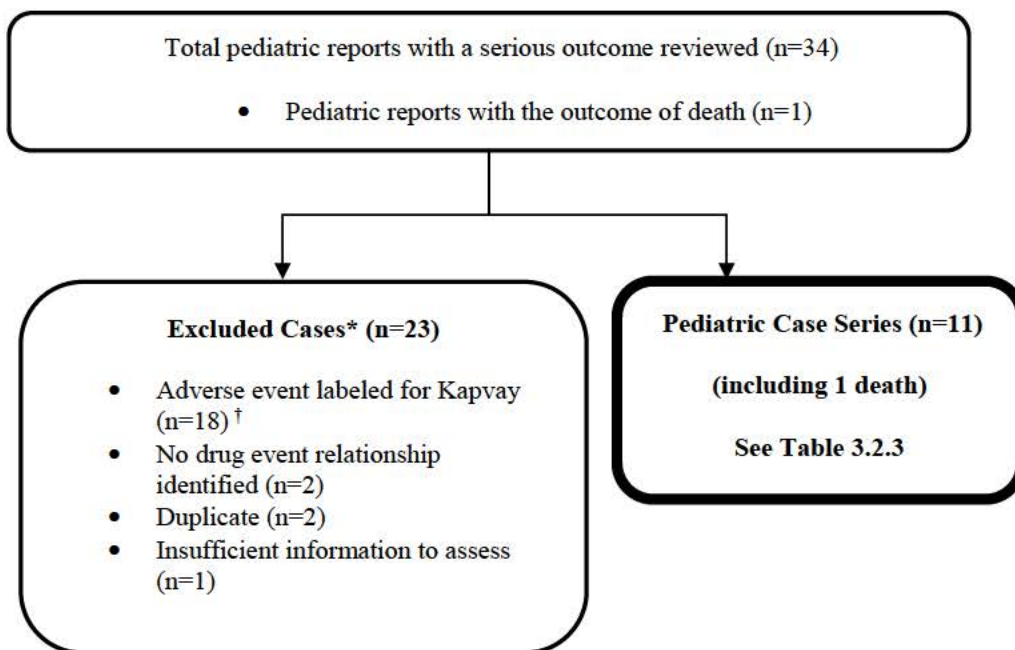
† For the purposes of this review, the following outcomes qualify as serious: death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, required intervention, and other serious important medical events.

‡ See Figure 3.2.2

3.2.2 Selection of Serious Pediatric Cases in FAERS

We identified 34 pediatric reports with a serious outcome (See Table 3.2.1). See **Figure 3.2.2** below for the specific selection of cases to be summarized in **Sections 3.3 and 3.4**.

Figure 3.2.2 Selection of Serious Pediatric Cases with Kapvay



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

† The labeled events described in more than one case included: hallucinations (4), aggression (3), and syncope (3).

3.2.3 Characteristics of Pediatric Case Series (N=11)

Appendix C lists all the FAERS case numbers, FAERS version numbers and Manufacturer Control Numbers for the Pediatric Case Series.

Age	6- <12 years	4
	12- < 17 years	7
Sex	Male	5
	Female	6
Country	United States	11
Reported Reason for Use (non-mutually exclusive)	ADHD	11
	Aggressive behavior	1
	Autism	1
Serious Outcome*	Death	1
	Hospitalized	1
	Other serious	9

* For the purposes of this review, the following outcomes qualify as serious: death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, required intervention, and other serious important medical events. Reports may have more than one outcome.

3.3 SUMMARY OF FATAL PEDIATRIC ADVERSE EVENT CASES (N=1)

3.3.1 Psychiatric Adverse Events (n=1)

We identified one case of completed suicide with the use of Kapvay.

Suicide (n=1)

- **FAERS #9303060, US, Direct, FDA Received 05/21/13**

A 15-year-old female “died as a result of completed suicide or self-injury resulting in accidental death by strangulation. No prior history of suicide attempts. Dose of Kapvay increased one month before death. The manner of death has yet to be determined by the coroner.” Medical history was significant for ADHD, oppositional defiant disorder (ODD), occasional substance use (no drugs found on autopsy), and migraines. Concomitant medications included atomoxetine, norethindrone acetate and ethinyl estradiol and ferrous fumarate kit, and gabapentin. The patient received Kapvay 0.2 mg twice daily for nine months for ADHD and was increased to an unknown dose one month before her death.

