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 Review

Date:	May 24, 2018
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Product Names:	Aptensio XR (methylphenidate hydrochloride) extended-release capsule QuilliChew ER (methylphenidate hydrochloride) extended-release chewable tablet
Pediatric Labeling Approval Date:	April 17, 2015 (Aptensio XR) December 4, 2015 (QuilliChew ER)
Application Type/Number:	NDA 205831 (Aptensio XR) NDA 207960 (QuilliChew ER)
Applicant/Sponsor:	Rhodes Pharmaceuticals L.P. (Aptensio XR) Pfizer, Inc. (QuilliChew ER)
OSE RCM #:	2018-323

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EXECUTIVE SUMMARY

In accordance with the Food and Drug Administration Amendments Act (FDAAA) Pediatric Research Equity Act (PREA), the Division of Pharmacovigilance (DPV) evaluated postmarketing adverse event reports for Aptensio XR (methylphenidate hydrochloride extended-release capsule) and QuilliChew ER (methylphenidate hydrochloride extended-release chewable tablet) in pediatric patients (0-17 years old). This review focuses on serious, unlabeled adverse events and lack of effect cases reported with Aptensio XR or QuilliChew ER in pediatric patients.

Aptensio XR was first approved by FDA in April 2015 and is indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in patients aged 6 to 17 years old. QuilliChew ER was approved by FDA in December 2015 and is indicated for the treatment of ADHD in patients aged 6 to 17 years old.

DPV identified three pediatric cases with an unlabeled, serious adverse event, including two cases for Aptensio XR (from April 17, 2015 to December 31, 2017) and one case for QuilliChew ER (from December 4, 2015 to December 31, 2017), in the FDA Adverse Event Reporting System (FAERS) database. We did not identify any new safety signals or an increased severity or frequency of any labeled adverse events, and there were no pediatric deaths reported with Aptensio XR or QuilliChew ER.

Due to concerns for product quality issues and a history of a lack of effect with another methylphenidate product by one of the same manufacturers, we reviewed 23 non-serious cases reporting a lack of effect associated with either product [Aptensio XR (n=12) and QuilliChew ER (n=11)]. Possible contributing factors for lack of effect identified in this case series included a history of previously failed ADHD treatment and the need for Aptensio XR or QuilliChew ER dose titration. The latter factor was evidenced by reports of lack of effect early in the patient's therapy, doses at the lower end of the dosing range, and reports of dose increases as treatment. The majority of these cases did not provide information regarding the outcome of the event, limiting further assessment.

There is no evidence from these data that there are pediatric safety concerns with Aptensio XR or QuilliChew ER at this time. DPV will continue to monitor adverse events associated with the use of Aptensio XR and QuilliChew ER.

1 INTRODUCTION

1.1 PEDIATRIC REGULATORY HISTORY

Aptensio XR and QuilliChew ER (methylphenidate hydrochloride extended-release [ER]) are central nervous system (CNS) stimulants indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD). Aptensio XR was approved by the FDA on April 17, 2015; it is available in 10 mg, 15 mg, 20 mg, 30 mg, 40 mg, 50 mg, and 60 mg capsules. QuilliChew ER was approved by the FDA on December 4, 2015; it is available in 20 mg, 30 mg, and 40 mg chewable tablets. **Table 1** presents the FDA-approved dosing for Aptensio XR and QuilliChew ER in patients 6 years of age and older.[1,2]

Table 1. FDA-Approved Dosing for Aptensio XR and QuilliChew ER in Patients 6 Years of Age and Older

	Initial Dose	Titration	Maximum Dose
Aptensio XR	10 mg daily in the morning	Weekly increments of 10 mg	60 mg daily
QuilliChew ER	20 mg daily in the morning	Weekly increments of 10 mg, 15 mg, or 20 mg	60 mg daily

This Pediatric Research Equity Act (PREA) review was triggered by pediatric labeling changes from the initial approval of Aptensio XR and QuilliChew ER.

