

**Pediatric Focused Safety Review
Aripiprazole
Pediatric Advisory Committee
Meeting
September 12, 2017**

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Outline

- Background Information
 - Previous Pediatric Advisory Committee (PAC) Meetings
- Pediatric Research Equity Act (PREA) Studies
- Relevant Pediatric Labeling
- Drug Use Trends
- Adverse Events
- Summary

Background Information

- **Drug:** Aripiprazole
- **Therapeutic Category:** Atypical antipsychotic
- **Dose:** *Varies by indication*, initial dose 2 mg/day; recommended dose 5 -10 mg/day
- **Formulations:**
 - Oral tablets: 2 mg, 5 mg, 10 mg, 15 mg, 20 mg, and 30 mg
 - Oral disintegrating tablets: 10 mg and 15 mg
 - Oral solution: 1 mg/mL
 - Solution for immediate-release: 9.75 mg/1.3 mL (intramuscular injection)
 - Long-acting injectable (only for adult use)
- **Sponsor:** Otsuka Pharmaceutical Company, Limited

Background Information

Aripiprazole Oral formulation indications:

- **Schizophrenia** in adults and **adolescents 13 to 17 years**
- **Acute Treatment of Manic or Mixed Episodes associated with Bipolar I Disorder** as monotherapy and as an adjunct therapy to lithium or valproate in adults and **pediatric patients 10 to 17 years**
- Adjunctive Treatment of Major Depressive Disorder in adults
- **Irritability Associated with Autistic Disorder** in **pediatric patients 6 to 17 years**
- Treatment of **Tourette's Disorder** in **pediatric patients 6 to 18 years**
- Maintenance treatment of Bipolar I Disorder (acute treatment of manic and mixed episodes) as monotherapy and as adjunct therapy to lithium or valproate in adults
- Adjunctive treatment of major depressive disorder in adults

Aripiprazole Injectable formulation indications:

- Agitation associated with Schizophrenia or Bipolar Disorder in adults

Background Information

- **Original FDA approval:** November 15, 2002
- **Pediatric Research Equity Act (PREA) labeling changes:**
 - Schizophrenia: October 29, 2007
 - Section 1; Section 2.1; Section 6.1; Section 8.4; Clinical Studies 14.1
 - Irritability Associated with Autistic Disorder: November 19, 2009
 - Section 1.4 Indication; Section 2.4 Dosage and Administration; Section 14.4 Clinical Studies
- **PAC Meeting December 2009 - recommendations:**
 - Include additional information on weight gain to labeling.
 - Explore drug use data associated with the diagnosis of attention deficit hyperactivity disorder (ADHD) without other co-existing diagnoses.
 - Discussed concerns about the use of atypical antipsychotic drugs for ADHD; an update was shared with PAC.

Background Information

- **PREA Labeling Change:**
 - Bipolar I Disorder: February 16, 2011
 - Section 14.2 Clinical Studies
- **PAC Meeting:**
 - September 22, 2011
 - DPV Review: no labeling changes were recommended, continue routine pharmacovigilance.
 - PAC concurred; continue efforts to characterize reported events of pediatric metabolic effects.
- **PREA Labeling Change:***
 - Irritability Associated with Autistic Disorder: June 9, 2014
 - Section 2.4 Dosage and Administration; 14.4 Clinical Studies
 - Tourette's Disorder: December 12, 2014
 - Section 1 Indication; Section 2.5 Dosage and Administration; Section 8.4 Pediatric Use; Section 14.5 Clinical Studies

* Initiated current review

Irritability Associated with Autistic Disorder



- Two, 8-week efficacy and safety studies in patients 6 to 17 years diagnosed with irritability associated with autistic disorder and behaviors such as tantrums, aggression, self-injurious behaviors, or a combination of these behaviors.
- One, 12-week, randomized withdrawal, maintenance of efficacy study in the same pediatric patient population.
- Primary Efficacy Endpoints:
 - Change from baseline in **Irritability subscale of the Aberrant Behavior Checklist (ABC-I)**, and
 - **Clinical Global Impression-Improvement (CGI-I) scale**

Irritability Associated with Autistic Disorder



Efficacy Results in 8-week studies:

- Study 1: n=98, aripiprazole (2 to 15 mg/day); significantly improved scores on the ABC-I subscale and the CGI-I scale compared with placebo (PBO) at three aripiprazole doses (5 mg, 10 mg, 15 mg/day).
- Study 2: n=218, aripiprazole at three fixed doses (5 mg/day, 10 mg/day, or 15 mg/day) compared to PBO; significantly improved scores on irritability ABC-I subscale and the CGI-I scale compared with PBO at three aripiprazole doses (5 mg, 10 mg, 15 mg/day).

