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

Pediatric Postmarketing Pharmacovigilance and Drug Utilization Review

Date:	February 18, 2016
Safety Evaluator(s):	Courtney Suggs, PharmD, MPH Division of Pharmacovigilance I
Drug Use Analyst(s):	Travis Ready, PharmD Division of Epidemiology II
Team Leader(s):	Ida-Lina Diak, PharmD, MS Division of Pharmacovigilance I
	Rajdeep Gill, PharmD Division of Epidemiology II
Deputy Division Director:	Cindy Kortepeter, PharmD Division of Pharmacovigilance I
	Grace Chai, PharmD Deputy Director for Drug Utilization Division of Epidemiology II
Division Director(s):	Robert Levin, MD Division of Pharmacovigilance I
Product Name(s):	Symbyax (fluoxetine hydrochloride and olanzapine)
Pediatric Labeling Approval Date:	April 9, 2007
Application Type/Number:	NDA 21520
Applicant/Sponsor:	Lilly
OSE RCM #:	2015-1961

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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 and drug utilization data for Symbyax (olanzapine and fluoxetine) in pediatric patients. This review was triggered by an expanded indication from adults to pediatric patient 10-17 years for Symbyax.

Symbyax was first approved in 2003 and is indicated for the treatment of acute depressive episodes in Bipolar I Disorder and for treatment resistant depression. In 2013, FDA approved Symbyax for the treatment of acute depressive episodes associated with Bipolar I Disorder in patients 10 to 17 years of age.

In order to capture pediatric use of combination olanzapine and fluoxetine products and to provide context for the adverse event reports submitted to the FAERS database, drug utilization patterns were assessed. A nationally estimated number of 473 pediatric patients (2% of total patients) received combination olanzapine and fluoxetine prescriptions from U.S. outpatient retail pharmacies in 12-month period ending in June 2015, a decrease from nearly1,500 patients in 12-month period ending in June 2011. Among pediatric patients, patients aged 10-16 years accounted for approximately 90 to 95% of pediatric patients a year during the examined time. Psychiatry was the top prescriber specialty for combination olanzapine and fluoxetine, followed by family practice. According to an office-based physician surveys database there were no diagnoses reported in association with the use of combination olanzapine and fluoxetine in pediatric patients aged 0-16 years for July 2010 through June 2015.

The Division of Pharmacovigilance (DPV) searched the FDA Adverse Event Reporting System (FAERS) database for reports received from January 1, 2004 - June 30, 2015. DPV reviewed all pediatric cases reported with the use of Symbyax. There was one fatal case, one transplacental exposure, and 17 non-fatal cases. Due to the limited number of case reports for each event, it was difficult to draw any conclusions. The vast majority of adverse events reported to FDA were labeled events that are well characterized. Within the case series of unlabeled adverse events, there were no new patterns or trends suggestive of new or unexpected adverse events attributable to Symbyax. DPV recommends no labeling changes at this time, and will continue to monitor adverse events associated with the use of Symbyax.

1 INTRODUCTION

1.1 PEDIATRIC REGULATORY HISTORY

On April 9, 2007 a new dosing regimen for Symbyax, 3mg/25mg capsules, was approved. At the time of approval, the requirement for a pediatric safety and efficacy study for the treatment of major depressive episodes associated with bipolar disorder in patients 10 – 17 years old was deferred under PREA. The pediatric study requirement for children 0 – 9 years old was waived because the condition is difficult to diagnose and treat in this age group. The study was submitted by the Sponsor on November 14, 2012.

Symbyax was approved for use in pediatric patients on July 26, 2013. The indication was expanded for the treatment of acute depressive episodes in Bipolar I Disorder from adults to pediatric patients 10-17 years old. The safety and efficacy were established in a single 8-week randomized, placebo-controlled clinical trial in 255 pediatric patients. In pediatric Bipolar Depression, the starting dose is 3 mg/25 mg once daily (for ages 10 to 17 years). The pediatric Bipolar Depression maximum dose is 12 mg/50 mg. The starting dose in patients predisposed to hypotensive reactions, hepatic impairment, or with potential for slowed metabolism is 3 mg/25 mg to 6 mg/25 mg. The dose should be escalated cautiously in these patients.[1]The safety and efficacy for treatment resistant depression in patients less than 18 years have not been established. Symbyax is not approved for any indication in patients less than 10 years old.

