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Office of Surveillance and Epidemiology

Pediatric Postmarketing Pharmacovigilance and Drug Utilization Review

Date:	July 30, 2020
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Product Names:	Mydayis (mixed salts of a single-entity amphetamine) Adzenys ER (amphetamine)
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EXECUTIVE SUMMARY

This review evaluates FDA Adverse Event Reporting System (FAERS) reports in pediatric patients through age 16 years. The Office of Surveillance and Epidemiology (OSE) conducted this review in accordance with the Food and Drug Administration Amendments Act (FDAAA) Pediatric Research Equity Act (PREA). The review was triggered by pediatric studies completed under PREA for Mydayis and Adzenys ER at the time of initial approval. This review focuses on all unlabeled adverse events associated with all amphetamine and mixed salts of single-entity amphetamine products, including Mydayis extended-release (ER) capsules and Adzenys ER oral suspension, in pediatric patients.

Mydayis and Adzenys ER are central nervous system (CNS) stimulants indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in patients ≥ 13 years and ≥ 6 years, respectively. Mydayis was approved by FDA on June 20, 2017. It is supplied as ER capsules in 12.5 mg, 25 mg, 37.5 mg and 50 mg. Adzenys ER was approved by FDA on September 15, 2017. It is supplied as an ER suspension containing 1.25 mg amphetamine per mL.

We reviewed all FAERS reports with amphetamine and mixed salts of single-entity amphetamine products, including the two products (i.e., Mydayis and Adzenys ER), from January 1, 2006 to May 15, 2019. From 2006 to 2018, a range of approximately 1 to 1.2 million pediatric patients younger than 17 years of age received dispensed prescriptions for amphetamine or mixed salts of single-entity amphetamine products annually, of which the majority of patients were 6-16 years of age. The majority of FAERS reports described adverse events that were consistent with the known adverse reactions described in labeling or conditions associated with ADHD (i.e., comorbid mental disorders). We did not identify an increase in severity in the labeled adverse events associated with amphetamines.

Of the six cases with adverse events of interest, we identified two cases describing a fatal outcome and four cases describing non-fatal unlabeled adverse events. Both fatal reports described risk factors that may have contributed to the fatal outcome. Additionally, the extent of the causal association between amphetamines or mixed salts of single-entity amphetamine products and death was difficult to determine given the reported information. Of the four non-fatal adverse events, two cases described glaucoma or borderline glaucoma. Both cases reported a long latency period to developing glaucoma and had limited information that precluded a meaningful causality assessment.

Of the remaining two non-fatal unlabeled adverse events, one case reported necrotizing vasculitis and the other case reported acute dystonia. Due to lack of additional reported cases in FAERS, the single case of necrotizing vasculitis identified in this review does not represent a new safety signal at this time. The acute dystonia case was associated with amphetamine withdrawal after concomitant use of amphetamines and antipsychotics in a child. The case reported a positive dechallenge and close temporal relationship. The biological plausibility and presence of additional reported cases in FAERS represents a newly identified safety signal (NISS).

FDA opened NISS #1102 for the drug-drug interaction (DDI) between ADHD stimulants/atomoxetine and antipsychotics associated with acute hyperkinetic disorders and notified the Applicant of the opening of this NISS for further investigation. OSE and the Division of Psychiatry (DP) performed three additional reviews for this safety signal; the full assessment of this DDI is described in separate signal review documents. OSE identified 36

cases (11 probable and 25 possible cases) of acute hyperkinetic movement disorder associated with the concomitant use of ADHD stimulants/atomoxetine and antipsychotics. From an ADHD stimulant perspective, most of the cases were reported with methylphenidate products (n=23), followed by amphetamine products (n=9), and atomoxetine (n=4). From an antipsychotic perspective, all 36 cases were reported with second generation antipsychotics (SGAs) [risperidone (n=20), aripiprazole (n=11), olanzapine (n=2), quetiapine (n=1), paliperidone (n=1), and ziprasidone (n=1)]. As a result of this investigation, the totality of the evidence was supportive of a DDI between methylphenidate products and risperidone; the evidence was not as strong for the amphetamine products. Therefore, we recommended the incorporation of this DDI into all oral risperidone and methylphenidate product labeling within the Drug Interaction section. A full description of the assessment of this DDI is described in separate signal review documents.

Based on the findings from this pediatric postmarketing pharmacovigilance review, OSE recommended further evaluation of the DDI between ADHD stimulants/atomoxetine and antipsychotics associated with acute hyperkinetic disorders. The DDI evaluation was concurrent with the pediatric postmarketing pharmacovigilance review and is described in separate documents from OSE and DP; the signal review led to labeling recommendations for risperidone and methylphenidate products. OSE recommends no additional regulatory action based on this pediatric postmarketing pharmacovigilance review. OSE will continue routine pharmacovigilance for all amphetamine and mixed salts of single-entity amphetamine products.

1 INTRODUCTION

This review evaluates FDA Adverse Event Reporting System (FAERS) reports in pediatric patients through age 16 years. The Office of Surveillance and Epidemiology (OSE) conducted this review in accordance with the Food and Drug Administration Amendments Act (FDAAA) Pediatric Research Equity Act (PREA). This review focuses on all unlabeled adverse events associated with all amphetamine and mixed salts of single-entity amphetamine products, including Mydayis extended-release (ER) capsules and Adzenys ER oral suspension, in pediatric patients. Mixed salts of single-entity amphetamine products refer to the following salts: dextroamphetamine saccharate\amphetamine aspartate monohydrate\dextroamphetamine sulfate\amphetamine sulfate. In this document products that contain some or all of these salts will be referred to as mixed salts of single-entity amphetamine products.

1.1 PEDIATRIC REGULATORY HISTORY

Mydayis and Adzenys ER are central nervous system (CNS) stimulants indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in patients 13 years and older and 6 years and older respectively. Mydayis was approved by FDA on June 20, 2017. It is supplied in ER capsules in 12.5 mg, 25 mg, 37.5 mg and 50 mg. Adzenys ER was approved by FDA on September 15, 2017. It is supplied as an ER suspension containing 1.25 mg amphetamine per mL. The dosage and administration for Mydayis and Adzenys ER are summarized in **Table 1**.

