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Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Pediatric Postmarketing Pharmacovigilance and Drug Utilization Review

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Product Name(s):	Abilify (aripiprazole)
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Application Type/Number:	NDA 21436, 21713, 21729, 21866
Applicant/Sponsor:	Otsuka Pharmaceutical Co., Ltd.
OSE RCM #:	2016-2433

****This document contains proprietary drug use data obtained by FDA under contract. The drug use data/information cannot be released to the public/non-FDA personnel without contractor approval obtained through the FDA/CDER Office of Surveillance and Epidemiology.****

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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 aripiprazole in pediatric patients.

The oral formulation of aripiprazole was first approved by FDA in 2002, and is currently indicated for schizophrenia, acute treatment of manic and mixed episodes associated with Bipolar I, adjunctive treatment of major depressive disorder, irritability associated with autistic disorder, and treatment of Tourette's disorder. The approved pediatric labeling is for schizophrenia in age 13 to 17 years, bipolar I disorder in 10 to 17 years, irritability associated with autistic disorder in 6 to 17 years, and Tourette's disorder in 6 to 18 years.

The Division of Pharmacovigilance (DPV) identified 78 domestic pediatric cases with serious, unlabeled events as well as all fatal events reported with aripiprazole use from May 1, 2011 through November 30, 2016 in the FDA Adverse Event Reporting System (FAERS) database. There were no new safety signals identified, no apparent increase in the severity or frequency of any labeled adverse events, and there were no deaths directly associated with aripiprazole. There were 14 fatal cases and 64 non-fatal cases in the case series. Twelve of the fatal cases reported a cause of death, and none of the causes of death were attributed solely to aripiprazole. Five of the deaths were related to suicidal behavior, only one of which provided sufficient information to determine a possible causal relationship between aripiprazole and the suicidal behavior. Of note, aripiprazole carries a Boxed Warning for "suicidal thoughts and behaviors" specifically for children, adolescents, and young adults using aripiprazole as antidepressant therapy. Over half of the 64 non-fatal cases (n=35) reported drug ineffective, product substitution issue, condition aggravated, drug effect decreased, or described other adverse events related to lack of effect.

Drug utilization patterns were assessed to capture pediatric use of oral aripiprazole and to provide context for the adverse event reports submitted to the FAERS database. The outpatient retail pharmacy utilization data showed that pediatric patients 0 to 17 years old accounted for 18% (517,000 patients) of the total patients who received dispensed prescriptions for oral aripiprazole from June 2014 through November 2016, cumulative.

Overall, there were no clear patterns of reported adverse events in the FAERS cases or trends in drug utilization to suggest a new safety signal associated with oral formulations of aripiprazole in pediatric patients at this time. Additionally, there have been multiple OSE reviews addressing safety issues with aripiprazole in the pediatric population conducted since approval, including two DPV reviews prepared for the Pediatric Advisory Committee meetings in December 2009 and September 2011. DPV recommends no labeling changes at this time. DPV will continue standard pharmacovigilance monitoring.

1 INTRODUCTION

1.1 PEDIATRIC REGULATORY HISTORY

Abilify (aripiprazole), an atypical antipsychotic, received FDA approval on November 15, 2002. The mechanism of action of aripiprazole is unknown; however, it has been proposed that the efficacy of aripiprazole is mediated through a combination of partial agonist activity at D_2 and 5-HT_{1A} receptors and antagonist activity at 5-HT_{2A} receptors. Table 1.1 below provides the recommended dosing schedule for aripiprazole and its corresponding indication.[1]

Table 1.1. Dosage and Administration of Aripiprazole, Per Indication and Population, Sorted by Approval Date*

Indication and Population	Initial Dose†	Recommended Dose	Maximum Dose	Approval Date
Schizophrenia – adults	10-15 mg/day	10-15 mg/day	30 mg/day	November 15, 2002
Bipolar I disorder (acute treatment of manic and mixed episodes) – adults: monotherapy	15 mg/day	15 mg/day	30 mg/day	September 29, 2004
Agitation associated with schizophrenia or bipolar mania – adults	9.75 mg injected IM	--	30 mg/day injected IM	November 20, 2006
Schizophrenia – adolescents (ages 13 – 17)‡	**2 mg/day**	**10 mg/day**	**30 mg/day**	**October 29, 2007**
As an adjunct to antidepressants for the treatment of major depressive disorder – adults	2-5 mg/day	5-10 mg/day	15 mg/day	November 16, 2007
Bipolar I disorder (acute treatment of manic and mixed episodes) – pediatric patients (age 10 – 17): monotherapy or as an adjunct to lithium or valproate	**2 mg/day**	**10 mg/day**	**30 mg/day**	**February 27, 2008**
Bipolar I disorder (acute treatment of manic and mixed episodes) – adults: adjunct to lithium or valproate	10 – 15 mg/day	15 mg/day	30 mg/day	May 6, 2008
Irritability associated with autistic disorder – pediatric patients (ages 6 – 17 years)	**2 mg/day**	**5-10 mg/day**	**15 mg/day**	**November 19, 2009**

Table 1.1. Dosage and Administration of Aripiprazole, Per Indication and Population, Sorted by Approval Date*				
Indication and Population	**Initial Dose†**	**Recommended Dose**	**Maximum Dose**	**Approval Date**
Tourette's disorder (ages 6-18 years)	**2 mg/day**	**5-10 mg/day**	**10-20 mg/day§**	**December 12, 2014**

* Indications related to maintenance treatment in adults were omitted from this table, which includes maintenance treatment of schizophrenia (approved Aug 28, 2003), maintenance treatment of bipolar I disorder (Mar 1, 2005), and maintenance treatment of bipolar I disorder as an adjunct to lithium or valproate (Feb 16, 2011).
† All routes of administration are oral unless otherwise specified.
‡ Pediatric indications emphasized in **bold.**
§ Max dose is 10 mg/day for patients < 50 kg, and 20 mg/day for patients ≥ 50 kg.

Aripiprazole is available in a 2 mg, 5 mg, 10 mg, 15 mg, 20 mg, and 30 mg tablet, in addition to a 10 mg and 15 mg orally disintegrating tablet, a 1 mg/ml oral solution, and a 9.75 mg/1.3 mL solution for intramuscular injection. Aripiprazole is also available as a long-acting injectable, which is indicated for treatment of schizophrenia in adults only.

This Pediatric Research Equity Act (PREA) review triggered as a result of a clinical trial (CN138603) in pediatric patients with irritability associated with autistic disorder, conducted by the sponsor as part of a postmarketing requirement (#1570-1) requested by the Division of Psychiatry Products (DPP) on November 19, 2009. The 12-week maintenance efficacy trial with a randomized withdrawal design in pediatric patients (6 to 17 years of age; n = 85) with irritability associated with autistic disorder failed to demonstrate the efficacy of oral aripiprazole for this indication.[2] The results of the trial were incorporated into aripiprazole labeling on June 9, 2014:

> DOSAGE AND ADMINISTRATION
> 2.4 Irritability Associated with Autistic Disorder
> *Pediatric Patients*
>
> Maintenance Treatment: In a clinical trial with ABILIFY conducted in children and adolescents (6 to 17 years of age), the efficacy of ABILIFY for the maintenance treatment of irritability associated with autistic disorder was not established [see Use in Specific Populations (8.4)]. Patients should be periodically reassessed to determine the continued need for maintenance treatment.
>
> USE IN SPECIFIC POPULATIONS
> 8.4 Pediatric Use
> A maintenance trial was conducted in pediatric patients (6 to 7 years of age) with irritability associated with autistic disorder. The first phase of the trial was an open-label,

flexibly dosed (aripiprazole 2 to 15 mg/day) phase in which patients were stabilized (defined as > 25% improvement on the ABC-I subscale, and a CGI-I rating of "much improved" or "very much improved") on ABILIFY for 12 consecutive weeks. Overall, 85 patients were stabilized and entered the second, 16-week, double-blind phase where they were randomized to either continue ABILIFY treatment or switch to placebo. In this trial, the efficacy of ABILIFY for the maintenance treatment of irritability associated with autistic disorder was not established.

The labeling changes apply to the following aripiprazole formulations: oral tablets (NDA 21436), oral solution (NDA 21713), orally disintegrating tablets (NDA 21729), and immediate acting intramuscular injection (NDA 21866). Although the immediate acting intramuscular injection formulation of aripiprazole labeling is linked with the oral formulations' labeling, it is indicated for agitation associated with schizophrenia or bipolar mania only, and is not indicated for the treatment of irritability associated with autistic disorder. The focus of this review is oral formulations of aripiprazole, because injectable formulations were not studied in the clinical trial that led to the above labeling changes, and the injectable formulations of aripiprazole are not indicated for the treatment of irritability associated with autistic disorder or any other pediatric indication.