In the placebo-controlled clinical trial in patients 10 to 17 years old, somnolence-related adverse events were commonly reported with drug treatment, occurring in 23.5% of drug-treated patients compared with 2.4% of placebo-treated patients. The types of adverse reactions observed with olanzapine and fluoxetine hydrochloride in children and adolescents were similar to adults, but the magnitude and frequency of some changes were greater in children and adolescents than adults. These included increases in lipids, hepatic enzymes, and prolactin, and increases in the QT interval. The frequency of weight gain greater than or equal to 7%, and the magnitude and frequency of increases in lipids, hepatic analytes, and prolactin in children and adolescents treated with olanzapine and fluoxetine hydrochloride were similar to those observed in adolescents treated with olanzapine monotherapy. Overall, 14.1% of the 170 patients in the olanzapine and fluoxetine hydrochloride group discontinued due to adverse reactions compared with 5.9% of the 85 patients for placebo. Adverse reactions leading to discontinuation associated with the use of olanzapine and fluoxetine hydrochloride were weight increased (2.9%), suicidal ideation (1.8%), bipolar disorder (1.2%), and somnolence (1.2%) versus placebo patients which had 0% incidence of weight increased, bipolar disorder, and somnolence, and a 1.2% incidence of suicidal ideation.[2]

1.2 HIGHLIGHTS OF LABELED SAFETY ISSUES[1]

Boxed Warning:

Symbyax contains a boxed warning for suicidal thoughts and behaviors; and increased mortality in elderly patients with dementia-related psychosis.

Contraindications:

- *Monoamine Oxidase Inhibitors (MAOI):* Because of the risk of serotonin syndrome, do not use MAOIs intended to treat psychiatric disorders with SYMBYAX or within 5 weeks of stopping treatment with SYMBYAX. Do not use SYMBYAX within 14 days of stopping an MAOI intended to treat psychiatric disorders. In addition, do not start SYMBYAX in a patient who is being treated with linezolid or intravenous methylene blue.
- *Pimozide:* Do not use. Risk of QT interval prolongation.
- *Thioridazine:* Do not use. Risk of QT interval prolongation. Do not use thioridazine within 5 weeks of discontinuing SYMBYAX.

Warnings and Precautions:

- Neuroleptic Malignant Syndrome: Manage with immediate discontinuation and close monitoring.
- Metabolic Changes: Atypical antipsychotic drugs have been associated with metabolic changes including hyperglycemia, dyslipidemia, and weight gain.
    - Hyperglycemia and Diabetes Mellitus: In some cases extreme and associated with ketoacidosis or hyperosmolar coma or death. Monitor for symptoms of hyperglycemia. Perform fasting blood glucose testing before beginning, and periodically during treatment.
    - Dyslipidemia: Appropriate clinical monitoring is recommended, including fasting blood lipid testing before beginning, and periodically during, treatment.
    - Weight gain: Consider potential consequences of weight gain. Monitor weight regularly.
- Serotonin Syndrome: Serotonin syndrome has been reported with SSRIs and SNRIs, including SYMBYAX, both when taken alone, but especially when co-administered with other serotonergic agents (including triptans, tricyclic antidepressants, fentanyl, lithium, tramadol, tryptophan, buspirone and St. John's Wort). If such symptoms occur, discontinue SYMBYAX and initiate supportive treatment. If concomitant use of SYMBYAX with other serotonergic drugs is clinically warranted, patients should be made aware of a potential increased risk for serotonin syndrome, particularly during treatment initiation and dose increases.
- Angle-Closure Glaucoma: Angle-closure glaucoma has occurred in patients with untreated anatomically narrow angles treated with antidepressants.
- Allergic Reactions and Rash: Discontinue upon appearance of rash or allergic phenomena.
- Activation of Mania/Hypomania: Screen for Bipolar Disorder and monitor for activation of mania/hypomania.
- Tardive Dyskinesia: Discontinue if clinically appropriate.
- Orthostatic Hypotension: Can be associated with bradycardia and syncope. Risk is increased during initial dose titration. Use caution in patients with cardiovascular disease or cerebrovascular disease, and those conditions that could affect hemodynamic responses.
- Leukopenia, Neutropenia, and Agranulocytosis: Has been reported with antipsychotics, including SYMBYAX. Patients with a history of a clinically significant low white blood cell