A 12-week randomized withdrawal study in 85 patients, 6 to 17 years of age, with irritability associated with autistic disorder failed to establish long-term maintenance.

Tourette's Disorder

- Two studies:
 - An 8-week, PBO-controlled, fixed dose trial (patients 7 to 17 years)
 - A 10-week, PBO-controlled, flexible dose trial (6 to 18 years) in patients with Tourette's Disorder.

- Primary Efficacy Endpoints:
 - Change from Baseline to endpoint in the **Total Tic Score (TTS)** $\geq 20 - 22$ on the **Yale Global Tic Severity Scale (YGTSS)** which measures current tic severity.
 - **Clinical Global Impressions (CGI) Scale for Tourette's Syndrome (CGI-TS)**

Tourette's Disorder

Efficacy Results:

- Study 1: n=133, 7 to 17 years, aripiprazole (low dose - weight < 50 kg, 2 to 5 mg/day; high dose - weight ≥ 50 kg, 2 to 10 mg/day);
 - Aripiprazole high dose and low dose groups demonstrated statistically significantly improved scores on the YGTSS TTS and CGI-TS scale compared to PBO.

- Study 2: n=61, 6 to 18 years, aripiprazole (2 mg to 20 mg/day);
 - Aripiprazole demonstrated statistically significantly improved scores on the YGTSS TTS scale compared with PBO.

Relevant Pediatric Safety Labeling



Boxed Warning

- 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.

Relevant Pediatric Safety Labeling

Section 2 Dosage and Administration

- **Section 2.1 Schizophrenia**
 - Adolescents 13 to 17 years
- **Section 2.2 Bipolar I Disorder**
 - Pediatric patients 10 to 17 years
- **Section 2.4 Irritability Associated with Autistic Disorder**
 - Pediatric patients, 6 to 17 years; however, maintenance treatment of irritability associated with autistic disorder was not established.
- **Section 2.5 Tourette's Disorder**
 - Pediatric patients 6 to 18 years



Relevant Pediatric Safety Labeling

Section 5 Warnings and Precautions

- Section 5.3 Suicidal Thoughts and Behaviors in Children, Adolescents, and Young Adults
- Section 5.4 Neuroleptic Malignant Syndrome
- Section 5.5 Tardive Dyskinesia
- Section 5.6 Metabolic Changes
 - Hyperglycemia/diabetes mellitus, dyslipidemia, and weight gain.
- Section 5.7 Pathologic Gambling and other Compulsive Behaviors
- Section 5.8 Orthostatic Hypotension



Relevant Pediatric Safety Labeling

Section 5 Warnings and Precautions

- Section 5.9 Falls
- Section 5.10 Leukopenia, Neutropenia, and Agranulocytosis
- Section 5.11 Seizures/Convulsions
- Section 5.12 Potential for Cognitive and Motor Impairment
- Section 5.13 Body Temperature
 - Disruption of the body's ability to reduce core body temperature.
- Section 5.14 Suicide



Relevant Pediatric Safety Labeling

Section 6.1 Clinical Trials Experience

Commonly observed adverse reactions (incidence $\geq 5\%$ and at least twice that for PBO) were:

- Pediatric patients (13 to 17 years) with **schizophrenia**: extrapyramidal disorder, somnolence and tremor.
- Pediatric patients (10 to 17 years) with **bipolar mania**: somnolence, extrapyramidal disorder, fatigue, nausea, akathisia, blurred vision, salivary hypersecretion, and dizziness.
- Pediatric patients (6 to 17 years) with **irritability associated 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, and fatigue.

Relevant PREA Safety Labeling

Section 14 Clinical Studies (Pediatrics)

- Subsection 14.1 Schizophrenia
- Subsection 14.2 Bipolar Disorder
- Subsection 14.4 Irritability Associated with Autistic Disorder, two clinical studies are described.
- Subsection 14.5 Tourette's Disorder, two clinical studies are described.

Pediatric Drug Utilization

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**

	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%

* 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

Source: IMS Health, Total Patient Tracker™. June 2014 – November 2016.