Aptensio XR

The Aptensio XR labeling states the following under USE IN SPECIAL POPULATIONS, Pediatric Use: *"The safety and effectiveness of APTENSIO XR in pediatric patients under six years have not been evaluated. The safety and effectiveness of APTENSIO XR have been established in pediatric patients ages 6 to 17 years in two adequate and well-controlled clinical trials [see Clinical Studies (14)]. The long-term efficacy of methylphenidate in pediatric patients has not been established."*[1]

The two pivotal clinical trials that supported the safety and efficacy of Aptensio XR for the treatment of ADHD were: 1) Study 1 (National Clinical Trial [NCT] identifier: NCT01269463) - a randomized, double-blind, single center, placebo-controlled, flexible-dose, cross-over trial in pediatric patients aged 6 to 12 years (N=26), and 2) Study 2 (NCT01239030) - a randomized, double-blind, multicenter, placebo-controlled, fixed–dose trial in pediatric patients 6 to 17 years (N=230).[1]

QuilliChew ER

The QuilliChew ER labeling states the following under USE IN SPECIAL POPULATIONS, Pediatric Use: *"The safety and effectiveness of QuilliChew ER have been established in pediatric patients ages 6 to 17 years. Use of QuilliChew ER in these age groups is based on one adequate*

and well-controlled clinical study in pediatric patients 6 to 12 years old, pharmacokinetic data in adolescents and adults, and safety information from other methylphenidate-containing products. The long-term efficacy of methylphenidate in pediatric patients has not been established [see Clinical Pharmacology (12), Clinical Studies (14)]. Safety and efficacy in pediatric patients below the age of 6 years have not been established."[2]

The pediatric clinical study for QuilliChew ER conducted in pediatric patients 6 to 12 years old was a laboratory classroom study that consisted of 90 pediatric subjects (NCT01654250).[2]

1.2 HIGHLIGHTS OF LABELED SAFETY ISSUES

The current approved labeling for Aptensio XR and QuilliChew ER contain similar safety information in the Highlights section. Differences are listed below.

Aptensio XR

The following is an excerpt from the Aptensio XR labeling:[1]

WARNING: ABUSE AND DEPENDENCE

See full prescribing information for complete boxed warning.

- **CNS stimulants, including APTENSIO XR, other methylphenidate- containing products, and amphetamines, have a high potential for abuse and dependence (5.1, 9.2, 9.3)**
- **Assess the risk of abuse prior to prescribing, and monitor for signs of abuse and dependence while on therapy (5.1, 9.2)**

----------**CONTRAINDICATIONS**----------

- Known hypersensitivity to methylphenidate or product components (4)
- Concurrent treatment with a monoamine oxidase inhibitor (MAOI), or use of an MAOI within the preceding 14 days (4)

----------**WARNINGS AND PRECAUTIONS**----------

- *Serious Cardiovascular Events:* Sudden death has been reported in association with CNS stimulant treatment at recommended doses in pediatric patients with structural cardiac abnormalities or other serious heart problems. In adults, sudden death, stroke, and myocardial infarction have been reported. Avoid use in patients with known structural cardiac abnormalities, cardiomyopathy, serious heart arrhythmias, or coronary artery disease. (5.2)
- *Blood Pressure and Heart Rate Increases:* Monitor blood pressure and pulse. Consider the benefits and risks in patients for whom an increase in blood pressure or heart rate would be problematic. (5.3)
- *Psychiatric Adverse Reactions:* Use of stimulants may cause psychotic or manic symptoms in patients with no prior history, or exacerbation of symptoms in patients with pre-existing psychiatric illness. Evaluate for bipolar disorder prior to APTENSIO XR use. (5.4)
- *Priapism:* Cases of painful and prolonged penile erections and priapism have been reported with methylphenidate products. Immediate medical attention should be sought if signs or symptoms of prolonged penile erections or priapism are observed. (5.5)
- *Peripheral Vasculopathy, including Raynaud's Phenomenon:* Stimulants used to treat ADHD are associated with peripheral vasculopathy, including Raynaud's phenomenon. Careful observation for digital changes is necessary during treatment with ADHD stimulants. (5.6)
- *Long-Term Suppression of Growth:* Monitor height and weight at appropriate intervals in pediatric patients. (5.7)