count (WBC) or drug induced leukopenia/neutropenia should have their complete blood count (CBC) monitored frequently during the first few months of therapy. Consider discontinuing SYMBYAX at the first sign of a clinically significant decline in WBC in the absence of other causative factors.
- Seizures: Use cautiously in patients with a history of seizures or with conditions that lower the seizure threshold.
- Abnormal Bleeding: SSRIs increase the risk of bleeding. Use with NSAIDs, aspirin, warfarin, or other drugs that affect coagulation may potentiate the risk of gastrointestinal or other bleeding.
- Hyponatremia: Can occur in association with syndrome of inappropriate antidiuretic hormone (SIADH). Consider discontinuing SYMBYAX if symptomatic hyponatremia occurs (SIADH).
- Potential for Cognitive and Motor Impairment: Has potential to impair judgment, thinking, and motor skills. Caution patients about operating machinery.
- QT Prolongation: QT prolongation and ventricular arrhythmia including Torsade de Pointes have been reported with fluoxetine. Use with caution in conditions that predispose to arrhythmias or increased fluoxetine exposure. Use cautiously in patients with risk factors for QT prolongation.
- Hyperprolactinemia: May elevate prolactin levels.
- Long Elimination Half-Life of Fluoxetine: Changes in dose will not be fully reflected in plasma for several weeks.

Adverse Reactions:

Most common adverse reactions (≥5% and at least twice that for placebo) in adults: sedation, weight increased, appetite increased, dry mouth, fatigue, edema, tremor, disturbance in attention, blurred vision. Children and adolescents: sedation, weight increased, appetite increased, tremor, triglyceride increased, hepatic enzymes increased.

Drug Interactions:

- Monoamine Oxidase Inhibitor (MAOI).
- Drugs Metabolized by CYP2D6: Fluoxetine is a potent inhibitor of CYP2D6 enzyme pathway.
- Tricyclic Antidepressants (TCAs): Monitor TCA levels during coadministration with SYMBYAX or when SYMBYAX has been recently discontinued.
- CNS Acting Drugs: Caution is advised if the concomitant administration of SYMBYAX and other CNS-active drugs is required.
- Antihypertensive Agent: Enhanced antihypertensive effect.
- Levodopa and Dopamine Agonists: May antagonize levodopa/dopamine agonists.
- Benzodiazepines: May potentiate orthostatic hypotension and sedation.
- Clozapine: May elevate clozapine levels.
- Haloperidol: Elevated haloperidol levels have been observed.
- Carbamazepine: Potential for elevated carbamazepine levels and clinical anticonvulsant toxicity.
- Phenytoin: Potential for elevated phenytoin levels and clinical anticonvulsant toxicity.
- Alcohol: May potentiate sedation and orthostatic hypotension.

- Serotonergic Drugs.
- Fluvoxamine: May increase olanzapine levels; a lower dose of the olanzapine component of SYMBYAX should be considered
- Drugs that Interfere with Hemostasis: (e.g., NSAIDs, Aspirin, Warfarin, etc.): May potentiate the risk of bleeding.
- Drugs Tightly Bound to Plasma Proteins: Fluoxetine may cause shift in plasma concentrations.
- Drugs that Prolong the QT Interval: Do not use SYMBYAX in combination with thioridazine or pimozide. Use SYMBYAX with caution in combination with other drugs that prolong the QT interval.

Use in Specific Populations:

- Pregnancy: SYMBYAX should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.
- Nursing Mothers: Breast feeding is not recommended.
- Pediatric Use: Safety and efficacy of Symbyax for the treatment of bipolar I depression in patients under 10 years of age have not been established. Safety and efficacy of Symbyax for treatment resistant depression in patients under 18 years of age have not been established.
- Hepatic Impairment: Use a lower or less frequent dose in patients with cirrhosis.