1.2 HIGHLIGHTS OF LABELED SAFETY ISSUES

WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS AND SUICIDAL THOUGHTS AND BEHAVIORS WITH ANTIDEPRESSANT DRUGS

- **Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. ABILIFY is not approved for the treatment of patients with dementia-related psychosis.**
- **Increased risk of suicidal thinking and behavior in children, adolescents, and young adults taking antidepressants. Monitor for worsening and emergence of suicidal thoughts and behaviors.**

----------CONTRAINDICATIONS----------

- Known hypersensitivity to ABILIFY

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

- *Cerebrovascular Adverse Reactions in Elderly Patients with Dementia-Related Psychosis:* Increased incidence of cerebrovascular adverse reactions (e.g., stroke, transient ischemic attack, including fatalities)
- *Neuroleptic Malignant Syndrome:* Manage with immediate discontinuation and close monitoring
- *Tardive Dyskinesia:* Discontinue if clinically appropriate

- *Metabolic Changes:* Atypical antipsychotic drugs have been associated with metabolic changes that include hyperglycemia/diabetes mellitus, dyslipidemia, and body weight gain
- *Hyperglycemia/Diabetes Mellitus:* Monitor glucose regularly in patients with and at risk for diabetes
- *Dyslipidemia:* Undesirable alterations in lipid levels have been observed in patients treated with atypical antipsychotics
- *Weight Gain:* Weight gain has been observed with atypical antipsychotic use. Monitor weight
- *Pathological Gambling and Other Compulsive Behaviors:* Consider dose reduction or discontinuation
- *Orthostatic Hypotension:* Monitor heart rate and blood pressure and warn patients with known cardiovascular or cerebrovascular disease, and risk of dehydration or syncope
- *Leukopenia, Neutropenia, and Agranulocytosis:* have been reported with antipsychotics including ABILIFY. Patients with a history of a clinically significant low white blood cell count (WBC) or a drug-induced leukopenia/neutropenia should have their complete blood count (CBC) monitored frequently during the first few months of therapy and discontinuation of ABILIFY should be considered at the first sign of a clinically significant decline in WBC in the absence of other causative factors
- *Seizures/Convulsions:* Use cautiously in patients with a history of seizures or with conditions that lower the seizure threshold
- *Potential for Cognitive and Motor Impairment:* Use caution when operating machinery
- *Suicide:* The possibility of a suicide attempt is inherent in schizophrenia and bipolar disorder. Closely supervise high-risk patients

----------**ADVERSE REACTIONS**----------

Commonly observed adverse reactions (incidence ≥5% and at least twice that for placebo) were:

- Adult patients with schizophrenia: akathisia
- Pediatric patients (13 to 17 years) with schizophrenia: extrapyramidal disorder, somnolence, and tremor
- Adult patients (monotherapy) with bipolar mania: akathisia, sedation, restlessness, tremor, and extrapyramidal disorder
- Adult patients (adjunctive therapy with lithium or valproate) with bipolar mania: akathisia, insomnia, and extrapyramidal disorder
- Pediatric patients (10 to 17 years) with bipolar mania: somnolence, extrapyramidal disorder, fatigue, nausea, akathisia, blurred vision, salivary hypersecretion, and dizziness
- Adult patients with major depressive disorder (adjunctive treatment to antidepressant therapy): akathisia, restlessness, insomnia, constipation, fatigue, and blurred vision
- Pediatric patients (6 to 17 years) with autistic disorder: sedation, fatigue, vomiting, somnolence, tremor, pyrexia, drooling, decreased appetite, salivary hypersecretion, extrapyramidal disorder, and lethargy
- Pediatric patients (6 to 18 years) with Tourette's disorder: sedation, somnolence, nausea, headache, nasopharyngitis, fatigue, increased appetite
- Adult patients with agitation associated with schizophrenia or bipolar mania: nausea

----------DRUG INTERACTIONS----------

Dosage adjustment due to drug interactions:

Factors	Dosage Adjustment of ABILIFY
Known CYP2D6 Poor Metabolizers	Administer half of usual dose
Known CYP2D6 Poor Metabolizers and strong CYP3A4 inhibitors	Administer a quarter of usual dose
Strong CYP2D6 or CYP3A4 inhibitors	Administer half of usual dose
Strong CYP2D6 and CYP3A4 inhibitors	Administer a quarter of usual dose
Strong CYP3A4 inducers	Double usual dose over 1 to 2 weeks

----------USE IN SPECIFIC POPULATIONS----------

- Pregnancy: May cause extrapyramidal and/or withdrawal symptoms in neonates with third trimester exposure
- Nursing Mothers: Discontinue drug or nursing, taking into consideration importance of drug to the mother

10 OVERDOSAGE

10.1 Human Experience

In clinical trials and in postmarketing experience, adverse reactions of deliberate or accidental overdosage with oral ABILIFY have been reported worldwide. These include overdoses with oral ABILIFY alone and in combination with other substances. No fatality was reported with ABILIFY alone. The largest known dose with a known outcome involved acute ingestion of 1260 mg of oral ABILIFY (42 times the maximum recommended daily dose) by a patient who fully recovered. Deliberate or accidental overdosage was also reported in children (age 12 and younger) involving oral ABILIFY ingestions up to 195 mg with no fatalities.

Common adverse reactions (reported in at least 5% of all overdose cases) reported with oral ABILIFY overdosage (alone or in combination with other substances) include vomiting, somnolence, and tremor. Other clinically important signs and symptoms observed in one or more patients with ABILIFY overdoses (alone or with other substances) include acidosis, aggression, aspartate aminotransferase increased, atrial fibrillation, bradycardia, coma, confusional state, convulsion, blood creatine phosphokinase increased, depressed level of consciousness, hypertension, hypokalemia, hypotension, lethargy, loss of consciousness, QRS complex prolonged, QT prolonged, pneumonia aspiration, respiratory arrest, status epilepticus, and tachycardia.

1.3 PREVIOUS OSE POST-MARKETING SAFETY REVIEWS

OSE completed a total of 11 post-marketing safety reviews involving aripiprazole to-date. Of those, eight OSE reviews included pediatric cases, and these are summarized below. See Appendix A for a summary listing of the other three post-marketing safety reviews. There are no completed DPV reviews for oral aripiprazole that are currently pending regulatory action.

- October 4, 2005. A class review of **galactorrhea** with atypical antipsychotic drugs, including aripiprazole, in pediatric patients. The review supported further analysis of hyperprolactinemia and galactorrhea with atypical antipsychotics in order to update

risperidone labeling to reflect the increased numbers of reports of hyperprolactinemia and galactorrhea associated with risperidone relative to other atypical antipsychotic drugs.[3]

- March 7, 2007. The review focused on **laryngeal dystonia** associated with aripiprazole. The review of the Adverse Event Reporting System (AERS) database led to OSE recommending the addition of 'laryngeal spasm and dystonic reactions involving the pharynx, hypopharynx and/or tongue' to the PRECAUTIONS section of the product labeling.[4]

- April 29, 2008. A review of aripiprazole, olanzapine, quetiapine, risperidone and ziprasidone post-marketing cases coded with death in children 16 years old and younger. In general, for the **fatal cases** reviewed, most cases reported cardiac disorders/sudden death as the cause of death. The review recommended continued surveillance of the AERS database for deaths associated with pediatric patients treated with atypical antipsychotics with a particular focus on cardiac and diabetes related cases.[5]

- September 25, 2008. The review focused on the adverse events of **bone marrow failure, hemolytic anemia, hepatic failure, hepatitis fulminant, liver transplant, pancytopenia, and Torsade de pointes**. OSE did not identify an association between these adverse events and aripiprazole; therefore, OSE did not recommend any revisions to the aripiprazole labeling.[6]

- October 20, 2009. A Best Pharmaceuticals for Children Act (BPCA) review summarized the post-marketing reports of adverse events associated with the use of aripiprazole in pediatric patients (0-16 years of age) from Approval to May 1, 2009. A review of the 83 non-fatal post-marketing cases and 10 cases with an outcome of death did not identify any new safety concerns. Among the associated adverse events in these pediatric cases, **extrapyramidal symptoms** were the adverse event most often reported with 31 cases. The review revealed adverse events that are qualitatively similar to those currently found in the aripiprazole product labeling and described in the adult as well as the pediatric population.[7]

- July 28, 2011. A BPCA review summarized the post-marketing reports of adverse events associated with the use of aripiprazole in pediatric patients (0-16 years of age) from May 1, 2009 to May 1, 2011. A review of 155 non-fatal post-marketing cases and seven cases with an outcome of death did not identify any new safety concerns. Among the associated adverse events in these pediatric cases, **extrapyramidal symptoms** were the adverse event most often reported with 27 cases. The review revealed adverse events that are qualitatively similar to those currently found in the aripiprazole product labeling and described in the adult as well as the pediatric population.[8]

- April 8, 2014. A pharmacovigilance review of aripiprazole, asenapine, clozapine, iloperidone, lurasidone, olanzapine, paliperidone, risperidone, and ziprasidone and **drug screen false positive** cases included both pediatric and adult cases. Of the 30 cases involving aripiprazole, two cases involved pediatric patients, a 14 year old male patient who has a false positive urine test for marijuana and phencyclidine (PCP), and a 15 year old female patient who had a false positive urine test for barbiturates. The review found insufficient evidence to recommend regulatory action, and stated that DPV would continue to monitor the FDA Adverse Event Reporting System (FAERS) database for additional cases reporting confirmatory testing of PCP and methamphetamine in association with aripiprazole use.[9]

- March 10, 2016. A pharmacovigilance review of aripiprazole and **impulse-control disorders (pathological gambling, compulsive sexual behaviors, compulsive buying, and compulsive eating)** cases included both pediatric and adult cases. Of the 184 case reports included in the review, one case involved a pediatric patient aged 5 years, who experienced compulsive eating in association with aripiprazole treatment. The review recommend labeling changes to aripiprazole, including the addition of a new Warning and Precautions regarding pathological gambling and other compulsive behaviors. The labeling language recommended is non-specific in regards to patient age. A drug safety communication was issued on May 3, 2016, which specifically notes that cases of impulse-control problems included both adults and children.[10]

2 DRUG UTILIZATION DATA

2.1 METHODS AND MATERIALS

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

2.1.1 Data Sources Used

Sales Distribution Data

The IMS Health, IMS National Sales Perspectives™ database was used to obtain the nationally estimated number of units (bottles) sold for oral aripiprazole from manufacturers to all U.S. channels of distribution, from June 2014 through November 2016. The sales distribution data represent the amount of product sold from manufacturers to pharmacies and other setting of care; it does not reflect what is being sold to or administered to patients directly.

Outpatient Retail Settings

The IMS Health Total Patient Tracker (TPT) database was used to provide the nationally estimated number of patients stratified by patient age (0-5, 6-12, 13-17, and 18 years and older)

who received dispensed prescriptions for oral aripiprazole from U.S. outpatient retail pharmacy settings from June 2014 through November 2016, cumulative.