----------ADVERSE REACTIONS----------

The most common adverse reactions in double-blind clinical trials (> 5% and twice the rate of placebo) in pediatric patients 6 to 17 years were abdominal pain, decreased appetite, headache and insomnia. (6.1)

QuilliChew ER

The QuilliChew ER labeling is similar to the Aptensio XR labeling with the following exceptions:[2]

The WARNINGS AND PRECAUTIONS section contains one additional safety information specific to Quillichew ER:

- *Risks in Phenylketonurics*: QuilliChew ER extended-release chewable tablets contain phenylalanine, a component of aspartame. (5.8)

The ADVERSE REACTIONS section contains safety information from other methylphenidate products:

Based on accumulated data from other methylphenidate products, the most common (≥5% and twice the rate of placebo) adverse reactions are appetite decreased, insomnia, nausea, vomiting, dyspepsia, abdominal pain, weight decreased, anxiety, dizziness, irritability, affect lability, tachycardia, and blood pressure increased. (6.1)

2 POSTMARKET ADVERSE EVENT REPORTS

2.1 METHODS AND MATERIALS

2.1.1 FDA Adverse Event Reporting System (FAERS) Search Strategy

The Division of Pharmacovigilance (DPV) searched the FAERS database with the strategies described in **Table 2** for Aptensio XR and QuilliChew ER. See **Appendix A** for a description of the FAERS database.

Table 2. FAERS Search Strategies

	Search #1	**Search #2**
Date of Search	January 8, 2018	January 8, 2018
Time Period of Search	April 17, 2015* - December 31, 2017	December 4, 2015† - December 31, 2017
Search Type	FBIS Quick Query	FBIS Quick Query
Product Terms	Product Name: Aptensio XR NDA: 205831	Product Name: QuilliChew ER NDA: 207960
Search Parameters	All ages, all outcomes, worldwide	All ages, all outcomes, worldwide

Abbreviation: FBIS = FAERS Business Intelligence Solution
* U.S. approval date of Aptensio XR
† U.S. approval date of QuilliChew ER

2.2 RESULTS

2.2.1 Total Number of FAERS Reports by Age

Table 3. Total Adult and Pediatric FAERS Reports* from April 17, 2015 to December 31, 2017 with Aptensio XR

	All reports (U.S.)	Serious† (U.S.)	Death (U.S.)
Adults (≥ 18 years)	27 (7)	27 (7)	3 (0)
Pediatrics (0 - <18 years)	60 (34)	**43‡** (17)	1 (0)

* 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 1

Table 4. Total Adult and Pediatric FAERS Reports* from December 4, 2015 to December 31, 2017 with QuilliChew ER