2 DRUG UTILIZATION DATA

2.1 METHODS AND MATERIALS

Proprietary drug utilization databases available to the Agency were used to conduct these analyses. ***(See Appendix A for full database descriptions).*** The drug utilization analyses were conducted on marketed combination olanzapine and fluoxetine products only (Symbyax and generics combination products).

2.1.1 Determining Settings of Care

The IMS Health IMS National Sales Perspectives™ database was used to determine the various retail and non-retail channels of distribution for combination olanzapine and fluoxetine products. Approximately 81% of combination olanzapine and fluoxetine bottles of capsules were sold to outpatient retail pharmacies (i.e. chain stores, independent pharmacies, and food stores), 6% to non-retail settings (i.e. clinics, long term care, non-federal hospitals, etc.), and 12% to mail-order/specialty pharmacies, from July 2014 through June 2015.[1] As a result of these distribution patterns, only outpatient retail pharmacy utilization patterns were examined. Data from mail-order/specialty pharmacies and non-retail settings were not included in these analyses.

[1] IMS Health National Sales Perspective (NSP), JUL2014-JUN2015, Extracted JAN2015

2.1.2 Products Included[2]

Symbyax® and its generic versions only were included in this analysis:

Brand	Generic	Strength
SYMBYAX®	FLUOXETINE HYDROCHLORIDE; OLANZAPINE	EQ 25MG BASE; EQ 3MG BASE
SYMBYAX®	FLUOXETINE HYDROCHLORIDE; OLANZAPINE	EQ 25MG BASE; EQ 6MG BASE
SYMBYAX®	FLUOXETINE HYDROCHLORIDE; OLANZAPINE	EQ 50MG BASE; EQ 6MG BASE
SYMBYAX®	FLUOXETINE HYDROCHLORIDE; OLANZAPINE	EQ 25MG BASE; EQ 12MG BASE
SYMBYAX®	FLUOXETINE HYDROCHLORIDE; OLANZAPINE	EQ 50MG BASE; EQ 12MG BASE

2.1.3 Data Sources Used

The IMS Health, Total Patient Tracker™ (TPT) database was used to obtain nationally estimated numbers of patients who received outpatient retail prescriptions for combination olanzapine and fluoxetine products in the U.S., stratified by patient age (0-9, 10-16, and 17 years and older), by 12-month periods, from July 2010 through June 2015.

The IMS Health, National Prescription Audit™ (NPA) database was used to obtain nationally estimated numbers of prescriptions for combination olanzapine and fluoxetine products from the U.S outpatient retail settings, by prescriber specialty, from July 2010 through June 2015, cumulative. Diagnoses associated with combination olanzapine and fluoxetine product use as reported by U.S. office-based physician surveys, stratified by patient age (0-9, 10-16, and 17 years and older), were obtained from Encuity Research, LLC., Treatment Answers™ with Pain Panel database for the same cumulative time period. Diagnoses were coded according to the

[2] Source: Drugs@fda; http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.DrugDetails

International Classification of Diseases (ICD-9-CM) and 95% confidence intervals were obtained for the estimates.

2.2 RESULTS

2.2.1 Unique Patients for Combination Olanzapine and Fluoxetine

Table 1 displays the nationally estimated number of unique patients who received a prescription for combination olanzapine and fluoxetine products dispensed from an outpatient retail pharmacy in the U. S., stratified by patient age (0-9, 10-16 and 17 years and older), by12-month periods, from July 2010 through June 2015. The overall use of combination olanzapine and fluoxetine products declined from 51,000 patients during the 12-month period ending in June 2010 to 23,000 patients during the 12-month period ending in June 2015. During each 12-month period, adult patients 17 years and older accounted for the majority of use. Pediatric patients aged 0-16 years accounted for approximately 2 to 3% of total patients during each 12-month period examined. Approximately 1,500 pediatric patients received combination olanzapine and fluoxetine prescriptions dispensed during the 12-month period ending in June 2011, decreasing to nearly 500 patients during the 12-month period ending in June 2015. Among pediatric patients aged 0-16 years, patients aged 10-16 years accounted for the majority of use.