Extracted December 30, 2016. File: TPT 2016-2433; Abilify Peds 4-12-2017.xls.



Pediatric Diagnoses and Use of Aripiprazole: June 2014 to November 2016, cumulative¹

Top pediatric diagnoses associated with use of aripiprazole as reported from U.S. office-based physician surveys:

- 6 to 12 years: Infantile Autism (ICD-10 Code 2990)*
- 13 to 17 years: Affect Psychoses (ICD-10 Code 2969)*

No drug use mentions or associated diagnoses were captured in the 0-5 year age group.

*Drug use mentions are small for reliable national estimates of use by diagnoses. These mentions indicate that a given drug was mentioned during an office visit, but do not necessarily result in a prescription being generated.

¹Source, inVentiv Health Research & Insights, LLC Treatment Answers with Pain Panel, June 2014 through November 2016. Data Extracted December 2016.



FDA Adverse Event Reporting System (FAERS*)

May 1, 2011 to November 30, 2016

	All Reports (US)	Serious** (US)	Death (US)
Adults (≥ 17 yrs.)	11,334 (7556)	6,636 (2911)	766 (428)
Pediatrics (0 - <17 yrs.)	1,960 (1576)	891 (515)	37*** (32)
Seventeen yr olds (17 to <18)	250 (180)	133 (66)	5 (5)
All Ages	4,599 (3496)	2,256 (1173)	215 (116)

* May include duplicates and transplacental exposures

** Serious adverse drug experiences per regulatory definition (CFR 3414.80) include: death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, required intervention, and other serious important medical events.

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

Pediatric Case Selection

- Serious pediatric reports, *crude count* (n=581)
- Domestic, serious pediatric reports with outcome of death (n=37)

Excluded Cases* (n=503)

(Including 23 deaths - all duplicates)

- Labeled events (n=250)
- Duplicates (n=84, including 23 deaths)
- Indication or disease related (i.e., depression in a pt. with Bipolar I disorder) (n=72)
- No AE/unable to evaluate event (n=31)
- Alternative etiology (n=27)
- Transplacental or trans-mammary exposure (n=20)
- Adults (miscoded) (n=14)
- Use of injectable formulation of Abilify (n=4)
- Preconception paternal drug exposure (n=1)

* DPV reviewed these cases, but they were excluded from the pediatric case series.

Pediatric Case Series (n=78)

Including 14 deaths

Characteristics of Pediatric Case Series with oral aripiprazole

- **Gender**
 - Male (n=46)
 - Female (n=31)
 - Unknown (n=1)

- **Ages**
 - 0 to <1 month (n=1)
 - 1 month to < 2 years (n=1)
 - 2 to < 6 years (n=2)
 - 6 to < 12 years (n=25)
 - 12 to < 17 years (n=35)
 - 17 to < 18 years (n=14)

Characteristics of Serious Pediatric Cases with oral aripiprazole (n=78)

- Serious Outcomes*
 - Death: 14
 - One case transplacental exposure, premature infant, died at 6 days of age
 - Remaining 13 cases: children/adolescents 5 years to 17 years of age
 - Reported daily dose of aripiprazole: 3 mg to 30 mg (n=6)
 - 2 of 3 cases: toxicity to several concurrent medications, intentional overdose resulting in completed suicide.
 - 1 of these 3 cases did not explicitly report intent to self-harm.
 - Life-threatening: 1
 - Hospitalized: 19
 - Disability: 1
 - Congenital anomaly: 1
 - Other serious: 56

* Reports may have more than one outcome.

Pediatric Deaths (n=14)

- Suicide (n=5)
- Drug Overdose (n=1)
- Neuroleptic Malignant Syndrome (n=1)
- Metabolic Changes (n=1)
- Seizures/Convulsions (n=1)
- Hyperthermia (n=1)* ^
- Cardiac (n=1)
- Unknown (n=2)
- Not applicable (n=1)

Among 14 reported deaths, there is no discernible pattern for the reported unlabeled events.

*Unlabeled event

^ Temperature regulation and neuroleptic malignant syndrome are labeled events.