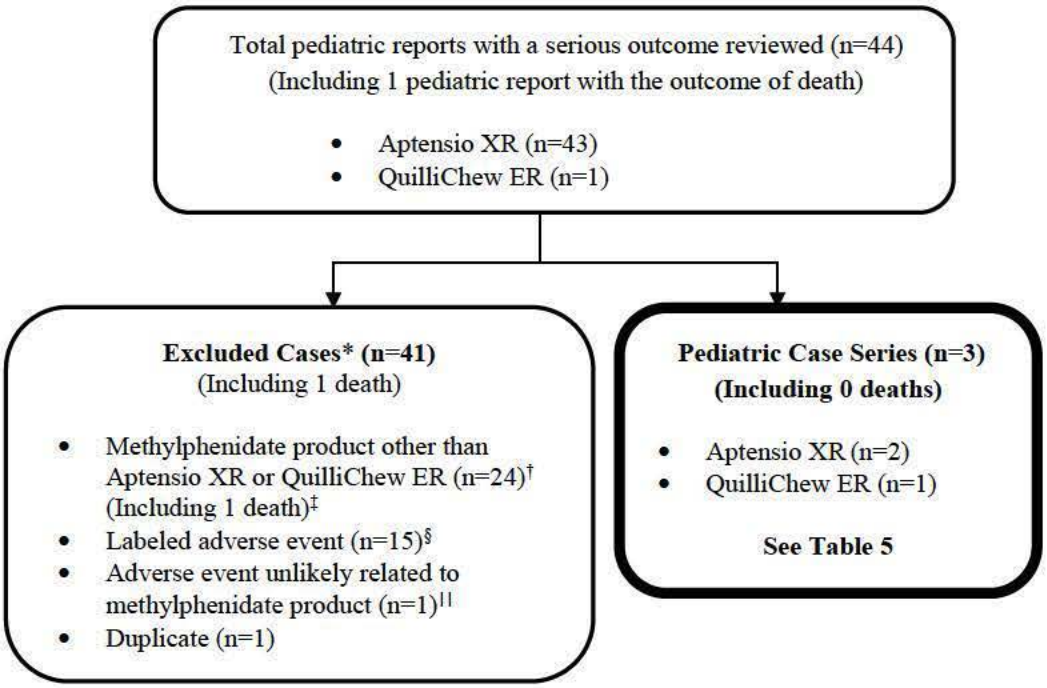
	All reports (U.S.)	Serious† (U.S.)	Death (U.S.)
Adults (≥ 18 years)	3 (3)	0 (0)	0 (0)
Pediatrics (0 - <18 years)	36 (36)	**1‡** (1)	0 (0)

* 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 1

2.2.2 Selection of Unlabeled, Serious Pediatric Cases in FAERS

We identified 44 pediatric reports with a serious outcome, including 43 pediatric reports for Aptensio XR (from April 17, 2015 to December 31, 2017) and 1 pediatric report for QuilliChew ER (from December 4, 2015 to December 31, 2017). **Figure 1** below presents the specific selection of cases to be summarized in **Sections 2.3 and 2.4.** Our pediatric case series included three cases.

Figure 1. Selection of Unlabeled, Serious Pediatric Cases with Aptensio XR and QuilliChew ER



* DPV reviewed these cases, but they were excluded from the case series for the reasons listed above.
† The focus of this pediatric review is on Aptensio XR and QuilliChew ER. We excluded cases concerning other methylphenidate formulations or brands, including the Canadian product Biphentin (methylphenidate controlled release capsule). We did not identify any new safety signals from these cases; the majority of these cases described labeled adverse events for methylphenidate.
‡ One foreign pediatric case with an outcome of death was reported with Biphentin in a 7-year-old male. This case reported limited information for assessment and was possibly confounded by the patient's underlying medical conditions. More than one month after the initiation of Biphentin, the patient expired after experiencing cardiovascular complications from subarachnoid and intraventricular hemorrhage that resulted from a ruptured intracranial aneurysm. Intracranial aneurysms may be congenital or acquired (i.e. head trauma, high blood pressure, or infection). The patient's past medical history of ureteropelvic junction obstruction could have resulted in chronic kidney disease and hypertension. CNS stimulants, including methylphenidate, are known to cause increases in blood pressure. The Biphentin labeling contains a Warnings (Aptensio XR labeling contains a Warnings and Precautions) regarding this adverse event, including instructions to monitor patients for hypertension. However, this case did not provide blood pressure measurements, additional clinical information, or any other past medical history for further evaluation of the potential risk factors or etiologies for the onset of the aneurysm.
§ A review of the cases did not detect labeled adverse events that were worsening in severity or frequency.
‖ One case reported worsening dyspnea in a 17-year-old female, who was on an unknown formulation of methylphenidate and multiple concomitant medications for an unknown duration of time; she was diagnosed with hereditary pulmonary arterial hypertension.

2.2.3 Characteristics of Pediatric Case Series

Appendix B lists all the FAERS case numbers, FAERS version numbers and Manufacturer Control Numbers for the pediatric case series.