Table 1. Mydayis and Adzenys ER Dosage and Administration[1,2]

Brand Name	Starting dose	Dose increase	Maximum
Mydayis	12.5 mg once daily in the morning	12.5 mg at weekly intervals	25 mg for patients 13 to 17 years
Adzenys ER	6.3 mg (5 mL) once daily in the morning	3.1 mg (2.5 mL) or 6.3 mg (5 mL) at weekly intervals	18.8 mg (15 mL) for patients 6 to 12 years 12.5 mg (10 mL) for patients 13 to 17 years

This review was triggered by pediatric studies completed under PREA for Mydayis and Adzenys ER at the time of initial approval.

Mydayis[2]

The safety and efficacy of Mydayis have been established in pediatric patients with ADHD ages 13-17 years in two-placebo controlled clinical studies (i.e., one pharmacokinetic trial in pediatric patients aged 6-17 years, one efficacy and safety trial in pediatric patients aged 6-17 years). The safety of Mydayis for pediatric patients (13-17 years) was established from one randomized trial

that included 78 adolescent patients. However, the efficacy of Mydayis was established in two short-term trials in pediatric patients (13-17 years) described below.

1. A 4-week, randomized, double-blind, multi-center, placebo-controlled, dose-optimization, safety and efficacy study was conducted in 157 pediatric patients 13 to 17 years old who met the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV TR) criteria for ADHD. Subjects were randomized in a 1:1 ratio to Mydayis or placebo group. The primary efficacy endpoint defined as the change from baseline of the ADHD-Rating Scale (RS) total score at week 4. Subjects were titrated from a dose of 12.5 mg/day until an optimal dose was reached to a maximum dose of 25 mg. Mydayis demonstrated a statistically significant treatment effect compared with placebo on change of ADHD RS-IV total scores from baseline to week 4. The most common adverse reactions reported in adolescents were decreased appetite, nausea, insomnia, upper abdominal pain, irritability and weight decreased.

2. A multi-center, randomized, double-blind, placebo-controlled, crossover study of Mydayis 25 mg/day was conducted in adolescent patients who met DSM-IV TR criteria for ADHD. The efficacy was determined using the Permanent Product Measure of Performance (PERMP), a skill adjusted math test that measures attention in ADHD. Mydayis treatment, compared to placebo, reached statistical significance at 2 to 16 hours post-dose.

Adzenys ER[1]

The safety and efficacy of Adzenys ER has been established based on adequate and well-controlled studies of a single-entity amphetamine product extended-release capsules in the treatment of ADHD. The most common adverse reaction reported in children (6-12 years) and adolescents (13-17 years) is abdominal pain, loss of appetite, insomnia, and weight loss.

1. A double-blind, randomized, placebo-controlled, parallel-group study was conducted in pediatric patients 6 to 12 years of age (N=584) who met DSM-IV criteria for ADHD.

2. A double-blind, randomized, multi-center, parallel-group, placebo-controlled study was conducted in adolescent patients 13 to 17 years of age (N=327) who met DSM- IV criteria for ADHD.

The Division of Pharmacovigilance (DPV) has not previously presented Mydayis nor Adzenys ER before the Pediatric Advisory Committee (PAC).

1.1.1 Other Amphetamine Products

OSE previously evaluated postmarketing adverse event reports with a serious outcome and drug utilization data for Adderall XR and immediate release Adderall formulations in pediatric patients. OSE's evaluations, dated January 5, 2006 and February 1, 2006 respectively, were prompted by the pediatric labeling changes on October 28, 2004 which granted pediatric exclusivity and extended the pediatric ages for the approved indications. FDA presented OSE's evaluation to the PAC on March 2006.[3] OSE's evaluations identified psychiatric and cardiovascular events as safety concerns for further investigation. In February 21, 2007, FDA

directed ADHD drug manufacturers to notify patients about cardiovascular and psychiatric adverse events.[4]

In September 2012 and April 2016, FDA presented OSE's pediatric postmarketing safety reviews on lisdexamfetamine to the PAC. OSE's evaluations for the September 2012 PAC did not identify any new safety concerns.[5,6] OSE's evaluation for the April 2016 PAC identified alopecia as a newly identified safety signal (NISS) reported in association with lisdexamfetamine.[7] Subsequent to the PAC presentation, DPV completed a postmarketing safety review of selected amphetamine products (including lisdexamfetamine) that were not already labeled for alopecia. On May 19, 2017, alopecia was added to the ADVERSE REACTIONS-Postmarketing Experience section of the labeling for lisdexamfetamine, dextroamphetamine, and methamphetamine. Additionally, on April 17, 2018, DPV evaluated the postmarketing pediatric adverse event reports for two other amphetamine products, Adzenys XR-ODT (amphetamine) and Dyanavel XR (amphetamine suspension). DPV's recommendation was to continue routine postmarketing surveillance.[8]

This review focuses on all unlabeled adverse events associated with all amphetamine (excluding lisdexamfetamine) or mixed salts of single-entity amphetamine products, including Mydayis and Adzenys ER, in pediatric patients from January 1, 2006 to May 15, 2019. Of note, OSE conducted a separate pediatric postmarketing pharmacovigilance and drug utilization review for lisdexamfetamine; therefore, we excluded lisdexamfetamine from this review.

1.2 RELEVANT LABELED SAFETY INFORMATION

The Mydayis labeling contains the following safety information within the Highlights of Prescribing Information:[2]

WARNING: ABUSE AND DEPENDENCE

See full prescribing information for complete boxed warning.