Pediatric Deaths

Suicide (n=5)

- 16 year old female, Depression (adjunct to escitalopram), died of suicide by hanging; taking escitalopram 20 mg/day and experiencing mood instability, aripiprazole 2.5 mg/day started as adjunctive therapy x 3 months; patient continued to have rage outbursts. Aripiprazole dose increased to 5 mg/day x 3 weeks. No prior history of suicide attempts.
- 16 year old female, Major Depressive Disorder with atypical features, died of suicide (unknown method and aripiprazole dose).
- 16 year old male, Diagnosis for aripiprazole treatment not reported, died of cardiac and/or respiratory arrest secondary to intentional drug overdose; acute ingestion of morphine sulfate, acetaminophen/hydrocodone.
- 17 year old male, Bipolar disorder, treated with aripiprazole for approximately 6 months. Died from self-inflicted gun-shot wound. Additional details not available.
- 17 year old female, Bipolar Disorder, died of hypoxic encephalopathy due to acute bupropion and aripiprazole overdose, but only bupropion reported in serology tests. Death attributed to bupropion.

Pediatric Deaths

Drug Overdose (n=1)

- 14 year old male, diagnosis for aripiprazole treatment not reported, died of cardiac and/or respiratory arrest secondary to drug poisoning; died post drug poisoning with quetiapine, codeine, unspecified laxative, aripiprazole, valproic acid, lisdexamfetamine, diphenhydramine, penicillin, meloxicam, clonidine, morphine, and sertraline. Suicide intent not reported.

Neuroleptic Malignant Syndrome (NMS) (n=1)

- 12 year old male, Bipolar disorder, died of possible neuroleptic malignant syndrome; aripiprazole 10 mg/day.

Pediatric Deaths

Metabolic Changes (n=1)

- 14 year old male, Cardiac arrest second to hyperglycemic, hyperosmolar, nonketotic syndrome (HHNS).

Seizures/Convulsions (n=1)

- 5 year old male, “Behavior disorder”, died of sudden unexpected death with epilepsy (SUDEP); concurrent medications carbamazepine and levetiracetam; aripiprazole 3 mg/day.

Pediatric Deaths

Hyperthermia (n=1)

- 11 year old male, Bipolar Disorder, died while playing outside, no cause of death reported; prescribed “several other medications” drugs not reported; internal body temperature 106 degrees, aripiprazole 30 mg/day.

Cardiac (n=1)

- 10 year old male, Diagnosis for aripiprazole treatment not reported, died of multiple organ failure, ischemic cardiomyopathy, coronary artery stenosis, congenital heart disease; aripiprazole treatment x 2 years (dose not reported).

Pediatric Deaths

Unknown (n=2)

- 13 year old female, Bipolar Disorder treated in combination with valproate, died secondary to drowning in a pool after saying she was “tired”; aripiprazole 10 mg/day and in prior week prescribed benzonatate for cough.
- 16 year old male, Autism, cause of death not reported, “died while taking aripiprazole for 3 months duration (dose not reported)”.

Not Applicable (n=1)

- 5 day old male with transplacental exposure died of complications related to Tetralogy of Fallot, including post-op hemothorax and hemopericardium. Maternal history of chromosomal micro-deletion 22 with Tetralogy of Fallot. Not causally related to aripiprazole.



Non-Fatal Serious Pediatric Adverse Events (n= 64)

- Worsening of underlying condition after switching from brand to generic drug (n=16), from one dosage formulation to another dosage formulation (n=3), or from generic to brand drug (n=1).
- Condition did not improve (n=11) or worsened (n=4) during aripiprazole treatment.
- Cerebrovascular infarction/cerebrovascular accident (CVA) (n=5)
- Gynecomastia (n=3)
- Hallucinations* (n=3)
- Pancreatitis/Pancreatic Disorder (n=2)
- Non-alcoholic Steatohepatitis (n=2)
- Drug screen false positive for amphetamines (n=2)

* Labeled for delirium

Non-Fatal Serious Pediatric Adverse Events (n=64)

One event each for of the following:

- Tooth loss
- Oral pain and stomatitis
- Hematemesis
- Hemoptysis
- Reflex Sympathetic Dystrophy-like Syndrome (RSDS)
- Priapism
- Ventricular Extrasystoles
- Cardiac Failure, Congestive
- Conductive Disorder
- Pituitary Tumor
- Skin striae
- Stevens-Johnson syndrome

There is no discernible
pattern for the
previously unlabeled
events.



Summary: Pediatric Safety Review

- The aripiprazole focused pediatric safety review is concluded.
- No new safety signals were identified.
- FDA recommends to continue ongoing, postmarketing safety monitoring.
- Does the Pediatric Advisory Committee concur?

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