Table 5. Characteristics of Pediatric Case Series with Aptensio XR and QuilliChew ER (N=3)

		Aptensio XR (N=2)	QuilliChew ER (N=1)
Age	6- <12 years	1	1
	12- < 18 years	1	0
Sex	Male	2	1
Reported Reason for Use	ADHD/ADD	1	1
	"Inability to focus"	1	0
Serious Outcome*	Life-threatening	1	0
	Other serious	1	1

Abbreviations: ADD = Attention Deficit Disorder; ADHD = Attention Deficit Hyperactivity Disorder

* 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.

2.3 SUMMARY OF FATAL PEDIATRIC ADVERSE EVENT CASE (N=0)

There were no pediatric deaths in the case series for Aptensio XR or QuilliChew ER.

2.4 SUMMARY OF NON-FATAL, UNLABELED, SERIOUS PEDIATRIC ADVERSE EVENT CASES (N=3)

2.4.1 Aptensio XR (n=2)

Suicidal ideation (n=1)

One case described the occurrence of mood swings and suicidal thoughts in a 16-year-old male who had been on Aptensio XR for eight months. He took Aptensio XR 20 mg (frequency not reported). The patient did not have any additional medical history and took vitamins concomitantly. Suicidal ideation resolved after the discontinuation of Aptensio XR.

Reviewer's comment: Suicidal ideation is a labeled adverse event under the Drug Abuse and Dependence section of the Aptensio XR labeling. We considered suicidal ideation unlabeled in this case, because it did not appear that the patient abused the medication. Limited information in this case regarding other possible risk factors, such the patient's social and family history, precludes a causality assessment. In the U.S., suicide is prevalent among youths. According to the Centers for Disease Control and Prevention, suicide was the second leading cause of death for youths aged 10 to 24 years old in the U.S. in 2016 (see ***Appendix C*** *for the top ten leading causes of death in 2016).*[3]

Furthermore, in 2006, the Office of Surveillance and Epidemiology (previously Division of Drug Risk Evaluation) evaluated psychiatric adverse events in ADHD clinical trials. This review did not identify evidence of a higher risk of suicidal events for the amphetamine or methylphenidate products compared to placebo.[4] The findings were presented to the Pediatric Advisory Committee in March 2006; the Committee did not recommend any changes related to suicidality to the labeling for ADHD medications.[5]

Formication (n=1)

One case reported formication in an 8-year-old male who initiated Aptensio XR 15 mg daily for "inability to focus." Following the first Aptensio XR dose, the patient became "hyperactive and felt as if his skin was crawling." Aptensio XR was discontinued and the events resolved. The patient was previously on a generic methylphenidate ER product without such adverse events.

Reviewer's comment: Formication is a form of paresthesia and tactile hallucination. Hallucination is labeled for Aptensio XR under Section 5.4 Psychiatric Adverse Reactions within the Warnings and Precautions.

2.4.2 QuilliChew ER (n=1)

Anger (n=1)

One case reported anger and face scratching in a 6-year-old male after seven days on QuilliChew ER for ADHD. Therefore, QuilliChew ER was discontinued and changed to mixed amphetamine salts. The reporter, a nurse, stated there were other possible etiologies for the anger (details not specified). Behavioral changes were also discussed. The outcome of the adverse events was not reported.

Reviewer's comment: Although there is a temporal association, the case provided insufficient information for causality assessment (missing information regarding the patient's medical history and possible alternative etiologies for anger). It is unknown if the behavioral changes were implemented. ADHD is associated with decreased tolerance to frustration, irritability, or emotional lability. Comorbid disorders, such as oppositional defiant disorder, occur with approximately half of the children with combined type of ADHD.[6]

2.5 ADVERSE EVENT OF INTEREST: LACK OF EFFECT (N=23)

We identified lack of effect as an adverse event of interest because both Aptensio XR and QuilliChew ER are new dosage forms for methylphenidate ER and because lack of effect is a previously identified signal with Quillivant XR. Reports of lack of effect with Quillivant XR were discussed in the pediatric postmarketing pharmacovigilance and drug utilization review written for the PAC Meeting on March 24, 2015.[7] More recently, on March 26, 2018, FDA issued a warning letter to Tris Pharma, Inc. for violations of Current Good Manufacturing Practice (CGMP) regulations for Quillivant XR.[8] Tris Pharma is also the drug manufacturing

facility for QuilliChew ER. Five lots of Quillivant XR failed dissolution testing between May and November 2016.