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

CONTRAINDICATIONS

- Known hypersensitivity to amphetamine products or other ingredients in MYDAYIS. (4)
- Use with monoamine oxidase (MAO) inhibitors, or within 14 days of the last MAO inhibitor dose. (4, 7.1)

WARNINGS AND PRECAUTIONS

- *Serious Cardiovascular Reactions:* 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 arrhythmia, or coronary artery disease. (5.2)
- *Blood Pressure and Heart Rate Increases:* Monitor blood pressure and pulse. Consider benefits and risks before use in patients for whom blood pressure increases may be problematic. (5.3)
- *Psychiatric Adverse Reactions:* May cause psychotic or manic symptoms in patients with no prior history, or

exacerbation of symptoms in patients with pre-existing psychosis. Evaluate for bipolar disorder prior to stimulant use. (5.4)

- *Long-Term Suppression of Growth:* Monitor height and weight in pediatric patients during treatment. (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)
- *Seizures:* May lower the convulsive threshold. If a seizure occurs, discontinue MYDAYIS. (5.7)
- *Serotonin Syndrome:* Increased risk when co-administered with serotonergic agents (e.g., SSRIs, SNRIs, triptans), but also during overdosage situations. If it occurs, discontinue MYDAYIS and initiate supportive treatment. (5.8)

ADVERSE REACTIONS

Most common adverse reactions in patients with ADHD (incidence ≥5% and at a rate at least twice placebo) are:

- Pediatrics (13 years and older): insomnia, decreased appetite, decreased weight, irritability, and nausea. (6.1)
- Adults: insomnia, decreased appetite, decreased weight, dry mouth, increased heart rate, and anxiety. (6.1)

The safety information within the Highlights of Prescribing Information for Adzenys ER is similar to Mydayis except for the "Adverse Reactions" section where the reactions are categorized by pediatric age [(6 to 12) and (13 to 17) years old]:[1]

ADVERSE REACTIONS

- Pediatric patients ages 6 to 12 years: Most common adverse reactions (≥5% and with a higher incidence than on placebo) were loss of appetite, insomnia, abdominal pain, emotional lability, vomiting, nervousness, nausea, and fever. (6.1)

2 METHODS AND MATERIALS

2.1 FAERS SEARCH STRATEGY

Adverse events associated with amphetamines or mixed salts of single-entity amphetamine products are not always reported by the trade name for the specific product. Therefore, to capture all adverse events reported with all amphetamines or mixed salts of single-entity amphetamine products since the presentation of Adderall to the PAC in 2006, we expanded our FAERS search strategy to include all amphetamine and mixed salts of single-entity amphetamine products, including the two products that triggered this review (i.e., Mydayis and Adzenys ER). OSE conducted a separate pediatric postmarketing pharmacovigilance and drug utilization review for lisdexamfetamine; therefore, we excluded lisdexamfetamine from this review. DPV searched the FAERS database with the strategy described in **Table 2**.

Table 2. FAERS Search Strategy[*]

Date of Search	May 29, 2019
Time Period of Search	January 1, 2006[†] - May 15, 2019
Search Type	FBIS Quick Query

Table 2. FAERS Search Strategy*	
Product Terms	*Product Active Ingredient*: Amphetamine aspartate monohydrate;amphetamine adipate\dextroamphetamine;amphetamine phosphate;amphetamine aspartate; amphetamine hydrochloride; amphetamines NOS; amphetamine\dextroamphetamine; amphetamine; dextroamphetamine hydrochloride; dextroamphetamine; dextroamphetamine saccharate; dextroamphetamine sulfate; amphetamine sulfate\dextroamphetamine; amphetamine aspartate\amphetamine sulfate\dextroamphetamine saccharate\dextroamphetamine sulfate;amphetamine sulfate; amphetamine aspartate\dextroamphetamine saccharate;amphetamine adipate
MedDRA Search Terms (Version 22.0)	All Preferred Terms (PTs)
Age (years)	0-16.99
* See Appendix A for a description of the FAERS database. † Data lock date of previous OSE amphetamine product postmarketing review for pediatric patients Abbreviations: FBIS= FDA Business Intelligence System, MedDRA=Medical Dictionary for Regulatory Activities	

2.2 DRUG UTILIZATION

Proprietary drug utilization databases available to the Agency were used to conduct these analyses. Detailed descriptions of the databases are provided in **Appendix B**.

2.2.1 Data Source Used

IQVIA, National Sales Perspectives™ (NSP) database was used to determine the settings of care where amphetamines or mixed salts of single-entity amphetamine products were sold from manufacturers to the various channels of distribution in the U.S. for 2018.

The IQVIA Total Patient Tracker™ (TPT) database was used to obtain a nationally estimated number of unique patients who received dispensed prescriptions for amphetamines or mixed salts of single-entity amphetamine products, stratified by age (<6 years, 6-12 years, 13-16 years, and ≥17 years), from U.S. outpatient retail pharmacies from January 2006 through December 2018.

3 RESULTS

3.1 FAERS

3.1.1 Total Number of FAERS Reports by Age

Table 3 presents the number of adult and pediatric FAERS reports, from January 1, 2006 to May 15, 2019, associated with amphetamines or mixed salts of single-entity amphetamine products.

Table 3. Total Adult and Pediatric FAERS Reports* Received by FDA from January 1, 2006 to May 15, 2019 with Amphetamine or Mixed Salts of Single-Entity Amphetamine Products

	All reports (U.S.)	Serious† (U.S.)	Death (U.S.)
Adults (≥ 17 years)	6,854 (6,166)	4,709 (4,052)	2,094 (1,751)
Pediatrics (0 - <17 years)	1,160 (1,063)	738 (644)	96‡ (92)