The inVentiv Health, LLC., Treatment Answers™ database was used to determine the top diagnoses associated with the use[a] of oral aripiprazole, stratified by patient age (0-5, 6-12, 13-17, and 18 and older) from June 2014 through November 2016, cumulative.

2.2 RESULTS

2.2.1 Sales Distribution Data

2.2.1.1 Settings of Care

From June 2014 through November 2016, sales data for oral aripiprazole by the number of packages sold from manufacturers to all U.S. settings of distribution indicated that approximately 76% of sales were to outpatient retail pharmacies, 18% to non-retail settings and 6% to mail order/specialty pharmacies.[11] Accordingly, only U.S. outpatient retail pharmacy utilization patterns were examined for oral aripiprazole. Data from mail-order/specialty pharmacies and non-retail settings, such as clinics and hospitals, were not included in this review.

2.2.2 Outpatient utilization data

2.2.2.1 Patient Data

Table 2.2.2.1 shows the nationally estimated number of patients who received dispensed prescriptions for oral aripiprazole, from U.S. outpatient retail pharmacies, stratified by patient age from June 2014 through November 2016.

Pediatric patients 0-17 years accounted for approximately 18% (517,000 patients) of the total patients. Among pediatric patients, 13-17 years old accounted for the majority of use (64% or 333,000 patients), followed by 6-12 years old (41% or 210,000 patients) and 0-5 years (2% or 9,800 patients).

[a] The term "drug use" refers to mentions of a drug in association with a diagnosis during a patient visit to an office-based physician. This term may be duplicated by the number of diagnosis for which the drug is mentioned. It is important to note that a "drug use" does not necessarily result in a prescription being generated. Rather, the term indicates that a given drug was mentioned during an office visit.

Table 2.2.2.1 **Nationally estimated number of patients* who received prescriptions for oral aripiprazole from U.S. outpatient retail pharmacies, stratified by patient age**, June 2014 through November 2016, cumulative**

	Patients (N)	Share(%)
Grand Total	**2,884,563**	***100%***
0-17 years	**517,403**	***17.9%***
0-5	**9,785**	***1.9%***
6-12	**209,527**	***40.5%***
13-17	**333,260**	***64.4%***
18 years and older	**2,376,542**	***82.4%***
Unknown Age	**46,204**	***1.6%***

Source: IMS Health, Total Patient Tracker™. June 2014 – November 2016. Extracted December 30, 2016. File: TPT 2016-2433 Abilify NDA 021436 Ped 12-30-16 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

2.2.2.2 Diagnosis Data

Table 2.2.2.2 shows the top diagnoses associated with the use of oral aripiprazole according to U.S. office-based physician survey database, stratified by patient age, from June 2014 through November 2016. No drug use mentions were recorded for pediatric patients 0-2 years old and 3-5 years old possibly due to low utilization. Approximately 1% of the total oral aripiprazole mentions were for patients 6-12 years old. Infantile autism, affect psychoses and depressive disorder were recorded as top diagnoses. Approximately 4% of total oral aripiprazole mentions were for patients 13-17 years old. Affect psychoses, manic-depressive and infantile autism were recorded as top diagnoses.

Caution is advised in interpreting projected annual mentions below 100,000 as the sample size is very small with correspondingly large confidence intervals. Of note, many measures for diagnoses fall below the threshold for reliable estimates.

Table 2.2.2.3 Top Diagnoses Associated with the Use of Oral Aripiprazole According to U.S. Office-Based Physician Surveys, Stratified by Patient Age, June 2014 through November 2016, cumulative.

	Uses (Thousands)	Share(%) Uses	95% Lower Confidence Level Uses(thousands)	95% Upper Confidence Level Uses(thousands)
Grand Total	**10,535**	***100%***	**9,967**	**11,103**
0-5	**0**	**-**	**-**	**-**
6-12	**139**	***1.3%***	**73**	**204**
2990 Infantile Autism	**33**	***23.6%***	**1**	**64**
2969 Affect Psychoses	**28**	***20.3%***	**<0.5**	**57**
3110 Depressive Disorder	**20**	***14.7%***	**<0.5**	**45**
2968 Manic-Depressive	**10**	***7.2%***	**<0.5**	**27**
2965 Bipolar Affect, Depress	**9**	***6.7%***	**<0.5**	**26**
3129 Conduct Disturbance	**9**	***6.4%***	**<0.5**	**25**
7992 Nervousness	**9**	***6.4%***	**<0.5**	**25**
7805 Sleep Disturbances	**9**	***6.2%***	**<0.5**	**25**
2989 Psychosis	**7**	***5.1%***	**<0.5**	**22**
3000 Anxiety States	**5**	***3.5%***	**<0.5**	**17**
13-17	**367**	**3.5%**	**261**	**473**
2969 Affect Psychoses	**101**	***27.5%***	**45**	**156**
2968 Manic-Depressive	**56**	***15.2%***	**15**	**97**
2990 Infantile Autism	**35**	***9.6%***	**2**	**68**
3098 Other Adjust Reaction	**33**	***8.9%***	**1**	**64**
2967 Bipolar Affective	**26**	***7.1%***	**<0.5**	**55**
3000 Anxiety States	**18**	***4.8%***	**<0.5**	**41**
2959 Schizophrenia	**15**	***4.1%***	**<0.5**	**37**
2989 Psychosis	**15**	***4.1%***	**<0.5**	**36**
3004 Neurotic Depression	**12**	***3.3%***	**<0.5**	**31**
3003 Obsessive-Compulsive Dis	**10**	***2.6%***	**<0.5**	**27**
All Others*	**47**	***12.7%***	**9**	**84**
18 years and older	**9,399**	***89.2%***	**8,862**	**9,936**
Unspecified Age**	**631**	***6.0%***	**492**	**770**

* The *All others* category is an aggregate of all other ICD-9 codes per patient age group.
** Unspecified Age represents drug use mentions that were not specified in terms of patient age.
Source: inVentiv Health Research and Insights, TreatmentAnswers ™ with Pain Panel, June 2014 through November 2016. Extracted December 2016. Source File: PDDA_2016-2433_Abilify_NDA_021436_Peds DX Jan 2016.xls
inVentiv Health Research & Insights LLC., recommends caution interpreting projected annual occurrences or mentions below 100,000 as the sample size is very small with correspondingly large confidence intervals.

3 POSTMARKET ADVERSE EVENT REPORTS

3.1 METHODS AND MATERIALS

3.1.1 FDA Adverse Event Reporting System (FAERS) Search Strategy

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

Table 3.1.1 FAERS Search Strategy	
Date of Search	January 6, 2017
Time Period of Search	May 1, 2011* - November 30, 2016
Search Type	Quick Query
Product Active Ingredient	Aripiprazole
Search Parameters	All ages, all outcomes, worldwide

* Start date was determined based on end date of last BPCA Abilify review, completed July 28, 2011, which included post-marketing reports of adverse events associated with the use of aripiprazole in pediatric patients from May 1, 2009 to May 1, 2011.

3.2 RESULTS

3.2.1 Total number of FAERS reports by Age

Table 3.2.1 Total Adult and Pediatric FAERS Reports* between May 01, 2011 and November 30, 2016 with Aripiprazole

	All reports (US)	**Serious† (US)**	**Death (US)**
Adults (≥ 17 years)	11334 (7556)	6636 (2911)	766 (428)
Pediatrics (0 - <17 years)	1960 (1576)	**891‡ (515)**	37§ (32)
Seventeen year olds (17 to 17.99999)‖	250 (180)	133‡ (66)	5 (5)

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

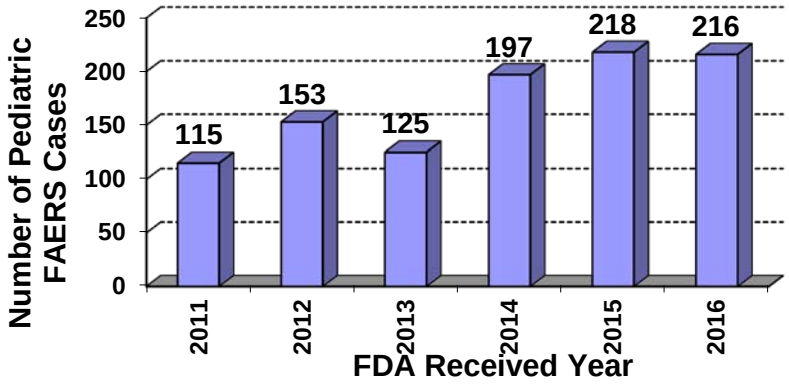
† For the purposes of this review, the following outcomes qualify as serious: death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, required intervention, and other serious important medical events.

‡See Figures 3.2.1 and 3.2.2

§ One additional report of pediatric death was identified among reports not reporting an age (foreign report where patient was described as "a child" of unspecified age).

‖ Since the clinical study leading to the labeling change included patients aged 17 years and younger, serious cases of patients aged <18 years will be included in this review.