DPV identified 23 cases [Aptensio XR (n=12) and QuilliChew ER (n=11)] reporting lack of effect, ranging from ineffectiveness to decreased duration of effect, among the non-serious pediatric adverse event cases. The reported PTs included: *Drug ineffective*, *Drug effect delayed*, *Drug effect incomplete*, or *Drug effect decreased*. **Table 6** presents the case characteristics of the pediatric case series of lack of effect with Aptensio XR and QuilliChew ER.

Appendix D lists all the FAERS case numbers, FAERS version numbers and Manufacturer Control Numbers for the pediatric lack of effect case series.

Table 6. Characteristics of Pediatric Cases of Lack of Effect in FAERS with Aptensio XR and QuilliChew ER (N=23)

	Aptensio XR (N=12)	QuilliChew ER (N=11)
Reported Reason for Use		
ADHD	11	11
"No focus"	1	0
Description of Lack of Effect		
Reports of "drug ineffective"	11	8
Reports of "decreased duration of effect"	1	3
Total Daily Dose		
10 mg/day	3	1
15 mg/day	1	0
20 mg/day	1	2
30 mg/day	2	3
40 mg/day	1	0
50 mg/day	1	1
Unknown	3	4
Time to Onset*		
First day	4	0
First week	2	1
<2 weeks	1	1
<1 month	1	2
1-2 months	0	1
~2 years	0	1
Unknown	4	5
Duration of Treatment†		
<1 month	7	4
1-2 months	2	0
>2 months or "several months"	0	2
~2 years	0	1
Unknown	3	4
Treatment for Lack of Effect		
Increased Aptensio XR or QuilliChew ER dose	6	4
Switched to another methylphenidate product	0	3
No treatment reported	3	4
Unknown	3	0
Outcome of Lack of Effect		
Ongoing	2	0
Resolution	2	1
Unknown	8	10

* Time to onset of the lack of effect from the initiation of Aptensio XR or QuilliChew ER.

† Duration of treatment use at the time of the report was calculated from the initiation date of Aptensio XR or QuilliChew ER to either the discontinuation date or manufacturer received date of the report (if the drug status was unknown or ongoing).

Aptensio XR

Of the 12 cases reporting lack of effect with Aptensio XR, 11 cases reported Aptensio XR was ineffective for ADHD or "no focus." One additional case reported a decreased duration of effect with Aptensio XR for ADHD (i.e. Aptensio XR "wears off" after an unspecified duration of time). Four of the 12 cases reported a historical use of another ADHD stimulant, but none of the cases reported a history of lack of effect with an ADHD stimulant. The time to onset of the lack of effect from the initiation of Aptensio XR was less than 1 week in 6 of the 12 cases, including 4 cases reporting lack of effect on the first day of use. In the remaining 6 cases, the time to onset was unknown (n=4) or less than 1 month from the initiation of Aptensio XR (n=2). The duration of Aptensio XR use at the time of the report was less than 1 month in the majority of the cases. Two cases reported the resolution of lack of effect following an increase in the Aptensio XR dose and 2 additional cases reported the event was ongoing at the time of the report; however, the remaining 8 cases did not report an outcome.