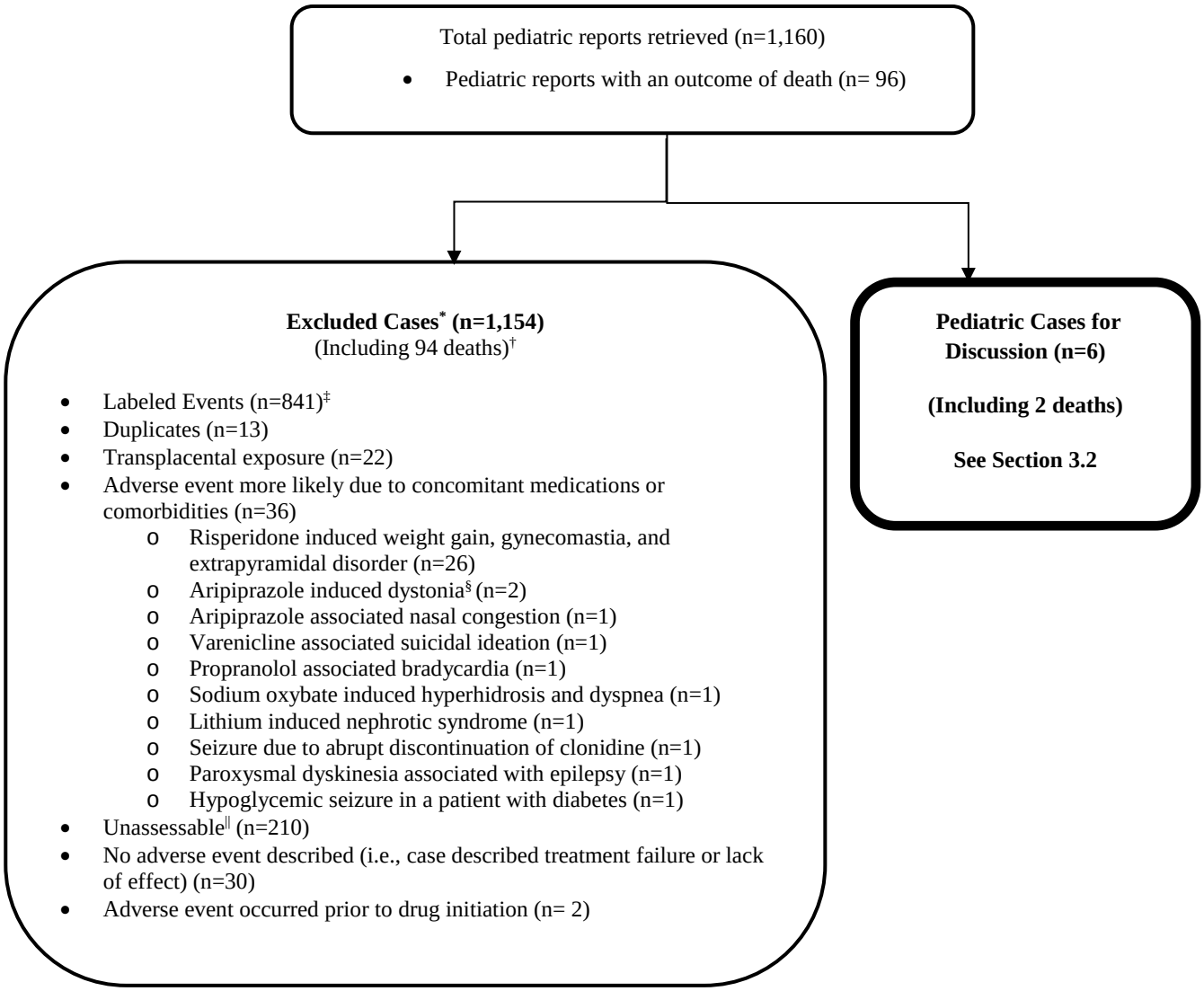
* May include duplicates and transplacental exposures, and have not been assessed for causality
† For the purposes of this review, the following outcomes qualify as serious: death, life- threatening, hospitalization (initial or prolonged), disability, congenital anomaly, required intervention, and other serious important medical events.
‡ Includes three additional reports of pediatric death identified among reports not reporting an age

3.1.2 Selection of Pediatric Cases in FAERS

Our FAERS search retrieved 1,160 pediatric reports with amphetamines or mixed salts of single-entity amphetamine products from January 1, 2006 to May 15, 2019. DPV-I screened the 1,160 reports and excluded reports from further analysis if they were only coded with labeled

PTs that did not reflect an apparent increase in severity of the labeled events. We conducted a hands-on review of all remaining pediatric reports and further excluded reports from the case series for various reasons, such as duplicate reports, the adverse event was unlikely to be causally related to the use of amphetamines or mixed salts of single-entity amphetamine products (e.g., adverse event occurred prior to drug initiation, co-morbid diseases or concomitant medications provide a more likely explanation for adverse events), no adverse event described, unassessable cases (i.e., cases that cannot be clinically assessed because information is insufficient, lacking or contradictory), or transplacental exposure. We summarize the remaining cases in the sections below. **Figure 1** presents the selection of cases for the pediatric case series.

Figure 1. Selection of Pediatric Cases with Amphetamines or Mixed Salts of Single-Entity Amphetamine Products



*DPV reviewed these cases, but they were excluded from further discussion for the reasons listed above
†The 94 excluded death cases included cases with labeled events (n=73), cases that were unassessable (n=17), cases that were duplicate (n=1), cases where no adverse event was described (n=2), and cases reporting transplacental exposure (n=1).
‡ Includes labeled cardiovascular, psychiatric, neurological, drug abuse, and vascular adverse events
§ The reported dystonia in these cases was induced by aripiprazole (labeled event) in pediatric patients who were not concomitantly on stimulants
|| Unassessable: case cannot be assessed for causality because there is insufficient clinical information (e.g., unknown temporality, missing past medical history or concomitant medication)

3.2 CHARACTERISTICS OF PEDIATRIC CASES

Appendix C contains a line listing of the six pediatric cases.

Table 4 summarizes the six FAERS cases in pediatric patients with amphetamines or mixed salts of single-entity amphetamine products received by FDA from January 1, 2006 to May 15, 2019.

Table 4. Characteristics of the FAERS Pediatric Cases with Amphetamines or Mixed Salts of Single-Entity Amphetamine Products Received by FDA from January 1, 2006 to May 15, 2019 (N=6)		
Age	6 – 12 years	4

	13 – 17 years	2
Sex	Male	4
	Female	2
Country	United States	6
Reported Reason for Use	ADHD	6
Serious Outcome*	Death	2
	Hospitalization	1
	Other Serious	4

* 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. A case may have more than one serious outcome.
Abbreviation: ADHD=Attention-Deficit Hyperactivity Disorder

3.2.1 Summary of Fatal Pediatric Cases (N=2)

We identified two fatal pediatric cases with amphetamines or mixed salts of single-entity amphetamine products. One case reported sudden death due to exertional heat stroke while on amphetamine for ADHD. The other case reported an adolescent who committed suicide a week and half after starting Adderall for ADHD. In both cases, the extent of the causal association between amphetamines or mixed salts of single-entity amphetamine products and death was difficult to determine given the available information. The cases are summarized below.