Figure 3.2.1 Serious Pediatric Reports (0 to <18 years old) for Aripiprazole, by year of FDA receipt between May 1, 2011 and November 30, 2016 (n=1024)

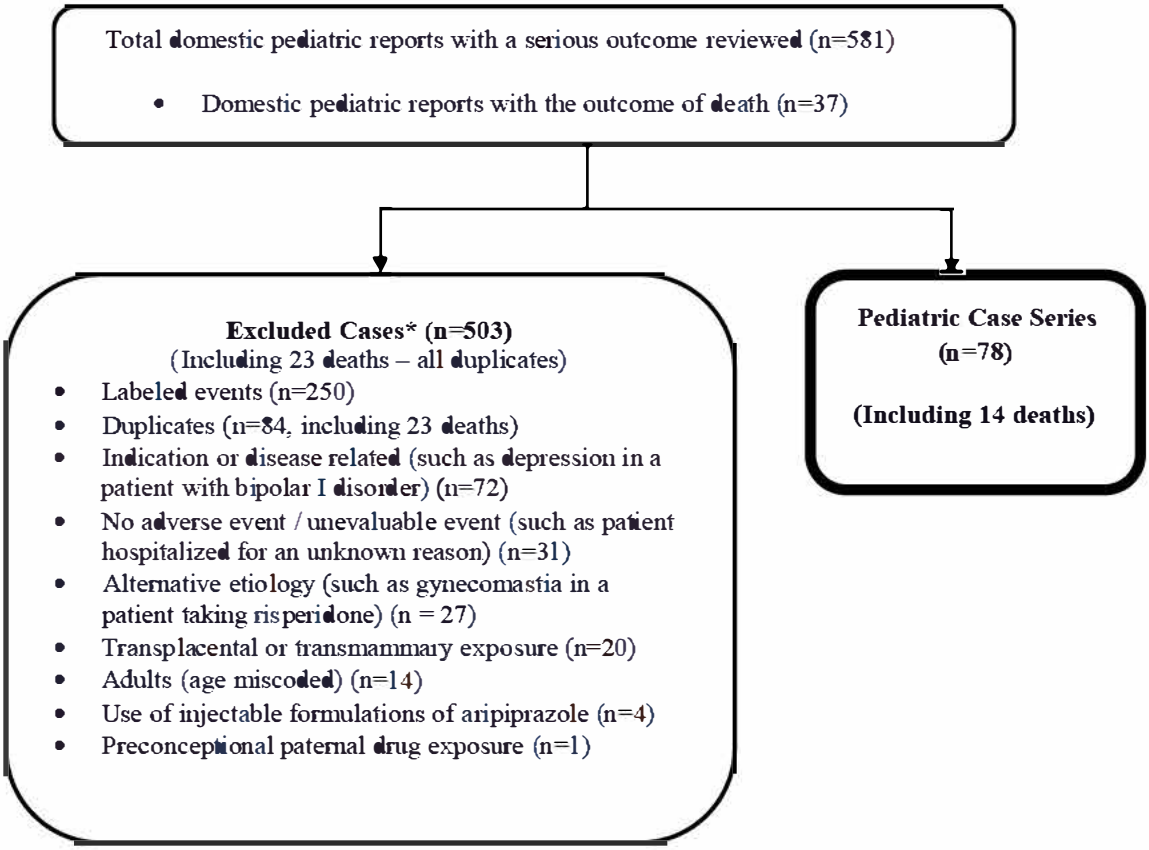


3.2.2 Selection of Serious Pediatric Cases in FAERS

DPV identified 1024 pediatric reports (including 17-year-olds) with a serious outcome (See Table 3.2.1). As there were an adequate number of domestic reports (n=581) for assessment, foreign reports were excluded from the case series (n=443). In order to focus on potential new safety issues, all cases that reported non-fatal labeled adverse events were excluded from the case series, unless the adverse event appeared to occur in greater frequency or severity than currently characterized in labeling. Additionally, any cases reporting adverse events that were better attributed to the underlying indication or another disease state (e.g. paranoia in a patient prescribed aripiprazole for treatment of schizophrenia) were also excluded. Since the focus of this review is oral formulations of aripiprazole, cases involving injectable formulations of aripiprazole were excluded from the case series. **All unique domestic fatal cases were included in the case series, regardless if they met any of the exclusion criteria.**

See **Figure 3.2.2** below for the selection of cases to be summarized in **Sections 3.3 and 3.4.**

Figure 3.2.2 Selection of Serious Pediatric Cases with Aripiprazole



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

3.2.3 Characteristics of Pediatric Case Series

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

Table 3.2.3 Characteristics of Pediatric Case Series with Aripiprazole (N=78)

Age	0 - < 1 month	1	
	1 month - <2 years	1	
	2 - < 6 years	2	
	6 - <12 years	25	
	12 - < 17 years	35	
	17 - <18 years	14	
Sex	Male	46	
	Female	31	
	Unknown	1	
Reported Reason for Use	Bipolar disorder		12
	Autism spectrum disorder (ASD)		8
	Affective disorder		5
	Accidental exposure		2
	Depression		5
	Aggression		4
	Anger		3
	Attention deficit/hyperactivity disorder (ADHD)		3
	Irritability		2
	Obsessive-compulsive disorder (OCD)		2
	Psychotic disorder		2
	Schizophrenia		2
	Agitation		1
	"HOHD"†		1
	Movement disorder		1
	Oppositional defiant disorder (ODD)		1
	Tic		1
	Transplacental exposure		1
	Unknown		22
Serious Outcome*	Death	14	
	Life-threatening	1	
	Hospitalized	19	
	Disability	1	
	Congenital anomaly	1	
	Other serious	56	

* 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.

† The case reported aripiprazole reason for use as "HOHD" without defining HOHD or providing sufficient past medical history to deduce the meaning of HOHD.

3.3 SUMMARY OF FATAL PEDIATRIC ADVERSE EVENT CASES (N=14)

A total of 14 cases in this case series reported death as an outcome. The fatal cases included one transplacental exposure case involving a premature baby who died six days after birth. The remaining 13 fatal cases included children and adolescents 5 to 17 years old, with a median age of 14 years old. The reported total daily dose of aripiprazole ingested ranged from 3 mg to 30 mg (n=6). Four of the 14 fatal cases reported an autopsy was performed, and 12 of the 14 fatal cases reported a proposed cause of death or cause of death determined by autopsy (see Table 3.3 below). Three cases involved toxicity to several concurrent medications, which were all received from the American Association of Poison Control Centers (AAPCC). Two of these three AAPCC cases explicitly reported intentional overdose resulting in a completed suicide, while the third case did not explicitly report intent to self-harm.

In addition to the two suicide cases involving toxicity to various medications, three of the 14 fatal cases reported a completed suicide (for a total of five cases reporting suicide): a 16-year-old female with a history of depression who hung herself, a 16-year-old female with a history of major depressive disorder and OCD who committed suicide by an unreported method, and a 17-year-old male with a history of bipolar disorder who shot himself. The one case involving suicide by hanging (FAERS #8973471, see Table 3.3) is possibly related to aripiprazole based on the temporal relationship between a dose increase in aripiprazole (from 2.5 mg to 5 mg daily) and the time to onset of event (3 weeks). Nonetheless, this case is confounded by the patient's underlying depression. Additionally, the risk of increased suicidal thinking and behavior in adolescents in association with aripiprazole is a known safety issue, for which aripiprazole has a Boxed Warning in its labeling. These cases are consistent with the known risk in the labeling.

Overall, none of the 14 fatal cases provided compelling evidence of a new safety signal for aripiprazole. Table 3.3 summarizes the causes of death for all 14 cases.

Table 3.3. Summary of fatal cases in case series, sorted by age (n=14)

FAERS Case #	Year Received	Age	Sex	Cause of death	Aripiprazole indication	Brief Narrative / Comments
10450650	2014	0.01	M	Tetralogy of Fallot, post-operative hemothorax and hemopericardium	Not applicable/ transplacental exposure	Transplacental exposure, limited information about other medications mother may have taken during pregnancy. Mother's past medical history (PMH) significant for chromosomal microdeletion 22 with Tetralogy of Fallot.

Table 3.3. Summary of fatal cases in case series, sorted by age (n=14)						
FAERS Case #	**Year Received**	**Age**	**Sex**	**Cause of death**	**Aripiprazole indication**	**Brief Narrative / Comments**
10262426	2012	5	M	Sudden Unexpected Death in Epilepsy	"Behavior disorder"	PMH of cerebral palsy and complex partial seizures. Concurrent medications included carbamazepine and levetiracetam. Prescribed aripiprazole 3 mg/day.
10450623	2014	10	M	Multiple organ system failure second to ischemic cardiomyopathy, coronary artery stenosis and congenital heart disease	Not reported	On aripiprazole (dose not reported) for 2 years, but it was discontinued one month prior to his death. No other information about the event was provided.
8563914	2012	11	M	"Dropped dead" while playing outside, specific cause not reported	Bipolar disorder	Prescribed aripiprazole 30 mg (frequency not reported), and was on "several other" unspecified medications. Autopsy was performed but results were not yet available except the "internal body temperature was 106 degrees."
8968754	2012	12	M	Possible neuroleptic malignant syndrome (NMS) (insufficient information to assess)	Bipolar disorder	Received aripiprazole 10 mg daily for approximately 10 months. Autopsy results showed patient had NMS, although reporter (patient's mother) did not explicitly report NMS was the cause of death. Concurrent medications included lamotrigine and topiramate.
8055007	2011	13	F	Sudden cardiovascular death second to drowning	Bipolar disorder in combination with valproate	Drowned in a pool shortly after saying she was "tired." Was on aripiprazole 10 mg (frequency not reported). A week prior to the event the patient had an ear infection and was prescribed benzonatate for cough.

Table 3.3. Summary of fatal cases in case series, sorted by age (n=14)						
FAERS Case #	**Year Received**	**Age**	**Sex**	**Cause of death**	**Aripiprazole indication**	**Brief Narrative / Comments**
8303764	2011	14	M	Cardiac and/or respiratory arrest second to drug poisoning	Not reported	AAPCC report with limited PMH information. Died following drug poisoning with quetiapine, codeine, unspecified laxative, aripiprazole, valproic acid, lisdexamfetamine, diphenhydramine, penicillin, meloxicam, clonidine, morphine, and sertraline. Suicidal intent was not reported.
12945376	2016	14	M	Cardiac arrest second to hyperglycemic hyperosmolar nonketotic syndrome (HHNS)	Not reported	Literature report. Medications included aripiprazole 15 mg daily, lisdexamfetamine 70 mg (frequency not reported), fluoxetine 20 mg daily, and insulin (dose and frequency not reported). Parents denied overdose. Hyperthermia a presenting sign of HHNS in this patient. Insulin administration was associated with worsening hyperthermia. Did not have symptoms of NMS or serotonin syndrome.
11236481	2015	16	F	Suicide (exact cause not reported)	Major depressive disorder with atypical features	Suicide by unknown method an unknown time after starting aripiprazole at an unknown dose. PMH included OCD and skin excoriation habit. Past drug history was unknown.
11815949	2015	16	M	Cardiac and/or respiratory arrest, second to intentional drug overdose	Not reported	AAPCC report with limited PMH information. Died after acute ingestion of morphine sulfate, acetaminophen/hydrocodone, escitalopram, cyclobenzaprine, aripiprazole, and an unknown drug.