Reviewer’s comments: This patient exceeded the maximum daily dose of Kapvay (0.4 mg/day) for one month prior to her death. Causality cannot be assessed due to the limited information provided, comorbidities, and concomitant medications. Atomoxetine’s label includes a Boxed Warning for suicidal ideation and gabapentin’s label includes a Warning for suicidal behavior and ideation.

3.4 SUMMARY OF NON-FATAL PEDIATRIC SERIOUS ADVERSE EVENT CASES (N=10)

The ten non-fatal pediatric serious adverse event cases reported lack of effect (n=7), psychiatric events (confusion, n=1, suicide attempt, n=1) and ocular events (diplopia, n=1).

3.4.1 Lack of Effect (n=7)

Two of the seven cases of lack of effect reported worsening of ADHD after switching from Kapvay to clonidine ER (Par) and resolution of ADHD symptoms after switching back to brand Kapvay. The remaining five cases reporting lack of effect with clonidine ER did not provide adequate clinical information such as history of adherence to assess drug-event causality. Only two of seven cases provided lot numbers.

Reviewer’s comments: About 20–35 % of subjects in clinical trials may have an inadequate response to initial stimulant treatment.⁵ There are multiple factors that may lead to inadequate response to treatment including poor adherence, severity and/or complexity of ADHD, inadequate stimulant dosing, and dose-limiting adverse effects.⁵ Because of the multiple factors that can cause inadequate response and the background rate of inadequate response in ADHD, we cannot attribute worsening of ADHD with the use of generic clonidine ER because most of the cases did not provide adequate clinical information for drug-event causality assessment. Furthermore, the paucity of cases providing lot numbers and reporting lack of effect associated with Par clonidine ER precludes the determination of a pattern of a possible culprit manufacturer or lot.

3.4.2 Psychiatric Adverse Events (n=2)

Confusion (n=1)

- **FDA 8632478, Mfr # US-SHIONOGI, INC-2012000198, US, Expedited, FDA Received 7/11/2012**

An 11-year-old male initiated Kapvay 0.1 mg daily for ADHD. His medical history was significant for bipolar affective disorder. Concomitant medications included aripiprazole. Kapvay was increased to 0.1 mg twice daily. One week later, the patient experienced confusion manifested by dropping things and not finishing his sentences. Kapvay was decreased to 0.1 mg daily, but the confusion persisted. Confusion resolved following Kapvay discontinuation.

Reviewer's comments: This case reported the onset of confusion one week after a dose increase of Kapvay and resolution of confusion after Kapvay discontinuation. Confusion may have been attributed to hypotension, sedation, or underlying comorbidities. Limited details preclude a more definitive causality assessment.

Suicide attempt (n=1)

- **FAERS #9254822, Mfr # US-SHIONOGI, INC-2013000172, US, Expedited, FDA Received 4/25/2013**

A 15-year-old male initiated Kapvay 0.1 mg daily for ADHD. Concomitant medication included clonazepam. The mother reported he had been taking clonazepam for a while and "was doing fine." The patient attempted suicide three weeks after Kapvay initiation for which he was hospitalized. Kapvay and clonazepam were discontinued on an unknown date. At the time of the report, the patient remained hospitalized.

Reviewer's comments: Causality cannot be assessed due to limited clinical information provided, comorbidities, and concomitant medications. Clonazepam is labeled for suicidal behavior and ideation under the Warnings and Adverse Reactions.

3.4.3 Ocular (n=1)

Diplopia (n=1)

- **FAERS #8968763, Mfr # US-SHIONOGI, INC-2012000324, US, Expedited, FDA Received 1/24/2013**

An 11-year-old male initiated Kapvay 0.1 mg for ADHD. His past medical history was significant for migraine headaches and obstructive sleep apnea. Concomitant medications included ibuprofen and butalbital/acetaminophen/caffeine. The patient received Kapvay 0.1 mg QHS for 1 week which was increased to 0.1 mg BID for 1 week then 0.1 mg QAM and 0.2 mg QHS. Three weeks later, the patient experienced double vision. Kapvay was decreased to 0.1 mg BID and the double vision resolved. The patient continued to have decreased attention and increased activity. When Kapvay was increased to 0.2 mg QHS, the double vision returned. Kapvay was tapered to 0.1 mg BID for one week then 0.1 mg QHS for an unknown duration. Kapvay was discontinued three weeks later. The patient recovered from the double vision.