FAERS #10696211v1, MCN:US-TEVA-532557, USA 2015[9]

A 15-year-old male (97 kg) developed exertional heat stroke during football training and subsequently died from complications of heat stroke. Past medical history was significant for ADHD. The patient took amphetamine/dextroamphetamine for ADHD for an unknown duration and had no other concomitant medications. The boy collapsed during football practice on a hot day. On arrival at an emergency department (ED), he had shallow and slow respirations (6/min). His blood pressure (BP) was 80/30 (units not reported), heart rate was 180, oxygen saturation was 92%, and his rectal temperature was 41.8ºC. He had an estimated Glasgow Coma Scale score of five. His skin was cool and wet, with a capillary refill time of more than three seconds. He vomited once. The boy was intubated and ventilated, and aggressively cooled. After 40 minutes, he was cooled to 39.4ºC; he became more combative and required sedation. There was moderate blood in the urine and urinalysis was positive for amphetamines and myoglobin. His systolic BP rose to 179 (diastolic was 62) at three hours after arrival with cooled saline infusions. He began receiving sodium nitroprusside due to decreased cardiac afterload. He was transferred to the pediatric intensive care unit (PICU). He developed worsening coagulopathy despite transfusion of blood products; he had worsening anemia, thrombocytopenia, leukopenia, and elevated serum creatinine and decreased urine output. An echocardiogram showed borderline mitral valve prolapse and low normal left ventricular function, with a shortening ejection fraction of 28%. He became increasingly hypotensive and hypoxic; nitroprusside was discontinued and he was placed on vasopressors with no improvement. Because of his deteriorating condition, he was placed on extracorporeal membrane oxygenation (ECMO). Blood cultures grew pneumococcus and his hypotension worsened despite increasing vasopressor and ECMO support. On hospital day 4, no further escalations of treatment were planned, and he passed away. The physician stated that receiving amphetamine for ADHD was a contributing factor to the death of this patient.

Reviewer comments: Heat stroke is not a labeled adverse event in the prescribing information of any amphetamine product. Heat stroke follows failure of thermoregulation that is manifested in findings of core body temperature of greater than 40°C (104°F), along with altered mental status, coma, or seizures.[10] This report describes exertional heat stroke, which can occur in young and healthy individuals who engage in strenuous exercise during periods of high ambient temperature and humidity. According to a recent analysis of surveillance data of reported exertional heat illness (EHI) among high school sports, 44.3% of EHIs occurred in American football preseason practices.[11] Predisposing factors such as medications and obesity can exacerbate exertional heat stroke.[10,12] Stimulants such as ephedra, cocaine and methamphetamine can affect thermoregulation and increase the body's temperature thereby increasing the individual's risk for heat stroke.[13] Additionally, stimulants may increase the risk of cardiovascular problems as they can increase blood pressure and heart rate.[14] However, given that the amphetamine dose or duration of treatment is unknown in this case, it is not possible to determine the extent to which the patient's prescribed amphetamine contributed to the development of a fatal heat stroke with the available information.

FAERS #14007201v1, direct report, USA 2017

A 13-year-old boy committed suicide a week and half after starting Adderall for ADHD after an uncharacteristic aggressive outburst. His past medical history was significant for ADHD. He was previously on Vyvanse and was recently switched to Adderall. His mother reported that she sent her son to his room after he yelled and hit her when she asked him to put away his toys and start working on his book report. According to his mother he has never had a similar aggressive outburst, but she recalls that he mentioned since switching to Adderall he felt "a lot angrier" at things that normally would not bother him. A few hours later he was found in his bedroom hanging from his bunk bed. The investigators found no evidence that his death was a planned suicide. According to the mother, her son was not suicidal and was not being treated for depression. However, he was seeing a counselor to help with his ADHD symptoms.

Reviewer comments: Suicide is not a labeled event in the prescribing information of amphetamines products. However, the prescribing information recommends screening all patients for psychiatric illness including family history of suicide prior to initiation of amphetamines for ADHD. Aggressive behavior or hostility has been reported in clinical trials and postmarking experience in some medications indicated for ADHD.[1,2] Studies have shown that amphetamines can be effective in reducing some emotional symptoms in patients with ADHD (e.g., anxiety) but can exacerbate other symptoms such emotional lability.[15] In our case, the patient was stable on Vyvanse (lisdexamfetamine) and was switched to Adderall for an unreported reason. Although the narrative states the patient did not have a history of similar aggressive episodes, there is no information about his baseline ADHD symptoms, mood, psychosocial milieu, past suicidal ideation and behavior, or history of evaluation by a healthcare professional. Therefore, it is difficult to determine the extent to which the patient's Adderall use contributed to the development of suicide with the available information reported in this case.

3.2.2 Summary of Non-Fatal Pediatric Cases (N=4)

The non-fatal pediatric cases reported unlabeled adverse events of acute dystonia/withdrawal syndrome, glaucoma/borderline glaucoma, and necrotizing vasculitis. We identified these unlabeled adverse events of interest in the pediatric population with amphetamines or mixed salts of single-entity amphetamine products.

FAERS #6085785v1, MCN: SPVI-2006-00094, USA 2006

Unlabeled Event: Glaucoma (n=1)
A six-year-old black female reportedly developed glaucoma seven months after starting Adderall XR for ADHD. The patient had no additional medical history and no concomitant medications. Her mother reported that the patient's eye pressure was normal one year prior. The patient was initially started on Adderall XR 5 mg daily. The report indicates that after seven months, the Adderall XR dose was increased to 30 mg and the patient's mother noted that her child "did not seem herself." The patient's mother reduced the dose to half a capsule daily and took the patient for an examination. The patient was found to have elevated ocular pressure but remained asymptomatic. The physician stated, "that this could be a sign of glaucoma" and asked the patient to return for reexamination in six months. The physician did not recommend stopping Adderall XR.

FAERS #6154767v1 MCN:SPV1-2006-00970, USA 2006

Unlabeled Event: Borderline Glaucoma (n=1)
A mother of an 8-year-old Caucasian male taking Adderall (immediate-release) and Adderall XR for ADHD reported the occurrence of borderline glaucoma and migraines after starting therapy with these medications. First, Adderall, 10 mg daily, was started for two years and then stopped in favor of Adderall XR, 20 mg daily. Four years after starting Adderall for ADHD, the patient was diagnosed as being "glaucoma suspect." At that time, the patient began having migraines. Adderall XR therapy was then stopped, and the patient was being treated with brimonidine tartrate eye drops with continued migraines.