Table 3.3. Summary of fatal cases in case series, sorted by age (n=14)						
FAERS Case #	**Year Received**	**Age**	**Sex**	**Cause of death**	**Aripiprazole indication**	**Brief Narrative / Comments**
10440514	2014	16	M	Not reported	Autism	Report from an Abilify sales representative. Patient died while taking aripiprazole. Received aripiprazole (dose not reported) for 3 months. No other information reported.
8973471	2012	16	F	Suicide by hanging	Adjunct to escitalopram for depression	PMH of depression, improved with escitalopram 20 mg but was experiencing mood instability and outbursts. Started aripiprazole 2.5 mg daily as adjunctive therapy, responded well after 3 months, but still had rage outbursts. Aripiprazole dose increased to 5 mg (frequency not reported). Three weeks after dose increase, committed suicide by hanging. Healthcare provider does not believe aripiprazole was responsible for patient's death, while mother does believe that aripiprazole contributed to death, "based upon what [the mother] read online." Patient had no history of prior suicide attempts.
10438024	2014	17	M	Suicide by self-inflicted gunshot wound	Bipolar disorder	Report from patient's mother. Patient was on aripiprazole for about six months. No additional information about the event was reported.
9839840	2014	17	F	Hypoxic encephalopathy due to acute bupropion toxicity, second to intentional drug overdose	Not reported	AAPCC report with limited PMH information. Died after acute ingestion of bupropion and aripiprazole. Only bupropion blood concentrations were reported on autopsy (0.21 mg/L; reference range not provided), and death was attributed to acute bupropion toxicity.

3.4 SUMMARY OF NON-FATAL PEDIATRIC SERIOUS ADVERSE EVENT CASES (N=64)

3.4.1 Lack of Effect-Related Adverse Events (n=35)

Thirty-five cases in the case series reported events related to product quality issue or nontherapeutic response that was attributed to aripiprazole. None of the cases provided sufficient evidence of a new safety signal. The following were the two major themes present among the 35 cases:

1) **Worsening of underlying condition after being switched from brand drug to generic drug (n=16), from one dosage formulation to another dosage formulation (e.g. from oral solution to oral tablet) (n=3), or from generic drug to brand drug (n=1)**: No specific trends in terms of manufacturer, lot number, or time to onset of event were identified. Thirteen of the 16 cases involving generic manufacturers reported reasons for use, which included: autism (n=3), bipolar disorder (n=3), affective disorder (n=2), irritability (n=2), aggression and anxiety (n=1), ASD and anxiety (n=1), bipolar disorder and ADHD (n=1), and OCD (n=1). All three cases involving dosage formulation changes were confounded by the underlying indication (OCD and bipolar disorder) or medical history (oculocerebrorenal syndrome / Lowe syndrome), and there was insufficient evidence to determine whether the adverse event (extreme agitation and temper tantrums in one case, dysmorphia in a second case, and decompensation of bipolar disorder in a third case) was drug related, and if drug related, whether the issue was a product quality issue, or a significant difference in absorption among the various aripiprazole formulations in these particular patients.

   Reviewer's Comment: Overall, there is insufficient evidence to indicate a product quality issue with a specific generic manufacturer or dosage formulation of aripiprazole. There are several different factors that could impact control of symptoms for the various indications reported (e.g. negative perception of generic drugs, other psychosocial stressors, changes to environment, and natural course of disease).

2) **Condition did not improve (n=11) or worsened (n=4) during aripiprazole treatment**: Ten of the 15 cases were unassessable due to incomplete information, and five cases were confounded by the patient's underlying disease (e.g. treatment refractory disease with failed multiple different antipsychotic treatment trials). Table 3.4.1 below summarizes the 15 cases, and notes whether the case reported a medical history significant for ASD (n=5), in order to determine if there were any reporting trends supporting or refuting the negative findings in the aripiprazole pediatric maintenance study for treatment of irritability associated with autistic disorder. Overall, these 15 cases did not reveal any new safety signals.

Table 3.4.1. Characteristics of cases describing lack of efficacy or condition aggravated with aripiprazole, not attributed to change in formulation or manufacturer, sorted by ASD status and age (N=15)

FAERS #	Age (y)	Reason for Use	Dose*	Duration	ASD
10653851	6	Aggression and hand banging	1 mg/day	NR	Yes
11993832	8	Unknown indication	NR	NR	Yes
9669895	13	Unknown indication	NR	NR	Yes
11265015	14	Psychotic disorder	10-15 mg/day	7 days	Yes
10269386	15	Aggression	NR	NR	Yes
9240100	9	Aggression	4 mg/day	NR	No
10069018	12	Schizophrenia	NR	NR	No
10676749	12	Bipolar disorder	2 mg	22-29 mo	No
10439851	14	Anger and Schizophrenia	5 mg/day	35 days	No
12609405	14	Movement disorder	NR	NR	No
12200913	14.48	Depression	10 mg/day	10 m	No
8296622	16	Unknown indication	NR	NR	No
10054986	17	Paranoid schizophrenia	NR	NR	No
10950271	17	Adjunctive treatment for insomnia, major depressive disorder, and anorexia nervosa	10 mg	1 mo	No
9277906	17	Unknown indication	NR	NR	No

* Omission of dose frequency means frequency was not reported
ASD = autism spectrum disorder; NR = not reported

3.4.2 Gastrointestinal and Hepatobiliary Disorders (n=8)

The following eight cases in the case series reported unlabeled events related to gastrointestinal and hepatobiliary disorders, including pancreatitis/pancreatic disorder (n=2), non-alcoholic steatohepatitis (n=2), tooth loss (n=1), oral pain and stomatitis (n=1), hematemesis (n=1), and hemoptysis (n=1). None of the cases provided sufficient evidence of a new safety signal.

Pancreatitis/Pancreatic Disorder (n=2)

One case reported a 7-year-old child (sex not specified) who was diagnosed with pancreatitis some unknown time after starting aripiprazole therapy. A second case reported a 17-year-old male who had been on aripiprazole therapy for 4.5 years and had "pancreatic complication." The report did not specify if the "pancreatic complication" was an adverse event that occurred sometime after initiation of aripiprazole treatment, or was part of the patient's medical history. Both cases provided limited clinical information, and did not include past medical history, time to onset of event from initiation of aripiprazole treatment, or outcome of events. Both cases are unassessable.

Non-alcoholic steatohepatitis (n=2)

Both cases are derived from the same literature report, which describes the occurrence of non-alcoholic steatohepatitis (NASH) and non-alcoholic fatty liver disease (NAFLD) in a 17-year-old

female and a 17-year-old male, respectively.[12] Both cases involve several concomitant medications and provide insufficient information to assess causality with aripiprazole specifically. In the case of the 17-year-old female, the patient was exposed to 31 different medications either shortly before or during the development of signs and symptoms of NASH, including quetiapine and lurasidone, both of which are labeled for metabolic adverse events. In both cases, the patients experienced weight gain while on aripiprazole therapy, and both patients were classified as obese at the time they first developed signs of NASH or NAFLD, with a BMI of 36 in the female patient and 33 in the male patient. The authors noted that while there are no data to support that atypical antipsychotics or "other weight-gain-inducing psychotropics" are separate risk factors for NASH and NAFLD, the metabolic abnormalities associated with these drugs may potentially contribute to known risk factors for NASH and NAFLD (e.g. obesity, type 2 diabetes mellitus, dyslipidemia, and metabolic syndrome).

Reviewer's Comment: Although NAFLD and NASH are unlabeled events, several metabolic risk factors associated with NAFLD, such as obesity, dyslipidemia, and type 2 diabetes mellitus, are labeled events for aripiprazole.

Tooth loss (n=1)
A 7-year-old male shed two of his primary molar teeth after being on aripiprazole for "almost one year." The reporter was the patient's parent, who mentioned being concerned that the reportedly premature loss of molar teeth was linked to aripiprazole. The reporter also mentioned the patient had a PMH of "significantly delayed bone age." The patient was concurrently taking somatropin and albuterol sulfate inhaler. Action taken with aripiprazole and outcome of events were not reported. The case did not include any additional information on the patient's PMH, or information regarding a physical or dental exam by a health care professional. The case provides insufficient information to assess.

Oral pain and stomatitis (n=1)
A 7.5-year-old male was prescribed aripiprazole oral tablets 2.5 mg by mouth once daily as adjunctive treatment for ADHD. Patient's concurrent medications included amphetamine salts. Four days after initiating aripiprazole, the patient complained of his mouth hurting. Three days later (seven days since initiating aripiprazole), the patient was seen by his pediatric dentist. The reporter (the patient's grandparent) stated that the patient "had at least 10 sores in his mouth that required laser treatment along with Magic Mouthwash with Lidocaine, Tylenol and Ibuprofen." The reporter specified that the only change in the patient's routine was aripiprazole – no diet changes, new food, or "stressors." No other symptoms were reported. At the time of the report, aripiprazole treatment was still ongoing. Outcome of event and PMH were not reported; thus, there was insufficient information to assess causality.

Hematemesis (n=1)
A 17-year-old male started vomiting blood "shortly after" being switched from risperidone to

aripiprazole 5 mg (frequency not reported) for bipolar disorder. No other information was provided for causality assessment.

Hemoptysis (n=1)
A 14-year-old male was prescribed aripiprazole 15 mg (frequency not reported) for vocal tics. After four weeks the patient was coughing up blood. Endoscopy was performed and was "normal." Final diagnosis was hemoptysis of unknown etiology. Concomitant drugs included escitalopram 10 mg once daily. Aripiprazole treatment was ongoing. Outcome of event was not reported.