QuilliChew ER

Of the 11 cases reporting lack of effect with QuilliChew ER, 8 cases reported QuilliChew ER was ineffective for ADHD and 3 cases reported a decreased duration of effect. Two of the 3 cases reporting a decreased duration of effect lacked details regarding the shortened duration of effect, but 1 case described the QuilliChew ER worked for 3-4 hours (but took 45 minutes to 1 hour to take effect). Of the 8 cases that reported drug ineffectiveness, 3 cases reported lack of effect with 1 or more ADHD stimulant prior to switching to QuilliChew ER. Seven cases provided complete dosing information and 6 of these cases reported a QuilliChew ER dose between 10 mg to 30 mg daily (lower end of the recommended dosing range of 20 mg to 60 mg daily). Four of these 6 cases reported drug ineffectiveness with less than 1 month of use; 1 additional case reported ineffectiveness after being on the same QuilliChew ER dose for almost 2 years, with a plan to increase the QuilliChew ER dose. Additionally, 1 case reported lack of effect with a particular lot of QuilliChew ER (medication worked on initial dispense but lacked effect with the second dispense). Only 1 case reported the resolution of lack of effect with QuilliChew ER after the patient was switched back to the previous methylphenidate product (methylphenidate transdermal system). The remaining cases did not report an outcome.

Summary

Of the 23 lack of effect cases, 19 cases (83%) reported decreased effectiveness with either Aptensio XR or QuilliChew ER, and the remaining 4 cases (17%) reported a decreased duration of effect. In 17 of the 23 cases, the reported lack of effect may reflect the fact that Aptensio XR or QuilliChew ER doses required titration, or the patient had treatment refractory ADHD. One additional case reported lack of effect with a particular lot, and the remaining 5 cases did not provide enough information to assess for potential causes for lack of effect. The majority of these cases (78%) did not provide information regarding the outcome of the lack of effect.

3 DISCUSSION

DPV identified three pediatric cases with an unlabeled, serious adverse event, including two cases for Aptensio XR (from April 17, 2015 to December 31, 2017) and one case for QuilliChew ER (from December 4, 2015 to December 31, 2017) in the FAERS database. We did not identify any new safety signals or an increased severity or frequency of any labeled adverse events, and there were no pediatric deaths reported with Aptensio XR or QuilliChew ER.

Due to concerns for product quality issues and a history of a lack of effect with another methylphenidate product by one of the same manufacturers, we reviewed 23 non-serious cases reporting a lack of effect associated with Aptensio XR (n=12) or QuilliChew ER (n=11). Possible contributing factors for lack of effect identified in this case series included a history of previously failed ADHD treatment and the need for Aptensio XR or QuilliChew ER dose titration. The latter factor was evidenced by reports of lack of effect early in the patient's therapy, doses at the lower end of the dosing range, and reports of dose increases as treatment. The majority of these cases did not provide information regarding the outcome of the event, limiting further assessment. Note that the PT *Drug ineffective* is the most commonly reported adverse event in the FAERS database.[9]

4 CONCLUSION

There is no evidence from these data that there are pediatric safety concerns with Aptensio XR or QuilliChew ER at this time.

5 RECOMMENDATIONS

DPV will continue to monitor adverse events associated with the use of Aptensio XR and QuilliChew ER.

6 REFERENCES

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7 APPENDICES

7.1 APPENDIX A. 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.

7.2 APPENDIX B. FAERS CASE NUMBERS, FAERS VERSION NUMBERS AND MANUFACTURER CONTROL NUMBERS FOR THE PEDIATRIC CASE SERIES WITH APTENSIO XR AND QUILLICHEW ER (N=3)

FAERS Case #	Version Number	Manufacturer Control #	Product
12317214	1	(blank)	Aptensio XR
12388779	1	(blank)	Aptensio XR
13961591	1	US-PFIZER INC-2017392487	QuilliChew ER