Reviewer comments: Glaucoma is not a labeled adverse event in the prescribing information of any amphetamines. The patients' ages suggest they did not have congenital glaucoma, which presents in infancy.[16] CNS stimulants exhibit sympathomimetic activity and may induce mydriasis provoking an increase in intraocular pressure.[17] Consequently, some stimulants such as Adderall are contraindicated in patients with glaucoma. A literature search of "amphetamines and glaucoma" in PubMed did not yield any additional case reports. An expanded search of the FAERS database using the Preferred Terms, Glaucoma and Borderline glaucoma, did not identify additional reports of glaucoma in pediatric patients associated with amphetamines.

FAERS #7124274v1 MCN: US-TYCO HEALTHCARE/MALLINCKRODT-T200901707, USA 2009[18]

Unlabeled event: Necrotizing Vasculitis(n=1)
A 10-year-old white female developed necrotizing vasculitis 10 months after starting dextroamphetamine for ADHD. Her past medical history was significant for ADHD with no

other concomitant medications. She had no family history of connective tissue disease, antiphospholipid syndrome or vasculitis. The patient was referred to the rheumatology clinic after experiencing one month of intermittent cyanosis and erythema of both feet, which was associated with pruritis and pain. Similar symptoms were not observed in her hands. One month before the onset of her symptoms her dextroamphetamine dose was increased from 10 to 30 mg. On physical examination her feet were cool to touch with poor capillary refill without skin breakdown or ulceration. The remainder of her skin was normal. Initial investigations were remarkable only for a positive antinuclear antibody (ANA) of 1:320 titer. The skin biopsy was consistent with necrosis of the malpighian layer with perivascular lymphocytic infiltration. The immunofluorescence staining revealed IgG and IgM deposition in the parakeratotic area. IgM and complement C3 deposition were noted in the vessels of the papillary and deep dermis. Destruction of the vessels in the papillary dermis with dense perivascular lymphocytic infiltrate in the papillary and deep dermis was noted, consistent with necrotizing vasculitis. Dextroamphetamine was discontinued and on reevaluation five days after stopping the medication, there was improvement in the color of the toes and the pain improved. The discoloration and pain resolved completely one month after drug discontinuation. She was switched to bupropion shortly after the discontinuation of dextroamphetamine without recurrence of her cyanosis.

Reviewer comments: Necrotizing vasculitis is not a labeled adverse event in the prescribing information of the amphetamine products. Vasculitis has multiple potential etiologies including inflammatory, autoimmune, malignant, and drug-induced.[19] Amphetamines are labeled for peripheral vasculopathy, including Raynaud phenomenon. Very rare sequelae of these adverse events include digital ulceration. Amphetamines are non-catecholamine, sympathomimetic amines with CNS stimulant activity. They exert their action by displacing noradrenaline and dopamine from storage areas on the nerve terminal into the synaptic junction. Increasing noradrenaline and dopamine concentrations can promote vasoconstriction and ischemia. Experimental models show that amphetamines can decrease vascular diameter and cause filling defects.[20] In patients with underlying vascular sensitivity this may lead to worsening of symptoms presenting as necrotizing vasculitis on histopathology.[18] The patient's presentation and biopsy findings are consistent with an inflammatory process. However, ANA in pediatric patients are nonspecific and can reflect a multitude of clinical conditions therefore the isolated positive ANA does not narrow the differential or indicate whether the symptoms reflect a drug reaction or primary inflammatory or autoimmune process.[21] DPV-I searched the FAERS database for additional cases in all ages using with the PT Necrotizing vasculitis reported with amphetamines but did not retrieve any additional cases.

FAERS#113939486v1 MCN: US-TEVA-364134USA. USA 2015[22]

Unlabeled event: Dystonia/withdrawal syndrome (n=1)

A 7-year-old boy (weight 47 kg) developed dystonic neck reactions after missing several doses of dextroamphetamine 30 mg. Past medical history was significant for ADHD and a learning disorder that was diagnosed after poor school performance. He was initially started on dextroamphetamine 30 mg for ADHD with reported symptom improvement. Due to the presence of facial tics and episodes of aggressiveness, aripiprazole 2 mg daily was initiated. Remarkable behavioral improvement was observed over the next two weeks and the parents reportedly

neglected to give him his daily dextroamphetamine dose. The patient presented with neck spasms on three different occasions on the same day and dystonic neck contraction the following day. Aripiprazole was decreased to 1 mg and dextroamphetamine 30 mg was reinitiated with resolution of the neck dystonia. Subsequently, the aripiprazole dose was increased back to 2 mg with symptomatic improvement.

Reviewer comments: Dystonia is not a labeled adverse event in the prescribing information of amphetamines. However, dystonia is a labeled adverse event with all antipsychotics.[23] Dystonia associated with antipsychotics may occur in susceptible individuals during the first few days of treatment.[23] Additionally, an elevated risk of acute dystonia is observed in males and younger age groups.[23] A potential mechanism for dystonic reaction with stimulant withdrawal after concomitant stimulant and atypical antipsychotics use rests on each drug class's effect on dopamine at the synaptic cleft. Stimulants exert their effect by inhibiting dopamine reuptake and increasing synaptic dopamine. Aripiprazole is a partial dopamine agonist with high affinity to D_2 receptors and can act as an antagonist when dopamine levels are elevated, such as when co-administered with stimulants. Abrupt withdrawal of co-administered stimulants, as in this case, can lead to replacement of dopamine with a partial agonist like aripiprazole that can act as an antagonist in this milieu resulting in a dystonic reaction. The resolution of dystonic reaction after re-introduction of stimulants reinforces the biologic plausibility of the mechanism of action. DPV-I searched the FAERS database in all ages for additional cases with the PT (Acute dystonia) associated with the concomitant use of amphetamines and antipsychotics and retrieved additional cases requiring further evaluation.