Reviewer's comments: Although there is a temporal relationship between initiation of aripiprazole and the onset of hemoptysis, potential confounders (such as physical trauma or infection) cannot be ruled out due to the unknown etiology of the hemoptysis, the lack of dechallenge with aripiprazole, and the unknown outcome of the event.

3.4.3 Nervous System Disorder (n=6)

The following six cases reported unlabeled adverse events related to nervous system disorders, including cerebral infarction/cerebrovascular accident (n=5) and complex regional pain syndrome (n=1). None of the cases provided sufficient evidence of a new safety signal.

Cerebral infarction/cerebrovascular accident (n=5)
Four cases reported cerebrovascular accident (CVA) and one case reported cerebral infarction (ages = 9-17 years, median = 17 years). Of the five cases, four cases provided very limited information, and did not include past medical history, dates of aripiprazole treatment, time to event from initiation of aripiprazole treatment, action taken with aripiprazole, or outcome of the event.

The fifth case involved a 9-year-old female prescribed aripiprazole 2 mg once daily for ODD. She had a medical history of depression and had discontinued quetiapine one day prior to initiating aripiprazole. Her aripiprazole dose was increased after two weeks to 2 mg twice daily. Nineteen days after starting aripiprazole and five days after the dose increase, she developed severe headaches. Thirty days after starting aripiprazole and 16 days after the dose increase, she was admitted to the hospital for "stroke like symptoms that included: a complete loss of feeling on her left side, severe headaches, tremor, her left side was freezing cold, nausea, blurred vision, and her left eye pupil was dilated." She was treated with ketorolac, diphenhydramine, hydration using saline, and metoclopramide. Aripiprazole was discontinued. Magnetic resonance imaging and computerized tomography scans were preformed while she was hospitalized, but results were not reported. She was discharged from the hospital after four days, still experiencing dizziness and mild headaches, but no other symptoms. At the time of the report, the patient was still being tested for the cause of the events. No information was provided regarding recent trauma or concomitant medications.

Reviewer's Comment: The treatment provided to the 9-year-old female upon hospitalization is not consistent with standard treatment for a CVA (but rather more consistent with treatment for migraine headache), and the report does not provide any confirmatory evidence that the patient actually experienced a stroke. The case did not provide any diagnosis for the patient's symptoms. Overall, all five cases reporting CVA or cerebral infarction lacked essential clinical information for assessment.

Reflex sympathetic dystrophy-like syndrome (RSDS) (n=1)

One literature case report described a 15-year-old female patient who presented with RSDS while on aripiprazole therapy.[13] The patient initiated aripiprazole 2 mg by mouth at night for complaints of extreme anger, aggression, and impulsivity. After three days, her dose was increased to 4 mg by mouth nightly. Two days after the dose increase, she noticed redness on both her feet and gradually increasing swelling to the point she was unable to wear her regular footwear. She also experience sharp shooting pain in her feet, which was diffuse, intermittent, and mainly on the ventral surface of her feet; the pain worsened with walking, and was localized to the feet. Thorough physical examination and laboratory testing revealed normal results. Two days after discontinuing aripiprazole she felt relief of her symptoms, and experienced complete resolution of symptoms within one week of discontinuation. She did not take any medications for pain, she was not hospitalized, and did not experience persistent disability. The author proposed a possible association between aripiprazole and RSDS, based on the positive dechallenge; however, the author also noted that "the natural history of RSDS is variable and unpredictable," and resolution of the syndrome may occur at any stage.

Reviewer's Comment: *This case provides information on a temporal relationship between aripiprazole and onset of RSDS, with a positive dechallenge and no apparent confounders. However, RSDS is not a well-defined syndrome, with a variable clinical course and unknown cause, and is based upon a diagnosis of exclusion. With only one case in the case series, and the possibility that the patient's RSDS may have resolved spontaneously, there is insufficient evidence to conclude whether a relationship between RSDS and aripiprazole truly exists.*

3.4.4 Reproductive System and Breast Disorders (n=4)

Four cases in the case series reported events related to reproductive system and breast disorders. Three cases in the case series reported the event gynecomastia, and one case reported the event priapism. Both gynecomastia and priapism are labeled events, but are specifically labeled under the "Adult" subsection of Section 6 ADVERSE REACTIONS of aripiprazole labeling; therefore, these cases are discussed here since they may not be considered labeled for the pediatric population.

Gynaecomastia (n=3)

Two cases involved 14-year-old males, and one case involved a 13-year-old male. All three cases were submitted by the patient's caregiver (either parent or grandparent), who reported the patient developed gynecomastia after starting treatment with aripiprazole. Only one case specified the

time to onset of gynecomastia, which was three months after initiation of aripiprazole. None of the cases reported prolactin levels or any other laboratory values. Outcome was not provided in any of the three cases.

Reviewer's comments: All three cases provided limited objective information, such as specific breast size and laboratory findings. Additionally, all cases are potentially confounded by pubertal gynecomastia due to the patients' ages.[14]

Priapism (n=1)
One case reported priapism in an 8-year-old male three days after starting aripiprazole 2.5 mg at bedtime for mood instability. The case did not provide PMH, action taken with aripiprazole, or the outcome of the event. The case provided insufficient information to assess.

3.4.5 Cardiac Disorders (n=3)

Three cases in the case series reported unlabeled adverse events related to cardiac disorders, including one case of each: ventricular extrasystoles, congestive cardiac failure, and conduction disorder. None of the cases provided sufficient evidence of a new safety signal. The three cases are summarized below:

Ventricular extrasystoles (n=1)
A 9-year-old female patient was prescribed aripiprazole 2 mg twice daily for restlessness, agitation, and self-stimulating behavior for 2-3 weeks. The case reported that either three weeks or three months after the patient had started therapy with aripiprazole, the patient experienced "irregular heartbeat" and was admitted to the hospital. She was diagnosed with sinus tachycardia and premature ventricular contractions (PVCs). She was discharged from the hospital the following day, and was "doing well" at the time of the report. On an unknown date, the physician had temporarily discontinued aripiprazole. The report did not specify why aripiprazole was discontinued. Prior to initiating aripiprazole, the patient had a baseline electrocardiogram (EKG) performed by pediatric cardiology and was given medical clearance to start aripiprazole treatment. Patient's PMH included ASD. Concurrent medications were not reported.

Reviewer's Comment: This case reports a temporal relationship (time to onset was either three weeks or three months; the report provides contradictory information) between aripiprazole and development of PVCs; however, it is unclear when or why aripiprazole was temporarily discontinued in relation to the event. Furthermore, this is the only case in the case series reporting PVCs, as well as none of the three previous aripiprazole pediatric postmarketing safety reviews completed by DPV identified any cases of PVCs or ventricular extrasystoles associated with aripiprazole. The limited and contradictory information reported, in addition to being the only case in the case series, provides insufficient evidence to rule out possible confounders and support a safety signal.

Cardiac failure congestive (n=1)
A 12-year-old female was prescribed aripiprazole 5 mg (frequency and indication not reported) while hospitalized. The patient was hospitalized "with drug overdose of escitalopram," and had a medical history of migraine, disruptive mood dysregulation disorder, and generalized anxiety disorder. "Several days" after starting therapy with aripiprazole she developed shortness of breath, orthopnea, and had an "enlarged liver on scan." She was diagnosed with "iatrogenic reaction to aripiprazole as congestive heart failure." Aripiprazole was discontinued, and improvement in dyspnea was seen after two days. At the time of the report (about one month after onset of the event), the patient reportedly completely recovered.

Reviewer's Comment: This case is confounded by the recent escitalopram overdose (cardiac failure is a labeled event for escitalopram). Additionally, the case reported that the patient "completely recovered," which brings into question the diagnosis of heart failure. The case provides insufficient information to characterize the severity of the shortness of breath, as well as dyspnea is a labeled event under the "Adults" subsection of Section 6 ADVERSE EVENTS of aripiprazole labeling. The clinical significance of "enlarged liver on scan" is also unassessable. Overall, the case does not provide sufficient clinical information for causality assessment.

Conduction disorder (n=1)
A 14-year-old male was noted to have early repolarization and nonspecific ST-elevation on an EKG while he was hospitalized for an unknown reason. A second EKG showed right ventricular delay. The patient also had an elevated creatine phosphokinase in the 900s (no units provided). The patient was on aripiprazole 10 mg in the morning and 15 mg in the evening for "mood disorder NOS" for four years. Aripiprazole treatment was ongoing at the time of the report. The patient's PMH was unknown.

Reviewer's Comment: The event has an unlikely temporal relationship to aripiprazole given that the time to onset was four years following initiating aripiprazole therapy. The case did not provide the patient's PMH or reason for hospitalization, and does not provide outcome of the event. The case provides insufficient information to assess.

3.4.6 Hallucinations (n=3)

Three cases in the case series reported unlabeled adverse events related to hallucinations, which were not better attributed to underlying disease or indication. None of the three cases provided sufficient evidence of a new safety signal.

One case reported auditory hallucination ("hearing voices") in a 16-year-old female, prescribed sertraline, benztropine, and aripiprazole. Indication for treatment and PMH were not reported; thus it is impossible to rule out if the event was related to underlying disease. One case reported visual and tactile hallucinations ("bees coming at him" and "felt people were touching him", respectively) in a 10-year-old male prescribed aripiprazole 2 mg (frequency not reported) for irritability associated with autistic disorder. The patient was switched off aripiprazole to

risperidone and continued to experience these hallucinations, indicating a negative dechallenge. In the last case, a 10-year-old male was prescribed aripiprazole for generalized mood disorder and generalized anxiety disorder, and developed unspecified hallucinations on an unknown date. Aripiprazole was discontinued, but outcome was not reported. The case provided insufficient information for assessment.