7.3 APPENDIX C. TEN LEADING CAUSES OF DEATH IN 2016 FOR AGES 0-24 YEARS OLD

10 Leading Causes of Death, United States
2016, All Races, Both Sexes

	Age Groups					
Rank	<1	1-4	5-9	10-14	15-19	20-24
1	Congenital Anomalies 4,816	Unintentional Injury 1,261	Unintentional Injury 787	Unintentional Injury 847	Unintentional Injury 4,152	Unintentional Injury 9,743
2	Short Gestation 3,927	Congenital Anomalies 433	Malignant Neoplasms 449	Suicide 436	Suicide 2,117	Suicide 3,606
3	SIDS 1,500	Malignant Neoplasms 377	Congenital Anomalies 203	Malignant Neoplasms 431	Homicide 1,816	Homicide 3,356
4	Maternal Pregnancy Comp. 1,402	Homicide 339	Homicide 139	Homicide 147	Malignant Neoplasms 596	Malignant Neoplasms 835
5	Unintentional Injury 1,219	Heart Disease 118	Heart Disease 77	Congenital Anomalies 146	Heart Disease 293	Heart Disease 656
6	Placenta Cord Membranes 841	Influenza & Pneumonia 103	Chronic Low. Respiratory Disease 68	Heart Disease 111	Congenital Anomalies 197	Congenital Anomalies 191
7	Bacterial Sepsis 583	Septicemia 70	Influenza & Pneumonia 48	Chronic Low. Respiratory Disease 75	Chronic Low. Respiratory Disease 80	Complicated Pregnancy 160
8	Respiratory Distress 488	Perinatal Period 60	Septicemia 40	Cerebro-vascular 50	Cerebro-vascular 62	Diabetes Mellitus 157
9	Circulatory System Disease 460	Cerebro-vascular 55	Cerebro-vascular 38	Influenza & Pneumonia 39	Diabetes Mellitus 54	Influenza & Pneumonia 135
10	Neonatal Hemorrhage 398	Chronic Low. Respiratory Disease 51	Benign Neoplasms 31	Septicemia 31	Influenza & Pneumonia 54	Chronic Low. Respiratory Disease 126

Source: Centers for Disease Control and Prevention – Injury Prevention & Control: Data & Statistics (WISQARS™). http://www.cdc.gov/injury/wisqars/leading_causes_death.html. Accessed March 28, 2018.

7.4 APPENDIX D. FAERS CASE NUMBERS, FAERS VERSION NUMBERS AND MANUFACTURER CONTROL NUMBERS FOR THE LACK OF EFFECT CASES REPORTED WITH APTENSIO XR AND QUILLICHEW ER (N=23)

FAERS Case #	Version Number	Manufacturer Control #	Product
11652982	2	US-PURDUE-USA-2015-0126564	Aptensio XR
11941327	2	US-PURDUE-USA-2015-0127572	
11941329	2	US-PURDUE-USA-2015-0127765	
12283316	2	US-PURDUE-USA-2016-0128894	
12283317	2	US-PURDUE-USA-2016-0129216	
12283318	2	US-PURDUE-USA-2016-0128919	
12574573	2	US-PURDUE-USA-2016-0130622	
12860795	1	US-PURDUE-USA-2016-0133345	
12860798	2	US-PURDUE-USA-2016-0133328	
13135046	2	US-PURDUE-USA-2017-0135940	
13461741	2	US-PURDUE-USA-2017-0138152	
13763645	2	US-PURDUE-USA-2017-0138489	
12380525	3	US-PFIZER INC-2016261915	QuilliChew ER
12731693	1	US-PFIZER INC-2016421054	
12884106	2	US-PFIZER INC-2016494505	
13390373	1	US-PFIZER INC-2017141795	
*13458603	1	PHEH2017US011214	
13395317	1	US-PFIZER INC-2017142084	
13510539	1	US-PFIZER INC-2017191475	
14014795	1	US-PFIZER INC-2017415028	
14091967	2	US-PFIZER INC-2017441461	
14096890	1	US-PFIZER INC-2017446552	
14151453	1	US-PFIZER INC-2017470892	
14329611	1	US-PFIZER INC-2017548641	

*Duplicate case

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

/s/

CARMEN CHENG
05/24/2018

IVONE E KIM
05/24/2018

VICKY C CHAN
05/24/2018

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05/24/2018