3.3 DRUG UTILIZATION

3.3.1 Settings of Care

In 2018, approximately 94% of amphetamines or mixed salts of single-entity amphetamine products were sold from manufacturers to U.S. retail channels of distribution, 5% to non-retail channels, and 1% to mail-order/specialty channels.[a] Only utilization data from the U.S. outpatient retail setting was included in the analysis.

3.3.2 Number of Patients

Table 5 below shows the nationally estimated number of patients who received dispensed prescriptions for amphetamine or mixed salts of single-entity amphetamine products from U.S. outpatient retail pharmacies from 2006 through 2018. The total number of patients who received dispensed prescriptions for amphetamines or mixed salts of single-entity amphetamine products increased from an estimated 2.8 million patients in 2006 to 5.1 million patients in 2018. Conversely, pediatric patients less than 17 years of age decreased from approximately 1.2 million patients in 2006 to 1 million patients in 2018. In 2018, pediatric patients 6-12 years of age accounted for approximately 61% (623,000 patients) of total pediatric patients, followed by pediatric patients 13-16 years of age at 38% (389,000 patients), and pediatric patients <6 years of age at 3% (32,000 patients). Similar proportions of pediatric use were observed throughout the

[a] IQVIA National Sales Perspectives™. 2018. Extracted November 2019. File: 2019-1440 NSP SE Amphetamine PREA.xlsx

study period. The increase in the use of amphetamines or mixed salts of single-entity amphetamine products was observed primarily in adult patients 17 years of age and older.

Table 5. Nationally Estimated Number of Patients Who Received a Dispensed Prescription for Amphetamine or Mixed Salts of Single-Entity Amphetamine Products, Stratified by Age* (<6 Years, 6-12 Years, 13-16 Years, and ≥17 Years), from U.S. Outpatient Retail Pharmacies, from January 2006 through December 2018.

	2006		2007		2008		2009		2010		2011		2012	
	Patients (N)	Share (%)	Patients (N)	Share (%)	Patients (N)	Share (%)	Patients (N)	Share (%)	Patients (N)	Share (%)	Patients (N)	Share (%)	Patients (N)	Share (%)
Total	**2,831,723**	**100%**	**2,802,474**	**100%**	**2,833,659**	**100%**	**2,916,368**	**100%**	**3,231,157**	**100%**	**3,837,085**	**100%**	**3,774,468**	**100%**
<17 years	1,211,727	43%	1,189,277	42%	1,050,328	37%	962,463	33%	972,267	30%	1,033,493	27%	951,533	25%
<6 years	44,763	4%	41,900	4%	38,436	4%	36,770	4%	38,721	4%	39,184	4%	36,316	4%
6-12 years	729,123	60%	711,100	60%	627,347	60%	575,081	60%	585,724	60%	624,104	60%	577,833	61%
13-16 years	456,613	38%	455,224	38%	402,283	38%	366,264	38%	359,109	37%	382,224	37%	350,328	37%
≥17 years	1,333,338	47%	1,552,350	55%	1,726,455	61%	1,901,511	65%	2,211,519	68%	2,747,971	72%	2,783,876	74%
Unspecified age	305,137	11%	87,419	3%	144,976	5%	135,843	5%	97,136	3%	124,829	3%	71,297	2%

	2013		2014		2015		2016			2017		2018	
	Patients (N)	Share (%)	Patients (N)	Share (%)	Patients (N)	Share (%)	Patients (N)	Share (%)		Patients (N)	Share (%)	Patients (N)	Share (%)
Total	**3,971,308**	**100%**	**4,296,199**	**100%**	**4,532,726**	**100%**	**4,844,652**	**100%**		**4,883,291**	**100%**	**5,085,183**	**100%**
<17 years	959,345	24%	999,868	23%	1,029,586	23%	1,042,706	22%	**Trend Break**	1,025,916	21%	1,025,048	20%
<6 years	35,703	4%	43,993	4%	39,169	4%	37,442	4%		34,076	3%	31,685	3%
6-12 years	587,842	61%	613,020	61%	631,675	61%	642,079	62%		631,676	62%	623,196	61%
13-16 years	351,656	37%	362,674	36%	375,896	37%	383,075	37%		379,270	37%	388,706	38%
≥17 years	2,973,450	75%	3,308,869	77%	3,556,757	78%	3,844,612	79%		3,867,671	79%	4,058,391	80%
Unspecified age	266,058	7%	155,766	4%	42,124	1%	7,836	<0.5%		43,192	1%	17,020	<0.5%

Source: IQVIA, Total Patient Tracker™. 2006-2018. Extracted December 2019. File: 2019-1440 TPT Amphetamine 0-5_6-12_13-16_17_ 2006-2018 report.xlsx

*Patient age is calculated using patient's year of birth and the year of a prescription, and some age misclassification is possible.

Unique patient counts may not be added across time periods or age groups due to the possibility of double counting those patients who are receiving treatment over multiple time periods or age into the next age group during the time period.

Prescription data and resulting projected patient estimates have been adjusted to account for prescriptions that have been voided or reversed for data starting January 2017 and onward. This has resulted in a trend break between data through December 2016 and data starting January 2017.

4 DISCUSSION

We reviewed all FAERS reports with amphetamine or mixed salts of single-entity amphetamine products, including the two products that triggered this review (i.e., Mydayis and Adzenys ER), from January 1, 2006 to May 15, 2019. From 2006 to 2018, a range of approximately 1 to 1.2 million pediatric patients younger than 17 years of age received dispensed prescriptions annually for amphetamine or mixed salts of single-entity amphetamine products, of which the majority of patients were 6-16 years of age. The majority of FAERS reports described adverse events that were consistent with the known adverse reactions described in labeling or conditions associated with ADHD. We did not identify an increase in severity in the labeled adverse events associated with amphetamines. Of the total FAERS reports evaluated, we identified six cases as adverse events of interest.

Of the six cases, we identified two cases describing a fatal outcome and four cases describing non-fatal unlabeled adverse events. Both fatal reports described risk factors that may have contributed to the fatal outcome. Additionally, the extent of the causal association between amphetamines or mixed salts of single-entity amphetamine products and death was difficult to determine given the reported information. Of the four non-fatal adverse events, two cases described glaucoma or borderline glaucoma. Both cases reported a long latency period to developing glaucoma and had limited information which precluded a meaningful causality assessment.