3.4.7 Drug screen false positive (n=2)

Two cases in the case series reported the adverse event drug screen false positive for amphetamines after an accidental exposure to aripiprazole. Both cases were derived from the same literature article, and refer to urine drug screening (UDS) done in the same institution using the same UDS immunoassay techniques. [15] In both cases confirmatory testing was performed and was negative for amphetamines. In the first case, the 20-month-old child was potentially exposed to several different medications, including alprazolam, clonazepam, fluvoxamine, buspirone, and aripiprazole (although the initial UDS was negative for benzodiazepines), obscuring the relationship between drug screen false positive and aripiprazole. In the second case, the 2-year-old child reportedly ingested one to three aripiprazole 15 mg tablets. The authors reported several limitations with their findings, including the poor specificity of UDS immunoassays, aripiprazole levels were not drawn to confirm suspicion that the false-positive amphetamine results were secondary to aripiprazole ingestion, and the cross-reaction in the initial UDS immunoassay may be specific to the institution's reagents and testing method, and not generalizable to all assay methods. Although the authors do not suspect that the families provided misinformation, the authors acknowledge that it is not possible to know what drugs were truly in the pill bottle or pill organizer.

Reviewer's comments: False positive drug screen reported with aripiprazole was reviewed by DPV in 2014 (see Section 1.3). The review found insufficient evidence to recommend regulatory action at that time. Although these two cases provide information of a possible association between aripiprazole ingestion and drug screen false positive, the association is confounded by the possibility that the false positive is a result of institution-specific testing methods.

3.4.8 Miscellaneous (n=3)

The remaining three cases reported one case each of pituitary tumor, skin striae, and Stevens-Johnson syndrome.

The case of pituitary tumor involved a 14-year-old male who had elevated T3/T4 levels, and was diagnosed with a pituitary tumor some unknown time after starting aripiprazole for an unknown indication. The patient was switched from aripiprazole to quetiapine, and his T3/T4 levels normalized at some unknown time. Outcome of pituitary tumor was not reported. The case provides insufficient information to assess.

The case of skin striae involved a 15-year-old female who developed "many" stretch marks "completely around both thighs." Dates of aripiprazole therapy or time to onset of stretch marks

were not provided. Outcome of the event was not provided. The case provides insufficient information to assess.

The case reporting Steven-Johnson syndrome is a direct report, submitted by the patient's mother. The reporter stated that her 15-year-old daughter took aripiprazole 2.5 mg daily by mouth for bipolar disorder. After one week of taking aripiprazole she developed flu-like symptoms, and sores in her mouth, throat, and "on eyes." Per the reporter, she was admitted to the hospital for Stevens-Johnson syndrome. Action taken with aripiprazole or outcome of event was not reported. Concomitant medications were not reported. The case provides insufficient information to assess.

4 DISCUSSION

DPV identified 78 domestic pediatric cases with serious, unlabeled events reported with aripiprazole use from May 1, 2011 through November 30, 2016 in the FAERS database. There were no new pediatric safety signals identified, no apparent increased severity or frequency of any labeled adverse events, and there were no deaths directly associated with aripiprazole.

There were 14 fatal cases and 64 non-fatal cases in the case series. Twelve of the fatal cases reported a cause of death, and none of the causes of death were attributed solely to aripiprazole. Five of the deaths were related to suicidal behavior, only one of which provided sufficient information to determine a possible causal relationship between aripiprazole and the suicidal behavior; however, this case is confounded by the patient's underlying depression. Of note, aripiprazole carries a Boxed Warning for "suicidal thoughts and behaviors" specifically for children, adolescents, and young adults using aripiprazole as antidepressant therapy.

Over half of the 64 non-fatal cases (n=35) reported drug ineffective, product substitution issue, condition aggravated, drug effect decreased, or described other adverse events related to lack of effect. Among these cases, 24% (n=17) complained of lack of effect with aripiprazole after switching between two different manufacturers (from brand to generic in all but one case). Studies indicate that negative perceptions of generic medications, particularly the perception that they are less effective than brand medications, are common in the general population.[16] The expectation that the generic drug will not work as well as the brand drug, and even that the generic drug will result in additional adverse reactions, may result in the manifestation of the lack of effect or adverse event (i.e. "nocebo" effect).[17] This phenomenon obscures the relationship between the adverse event and an actual quality issue with the generic formulation of the drug. Additionally, DPV did not identify any trends in reporting that would indicate a product quality issue with a specific manufacturer. In regards to lack of effect with aripiprazole more generally, 12 of the 15 cases did not provide sufficient information to determine if an adequate duration and dose of aripiprazole was trialed. Additionally, more than half (n=10) of the 15 cases that reported lack of effect with aripiprazole treatment reported off-label use (e.g. aggression, psychotic disorder not otherwise specified [NOS], and anorexia nervosa) or did not

report indication for use. Overall, there was insufficient clinical information to attribute causality to aripiprazole.

Of the remaining 29 cases that reported events across 15 system organ classes, there were no clear patterns or trends for a new safety signal. Twenty-six of the cases provided insufficient information to fully characterize the adverse event, assess causality to aripiprazole, and to rule out confounders. Two cases of the event drug screen false positive was reported in association with exposure to aripiprazole. This safety issue was reviewed by DPV in 2014, which concluded there was insufficient evidence for regulatory action at the time. The two cases in this case series do not add substantial new evidence to support regulatory action. One case provided sufficient information to establish a temporal relationship between initiation of aripiprazole and development of RSDS in a 15-year-old female, and which also reported a positive dechallenge. No other cases in the case series reported a similar event, coupled with the variable clinical course of RSDS, this one case alone is not a new safety signal.

Drug utilization patterns were assessed to capture pediatric use of oral aripiprazole and to provide context for the adverse event reports submitted to the FDA Adverse Event Reporting System (FAERS) database. The drug utilization data provided in this review showed that the majority of pediatric use of oral aripiprazole was in older pediatric patients aged 13-17 years, which is consistent with the present FAERS case series with a majority of the cases aged 12-17 years (77%). The outpatient retail utilization data showed that pediatric patients 0-17 years old accounted for approximately 18% (517,000 patients) of the total patients who were dispensed prescription for oral aripiprazole from June 2014 through November 2016, cumulative.

Findings from this review should be interpreted in the context of the known limitations of the databases used. We estimated that oral aripiprazole was distributed primarily to the outpatient setting based on the IMS Health, IMS National Sales Perspectives™. Accordingly, this review was focused on outpatient retail pharmacy utilization. Data were suggestive of utilization in patients ages younger than 6 years old where safety and efficacy of aripiprazole has not been established. It is important to note that 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.

5 CONCLUSION

There were no clear patterns of reported adverse events in the FAERS cases or trends in drug utilization to suggest a new safety signal associated with oral formulations of aripiprazole in pediatric patients at this time. Additionally, there have been multiple OSE reviews addressing safety issues with aripiprazole in the pediatric population conducted since approval, including two DPV reviews prepared for the Pediatric Advisory Committee meetings in December 2009 and September 2011.

6 RECOMMENDATIONS

DPV recommends no labeling changes at this time. DPV will continue standard pharmacovigilance monitoring.

7 REFERENCES

1 Abilify [Package Insert]. Rockville, MD: Otsuka America Pharmaceutical, Inc.; August, 2016 (https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=c040bd1d-45b7-49f2-93ea-aed7220b30ac. Accessed January 31, 2017)

2 Findling RL, Mankoski R, Timko K, Lears K, McCartney T, McQuade RD, et al. A randomized controlled trial investigating the safety and efficacy of aripiprazole in the long-term maintenance treatment of pediatric patients with irritability associated with autistic disorder. *J Clin Psychiatry*. 2014;75(1):22-30.

3 Phelan KM. Galactorrhea with atypical antipsychotic drugs in pediatric patients. FDA memorandum. PID# D050311. October 4, 2005.

4 Elekwachi O. Laryngeal dystonia associated with aripiprazole. FDA Postmarketing Safety Review. RCM 2006-346. March 7, 2007.

5 Diak I. A class review of postmarketing cases coded with death in children 16 years old and younger. FDA Postmarketing Safety Review. RCM 2007-1383. April 29, 2008.

6 Diak I. New Molecular Entity review follow-up and aripiprazole. FDA Postmarketing Safety Review. RCM 2007-2336. September 25, 2008.

7 Diak I. Pediatric postmarketing adverse event review focusing on extrapyramidal symptoms (i.e. akathisia, dyskinesia, dystonia, and tardive dyskinesia) and aggression and agitation associated with aripiprazole use. FDA Postmarketing Safety Review. RCM 2007-2363. October 20, 2009.

8 Salaam T. Pediatric Research Equity Act (PREA): Pediatric postmarketing adverse event review. FDA Postmarketing Safety Review. RCM 2011-1518. July 28, 2011.

9 Suggs C. A pharmacovigilance review of aripiprazole, asenapine, clozapine, iloperidone, lurasidone, olanzapine, paliperidone, risperidone, and ziprasidone and drug screen false positive. FDA Postmarketing Safety Review. RCM 2014-481. April 8, 2014.

10 Nevo ON. A pharmacovigilance review of aripiprazole and impulse-control disorders. FDA Postmarketing Safety Review. RCM 2015-2507. March 10, 2016.

11 IMS Health, IMS National Sales Perspectives™ Database. June 2014-November 2016. Extracted January 2017. File: NSP 2016-2433 aripiprazole 01-23-17.

12 Gracious BL, Bhatt R, Potter C. Nonalcoholic Fatty Liver Disease and Fibrosis in Youth Taking Psychotropic Medications: Literature Review, Case Reports, and Management. *J Child Adolesc Psychopharmacol.* 2015; 25(8):602-10.

13 Upadhyay A. Reflex sympathetic dystrophy-like syndrome, possibly caused by aripiprazole, in an adolescent patient. *J Child Adolesc Psychopharmacol.* 2014; 24(7):414-5.