Reviewer's comments: This case reported a temporal relationship between the onset of diplopia and initiation of Kapvay. A positive rechallenge was reported after Kapvay was readministered. Although BP values were not reported for this patient, it is plausible the event occurred secondary to the hypotensive effects of Kapvay; however, the presence of butalbital, a barbiturate, confounds causality assessment. Additionally, migraines may also cause diplopia.

4 DISCUSSION

Approximately 52,000 patients 17 years or younger received prescriptions for clonidine ER from outpatient retail pharmacies in the 12-month period from June 2016 through May 2017. Patients 17 years or younger accounted for between 81%-92% of patients receiving dispensed prescriptions for clonidine ER annually between June 2012 and May 2017. The majority of pediatric patients who received clonidine ER were 7-17 years old. Findings from this review should be interpreted in the context of the known limitations of the databases used. We estimated that clonidine ER was distributed primarily to the outpatient setting based on the QuintilesIMS, National Sales Perspectives™ database. Accordingly, this review was focused on outpatient retail pharmacy utilization. The data provided are based on dispensed prescription claims, these data do not undergo chart validation for accuracy of abstracted information from prescription level data.

A search of the FAERS database identified four pediatric cases with serious, unlabeled adverse events received by the FDA from April 10, 2012 to July 5, 2017. One case reported a death by suicide. The patient exceeded the maximum daily dose of Kapvay (0.4 mg/day) for one month prior to the incident. This case reported a temporal relationship between the dose increase of Kapvay and suicide; however, the patient's underlying comorbidities and concomitant medications labeled for suicidal ideation may have contributed to the event. Of the three non-fatal pediatric cases of Kapvay, one case reported a suicide attempt. This case contained limited information and was confounded by concomitant use of medication labeled for suicidal behavior and ideation.

According to the Centers for Disease Control and Prevention (CDC), approximately half of children diagnosed with ADHD have underlying disorders including behavior and conduct problems, learning disorders, anxiety and depression and difficult peer relationships.⁶ Consequently, it is difficult to perform causality assessments for suicides given the high background rate of underlying comorbidities in the ADHD population. Furthermore, suicide was the third leading cause of death in youths 10-14 years old and the second leading cause of death for youths aged 15 to 24 years old in the US in 2015 (see Appendix D for the top ten leading causes of death in 2015).⁷

All non-fatal post-marketing cases were confounded by underlying comorbidities, concurrent medication use, or contained insufficient information for assessment. No pediatric safety signals were identified. Based on the paucity of pediatric Kapvay reports relative to the utilization of Kapvay during this reporting period, the evidence does not suggest any new safety signals associated with the use of Kapvay at this time.

5 CONCLUSION

Due to the small number of events reported in the FAERS database for Kapvay relative to the utilization of Kapvay in the pediatric population, no pediatric safety signals for Kapvay were identified at this time.

6 RECOMMENDATIONS

DPV will continue postmarketing surveillance of adverse events associated with Kapvay use in pediatric patients.

7 REFERENCES

1. Concordia Pharmaceuticals Inc. Kapvay Package Insert. St. Michael, Barbados: August 2016.
2. Federal Register Volume 77, No. 29, Monday, February 13, 2012 Notices
3. Glass R. NDA 22331 Kapvay Clinical Review. October 20, 2014.
4. Huang V. Kapvay ER Pediatric Postmarket Adverse Event Review. June 25, 2012.
5. Childress, A, Sallee, F. Attention-Deficit/Hyperactivity Disorder with Inadequate Response to Stimulants: Approaches to Management. CNS Drugs 2014; 28:121–129
6. Centers for Disease Control and Prevention Attention-Deficit/Hyperactivity Disorder. <http://www.cdc.gov/ncbddd/adhd/conditions.html>
7. Centers for Disease Control and Prevention Injury Prevention & Control: Data & Statistics http://www.cdc.gov/injury/wisqars/leading_causes_death.html

8 APPENDICES

8.1 APPENDIX A. DRUG UTILIZATION DATABASE DESCRIPTIONS/LIMITATIONS

IQVIA, National Sales Perspectives™: Retail and Non-Retail

The IQVIA National Sales Perspectives™ measures the volume of drug products, both prescription and over-the-counter, and selected diagnostic products moving from manufacturers into various outlets within the retail and non-retail markets. Volume is expressed in terms of sales dollars, eaches, extended units, and share of market. These data are based on national projections. Outlets within the retail market include the following pharmacy settings: chain drug stores, independent drug stores, mass merchandisers, food stores, and mail service. Outlets within the non-retail market include clinics, non-federal hospitals, federal facilities, HMOs, long-term care facilities, home health care, and other miscellaneous settings.