Of the remaining two non-fatal adverse events of interest, one case reported necrotizing vasculitis and the other reported acute dystonia. We further explored the case reporting necrotizing vasculitis as an adverse event of interest. We searched for additional cases of necrotizing vasculitis in all age groups within the FAERS database. Our search did not identify any additional cases. The singular case of necrotizing vasculitis identified in this review does not represent a new safety signal at this time.

The remaining non-fatal report described acute dystonia associated with amphetamine withdrawal after concomitant use of amphetamines and antipsychotics in a child. Dystonia started after amphetamine withdrawal and the dystonia resolved after the stimulant re-introduction. The case reported a close temporal sequence; the reintroduction of the amphetamine contributing to the resolution of the adverse event supports a possible causal association. However, the antipsychotic dose was also reduced simultaneously, and dystonia is a labeled adverse event with all antipsychotics. The biological plausibility of this drug interaction is based on the effects of simulants and antipsychotics on dopamine at the synaptic cleft. We searched for additional cases of acute dystonia associated with concomitant use of amphetamines and antipsychotics in all age groups within the FAERS database. Our search identified additional cases requiring further evaluation.

FDA opened a NISS #1102 for the drug-drug interaction (DDI) between ADHD stimulants/atomoxetine and antipsychotics associated with acute hyperkinetic disorders and notified the Applicants of the opening of this NISS for further investigation. OSE and DP performed three additional reviews for this safety signal[24-26]; the full assessment of this DDI is described in separate signal review documents. OSE identified 36 cases (11 probable and 25 possible cases) of acute hyperkinetic movement disorder associated with the concomitant use of ADHD stimulants/atomoxetine and antipsychotics. From an ADHD stimulant perspective, most

of the cases were reported with methylphenidate products (n=23), followed by amphetamine products (n=9), and atomoxetine (n=4). From an antipsychotic perspective, all 36 cases were reported with second generation antipsychotics (SGAs) [risperidone (n=20), aripiprazole (n=11), olanzapine (n=2), quetiapine (n=1), paliperidone (n=1), and ziprasidone (n=1)]. As a result of this investigation, the totality of the evidence was supportive of a DDI between methylphenidate products and risperidone; the evidence was not as strong for the amphetamine products. Therefore, we recommended the incorporation of this DDI into all risperidone and methylphenidate product labeling within the Drug Interaction section.

5 CONCLUSION

OSE identified a DDI with the concomitant use of risperidone and methylphenidate products as a safety signal and the labeling of both products will be updated accordingly. The labeled adverse events reported in FAERS with amphetamine and mixed salts of single-entity amphetamine products in the pediatric population are consistent with the known adverse events described in labeling; there is no evidence of increased frequency or severity for these labeled events. The FAERS database analysis and the drug utilization data do not suggest a change in the overall benefit-risk profile of these products in the pediatric population.

6 RECOMMENDATION

Based on the findings from this pediatric postmarketing pharmacovigilance review, OSE recommended further evaluation of the DDI between ADHD stimulants/atomoxetine and antipsychotics associated with acute hyperkinetic disorders. The DDI evaluation was concurrent with the pediatric postmarketing pharmacovigilance review and is described in separate documents from OSE and DP. The signal reviews led to labeling recommendations for a DDI between risperidone and methylphenidate products. OSE recommends no additional regulatory action based on this pediatric postmarketing pharmacovigilance review. OSE will continue routine pharmacovigilance for all amphetamine and mixed salts of single-entity amphetamine products.

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8 APPENDICES

8.1 APPENDIX A. FDA ADVERSE EVENT REPORTING SYSTEM

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 FDA's postmarketing safety surveillance program for drug and therapeutic biological products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Council 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.

8.2 APPENDIX B. DRUG UTILIZATION DATABASE DESCRIPTIONS AND 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)

IQVIA Total Patient Tracker (TPT) is a national-level projected service designed to estimate the total number of unique (non-duplicated) patients across all drugs and therapeutic classes in the retail outpatient setting from U.S. retail pharmacies. Data are available back to January 2002 and are available 20 days after the close of the month. TPT uses prescription activity as part of its projection and integrates information from pharmacies and payers to eliminate duplicate patients and multiple prescription fills, producing quick and reliable unique patient counts. IQVIA has 92% coverage and a sample of ~58,900 retail pharmacies. IQVIA captures about 3.8 billion transactions annually. TPT is projected to the known universe of retail pharmacies.

Of note, the estimated prescription and/or patient counts provided are based on projections of sample prescription claims data and therefore have some degree of inherent sampling error. These estimates are not intended to be representations of exact enumerations and should be interpreted with caution particularly if they are based on a small sample size. In addition, the data cannot be validated due to lack of access to medical records in the data sources

8.3 APPENDIX C. FAERS LINE LISTING OF THE PEDIATRIC CASE SERIES (N=6)

	Initial FDA Received Date	FAERS Case #	Version #	Manufacturer Control #	Case Type	Age (years)	Sex	Country Derived	Serious Outcomes*
1	1/7/2015	10696211	1	US-TEVA-532557USA	Expedited	15	M	USA	DE,HO,OT
2	9/24/2017	14007201	1	-	Direct	13	M	USA	DE
3	8/8/2015	11393486	1	US-TEVA-586011USA	Expedited	7	M	USA	OT
4	7/5/2006	6085785	1	SPVI-2006-00094	Expedited	6	F	USA	OT
5	10/12/2006	6154767	1	SPV1-2006-00970	Expedited	8	M	USA	OT
6	9/21/2009	7124274	1	US-TYCO HEALTHCARE/MALLINCKRODT-T200901707	Expedited	10	F	USA	OT

*As per 21 CFR 314.80, the regulatory definition of serious is any adverse drug experience occurring at any dose that results in any of the following outcomes: Death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect, and other serious important medical events. Those which are blank were not marked as serious (per the previous definition) by the reporter, and are coded as non-serious. A case may have more than one serious outcome.
Abbreviations: DE=Death, HO=Hospitalization, OT=Other medically significant, M=Male, F=Female

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