14 Lemaine V, Cayci C, Simmons P, Petty P. Gynecomastia in Adolescent Males. *Semin Plast Surg.* 2013; 27(1):56-61.

15 Kaplan J, Shah P, Faley B, Siegel ME. Case Reports of Aripiprazole Causing False-Positive Urine Amphetamine Drug Screens in Children. *Pediatrics.* 2015; 136(6):e1625-8.

16 Colgan S, Faasse K, Martin LR, Stephens MH, Grey A, Petrie KJ. Perceptions of generic medication in the general population, doctors and pharmacists: a systematic review. *BMJ Open*. 2015; 5(12):e008915.

17 Weissenfeld J, Stock S, Lüngen M, Gerber A. The nocebo effect: a reason for patients' non-adherence to generic substitution? *Pharmazie*. 2010; 65(7):451-6.

8 APPENDICES

8.1 APPENDIX A. THREE PREVIOUS OSE POST-MARKETING SAFETY REVIEWS

- February 28, 2003. The sponsor submitted 15-day reports regarding five cases of **death** occurring in patients who had received aripiprazole. The AERS database was searched for any additional cases of death and two unique cases were retrieved. No common cause of death was reported. OSE agreed to carefully review follow-up information for the seven cases and continue to closely monitor future reports of patients receiving aripiprazole.[1]

- June 25, 2003. A literature review concerning the issue of **diabetes mellitus/hyperglycemia** associated with the atypical antipsychotic drugs. The findings of the review suggested that a risk management program be put in place for these drugs.[2]

- October 4, 2005. A class review of **pituitary tumors** with atypical antipsychotic drugs. The review recommended further investigation, perhaps including reanalysis of the risperidone NDA, in order to update the risperidone label to include increased hyperprolactinemia compared to other antipsychotic agents.[3]

8.2 APPENDIX B. DRUG UTILIZATION DATABASE DESCRIPTIONS/LIMITATIONS

IMS HEALTH, NATIONAL SALES PERSPECTIVES™: RETAIL AND NON-RETAIL

The IMS Health, IMS 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.

These data do not provide a direct estimate of use but do provide a national estimate of units sold from the manufacturer into the various channels of distribution. The amount of product purchased by these channels of distribution may be a possible surrogate for use, if we assume the facilities purchase drugs in quantities reflective of actual patient use.

IMS Health, Total Patient Tracker (TPT):

[1] Kortepeter C. Reports of death associated with aripiprazole. FDA Postmarketing Safety Review. February 28, 2003.

[2] Mosholder A. Literature review concerning the issue of diabetes mellitus/hyperglycemia associated with the atypical antipsychotic drugs. FDA Postmarketing Safety Review. June 25, 2003.

[3] Phelan K. A class review of pituitary tumors with atypical antipsychotic drugs. FDA Postmarketing Safety Review. October 4, 2005.

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.

inVentiv Health Research & Insights, LLC., TreatmentAnswers™

inVentiv Health Research & Insights, LLC., TreatmentAnswers™ and TreatmentAnswers™ with Pain Panel is a monthly survey designed to provide descriptive information on the patterns and treatment of diseases encountered in office-based physician practices in the U.S. The survey consists of data collected from over 3,200 office-based physicians representing 30 specialties across the United States that report on all patient activity during one typical workday per month. These data may include profiles and trends of diagnoses, patients, drug products mentioned during the office visit and treatment patterns. The Pain Panel supplement surveys over 115 pain specialists physicians each month. With the inclusion of visits to pain specialists, this will allow additional insight into the pain market. The data are then projected nationally by physician specialty and region to reflect national prescribing patterns.

The term "drug uses" to refer to mentions of a drug in association with a diagnosis during a patient visit to an office-based physician. This term may be duplicated by the number of diagnoses for which the drug is mentioned. It is important to note that a "drug use" does not necessarily result in a prescription being generated. Rather, the term indicates that a given drug was mentioned during an office visit.

Indications for use were obtained using a monthly survey of 3,200 office-based physicians. Although these data are helpful to understand how drug products are prescribed by physicians, the small sample size and the relatively low usage of these products limits the ability to identify trends in the data. In general, physician survey data are best used to identify the typical uses for the products in clinical practice, and outpatient prescription data are best used to evaluate utilization trends over time. Results should not be overstated when nationally projected estimates of annual uses or mentions fall below 100,000 as the sample size is very small with correspondingly large confidence intervals.

Given that statistical accuracy increases as the projected number of records increase, data below 100,000 projected mentions or occurrences may not represent national level trends, because results below this threshold represent insufficient raw physician responses prior to applied projection factors. Data below 100,000 (mentions or occurrences) do not represent sufficient portion of the population and is not representative of actual physician prescribing habits at a national level. In general, this physician survey database is most appropriate to identify the typical uses for a product in office-based physician’s clinical practice. Therefore, the patient exposure estimates reported in this review may not apply to other settings of care or other specialty offices in which these products may be prescribed or dispensed.

8.3 APPENDIX C. 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.

8.4 APPENDIX D. FAERS CASE NUMBERS, FAERS VERSION NUMBERS AND MANUFACTURER CONTROL NUMBERS FOR THE PEDIATRIC CASE SERIES WITH DRUG (N=78)

FAERS Case #	Version #	Manufacturer Control #
8055007	2	US-BRISTOL-MYERS SQUIBB COMPANY-15916315
8163957	1	US-BRISTOL-MYERS SQUIBB COMPANY-16092967
8163960	1	US-BRISTOL-MYERS SQUIBB COMPANY-16092942
8241285	1	US-BRISTOL-MYERS SQUIBB COMPANY-16210577
8254483	1	AUR-APL-2011-05768
8296622	1	US-BRISTOL-MYERS SQUIBB COMPANY-15316367
8303764	1	US-ASTRAZENECA-2011SE76017
10262426	1	(blank)
8477205	3	US-BRISTOL-MYERS SQUIBB COMPANY-16461923
8485432	1	US-BRISTOL-MYERS SQUIBB COMPANY-16412371
8563914	1	US-BRISTOL-MYERS SQUIBB COMPANY-16569956
8567772	1	US-BRISTOL-MYERS SQUIBB COMPANY-16583676
8635590	1	US-BRISTOL-MYERS SQUIBB COMPANY-16709495
8796129	2	US-BRISTOL-MYERS SQUIBB COMPANY-16946659
8965009	2	US-BRISTOL-MYERS SQUIBB COMPANY-17173220
8968754	1	US-BRISTOL-MYERS SQUIBB COMPANY-16722829
8973471	1	US-BRISTOL-MYERS SQUIBB COMPANY-16819112
9240100	1	US-PFIZER INC-2013117660
9277906	1	PHEH2013US010017
9669895	1	PHHY2013US120912
9839840	1	US-PAR PHARMACEUTICAL, INC-2014SCPR008177
9910878	1	US-BRISTOL-MYERS SQUIBB COMPANY-20155495
9996234	1	(blank)
10054986	2	PHHY2014US035820
10069018	1	US-ACTAVIS-2014-06768
10070256	1	US-BRISTOL-MYERS SQUIBB COMPANY-20608295
10249048	1	(blank)
10269386	2	US-DRREDDYS-USA/USA/14/0041373
10436552	2	US-BRISTOL-MYERS SQUIBB COMPANY-20346912
10436572	2	US-BRISTOL-MYERS SQUIBB COMPANY-20220299

10437278	2	US-BRISTOL-MYERS SQUIBB COMPANY-19625854
10437427	1	US-BRISTOL-MYERS SQUIBB COMPANY-20953444
10438024	2	US-BRISTOL-MYERS SQUIBB COMPANY-19827799
10438361	2	US-BRISTOL-MYERS SQUIBB COMPANY-19847243
10439836	2	US-BRISTOL-MYERS SQUIBB COMPANY-20037586
10439851	2	US-BRISTOL-MYERS SQUIBB COMPANY-20663043
10440514	2	US-BRISTOL-MYERS SQUIBB COMPANY-21367594
10450623	1	US-BRISTOL-MYERS SQUIBB COMPANY-21359989
10450650	3	US-BRISTOL-MYERS SQUIBB COMPANY-21385729
10508704	1	US-BRISTOL-MYERS SQUIBB COMPANY-21453287
10628670	2	US-BRISTOL-MYERS SQUIBB COMPANY-21547096
10629084	2	US-BRISTOL-MYERS SQUIBB COMPANY-21324108
10653851	1	(blank)
10676749	1	US-BRISTOL-MYERS SQUIBB COMPANY-BMS-2014-002304
10950271	1	US-APOTEX-2015AP007580
10957034	1	(blank)
11146654	1	(blank)
11199986	1	(blank)
11236481	1	US-BRISTOL-MYERS SQUIBB COMPANY-BMS-2015-041855
11259001	1	(blank)
11265015	1	(blank)
11275809	1	(blank)
11300773	1	(blank)
11302433	1	(blank)
11320462	1	(blank)
11381094	1	(blank)
11399452	1	(blank)
11588616	1	(blank)
11690545	1	US-BRISTOL-MYERS SQUIBB COMPANY-BMS-2015-074250
11696064	1	(blank)
11761478	1	US-GLAXOSMITHKLINE-US2015GSK165203
11764837	2	US-AUROBINDO-AUR-APL-2015-10460
11767616	1	US-GLAXOSMITHKLINE-US2015GSK165352
11815949	1	US-PFIZER INC-2015425860

11929682	1	(blank)
11993832	1	US-DRREDDYS-USA/USA/16/0068099
12037086	2	US-ALEMBIC PHARMACUETICALS LIMITED-2016SCAL000093
12059089	1	(blank)
12119364	1	(blank)
12200913	2	US-BRISTOL-MYERS SQUIBB COMPANY-BMS-2016-020063
12204801	1	(blank)
12273404	1	US-TEVA-647763USA
12385139	1	(blank)
12446437	1	(blank)
12573165	1	(blank)
12609405	1	US-BRISTOL-MYERS SQUIBB COMPANY-BMS-2016-061479
12679767	1	(blank)
12945376	1	US-BRISTOL-MYERS SQUIBB COMPANY-BMS-2016-094780

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