IQVIA, Total Patient Tracker™ (TPT):

Total Patient Tracker (TPT) is a national-level projected audit designed to estimate the total number of unique patients across all drugs and therapeutic classes in the retail outpatient setting over time. TPT derives its data from the Vector One® database which integrates prescription activity from a sample received from payers, switches, and other software systems that may arbitrage prescriptions at various points in the sales cycle. Vector One® receives over 2.1 billion prescription claims per year.

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

FDA Adverse Event Reporting System (FAERS)

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary (FPD).

FAERS data have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population

8.3 APPENDIX C. FAERS CASE NUMBERS, FAERS VERSION NUMBERS AND MANUFACTURER CONTROL NUMBERS FOR THE PEDIATRIC CASE SERIES WITH KAPVAY (N=11)

FAERS CASE NUMBER	FAERS VERSION NUMBER	MANUFACTURER CONTROL NUMBER
9303060	1	
9254822	1	US-SHIONOGI, INC-2013000172
8632478	2	US-SHIONOGI, INC-2012000198
8968763	2	US-SHIONOGI, INC-2012000324
9709372	3	US-PARPHARMACEUTICAL, INC-2013SCPR007780
10253198	1	
11300799	1	
10761501	1	
10338392	1	
10210799	1	
10338470	1	

8.4 APPENDIX D. TEN LEADING CAUSES OF DEATH IN 2015 FOR AGES 0-24 YEARS OLD

10 Leading Causes of Death, United States
2015, All Races, Both Sexes

Rank	Age Groups					
	<1	1-4	5-9	10-14	15-19	20-24
1	Congenital Anomalies 4,825	Unintentional Injury 1,235	Unintentional Injury 755	Unintentional Injury 763	Unintentional Injury 3,919	Unintentional Injury 8,595
2	Short Gestation 4,084	Congenital Anomalies 435	Malignant Neoplasms 437	Malignant Neoplasms 428	Suicide 2,061	Suicide 3,430
3	SIDS 1,568	Homicide 369	Congenital Anomalies 181	Suicide 409	Homicide 1,587	Homicide 3,146
4	Maternal Pregnancy Comp. 1,522	Malignant Neoplasms 354	Homicide 140	Homicide 158	Malignant Neoplasms 583	Malignant Neoplasms 886
5	Unintentional Injury 1,291	Heart Disease 147	Heart Disease 85	Congenital Anomalies 156	Heart Disease 306	Heart Disease 691
6	Placenta Cord Membranes 910	Influenza & Pneumonia 88	Chronic Low. Respiratory Disease 80	Heart Disease 125	Congenital Anomalies 195	Congenital Anomalies 191
7	Bacterial Sepsis 599	Septicemia 54	Influenza & Pneumonia 44	Chronic Low. Respiratory Disease 93	Influenza & Pneumonia 72	Diabetes Mellitus 144
8	Respiratory Distress 462	Perinatal Period 50	Cerebro-vascular 42	Cerebro-vascular 42	Chronic Low. Respiratory Disease 63	Chronic Low. Respiratory Disease 139
9	Circulatory System Disease 428	Cerebro-vascular 42	Benign Neoplasms 39	Influenza & Pneumonia 39	Cerebro-vascular 61	Complicated Pregnancy 120
10	Neonatal Hemorrhage 406	Chronic Low. Respiratory Disease 40	Septicemia 31	Two Tied 33	Diabetes Mellitus 52	Influenza & Pneumonia 112

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

AMY I CHEN
11/30/2017

SHEKHAR H MEHTA
12/01/2017

THAO T TRAN
12/01/2017

RAJDEEP K GILL
12/01/2017

MONICA MUNOZ
12/01/2017

GRACE CHAI
12/05/2017