Table 1: Nationally estimated number of patients with a prescription for combination olanzapine and fluoxetine products from U.S. outpatient retail pharmacies, stratified by patient age*, July 2010 - June 2015

	July 2010 - June 2011		July 2011 - June 2012		July 2012 - June 2013		July 2013 - June 2014		July 2014 - June 2015	
	Patients (N)	*Share %*	Patients (N)	*Share %*	Patients (N)	*Share %*	Patients (N)	*Share %*	Patients (N)	*Share %*
Grand Total	51,107	*100%*	38,756	*100%*	28,839	*100%*	24,855	*100%*	23,080	*100%*
0 - 16 Years	1,472	*2.9%*	1,047	*2.7%*	668	*2.3%*	573	*2.3%*	473	*2.1%*
0 - 9 Years	118	*8.0%*	92	*8.8%*	66	*9.9%*	57	*10.0%*	28	*5.9%*
10 - 16 Years	1,359	*92.3%*	963	*92.0%*	607	*90.9%*	518	*90.4%*	452	*95.6%*
17+ Years	49,638	*97.1%*	37,748	*97.4%*	28,199	*97.8%*	24,307	*97.8%*	22,567	*97.8%*
Unknown Age	44	*0.1%*	-	-	17	*0.1%*	37	*0.2%*	274	*1.2%*

Source: IMS Health Total Patient Tracker (TPT), MAT JUL2009-JUN2015, extracted JAN2016

*Patient age groups are inclusive of all patients up to the day before their next birthday. For example, patients aged 0-16 years include patients less than 17 years of age (16 years and 11 months). Patient age subtotals may not sum exactly due to patients aging during the study period, and may be counted more than once in the individual age categories. For this reason, summing across patient age bands or time periods is not advisable and will result in overestimates of patient counts.

2.2.2 Prescriber Specialty

Table 2 below shows the nationally estimated number of combination olanzapine and fluoxetine prescriptions from U.S. outpatient retail pharmacies, stratified by prescriber specialty, from July 2010 through June 2015, cumulative. Approximately 654,000 total prescriptions from outpatient retail pharmacies in the U.S. were captured during the examined time. Psychiatry was the top specialty accounting for 33% (approximately 213,000 prescriptions) of the total prescriptions, followed by family practice with 23% (148,000 prescriptions) and internal medicine with 12% (approximately 81,000 prescriptions). Pediatrics accounted for less than 1% of the total prescriptions dispensed (*data not shown*).

Table 2: Nationally estimated number of prescriptions for combination olanzapine and fluoxetine products from outpatient retail pharmacies in the U.S., stratified by prescriber specialty, from July 2010 through June 2015, cumulative

	July 2010 - June 2015	
	Prescriptions (N)	***Share%***
Total prescriptions	**654,203**	***100%***
PSYCHIATRY	213,440	*32.63%*
FAMILY PRACTICE	147,845	*22.60%*
INTERNAL MEDICINE	80,958	*12.38%*
NURSE PRACTITIONER	66,873	*10.22%*
OSTEOPATHIC MEDICINE	62,812	*9.60%*
PHYSICIAN ASSISTANT	30,080	*4.60%*
GENERAL PRACTICE	5,905	*0.90%*
SPECIALTY UNSPECIFIED	5,795	*0.89%*
NEUROLOGY	3,557	*0.54%*
All other specialties	36,938	*5.62%*

Source: IMS Health National Prescription Audit (NPA), JUL2010-JUN2015, Extracted JAN2016

2.2.3 Diagnoses Associated with Use

Table 3 shows the diagnoses associated with combination olanzapine and fluoxetine use expressed as *drug use mentions*[3], stratified by patient age (0-9, 10-16, & 17+ years), as reported by U.S. office-based physician surveys from July 2010 through June 2015, cumulative. No diagnoses were captured in pediatric patients between the ages of 0-16 years during the examined time. Among adult patients aged 17 years and older, "Bipolar Affective Not Otherwise Specified" (ICD-9, code 296.7) was the top diagnosis associated with combination olanzapine and fluoxetine use with a point estimate of 160,000 use mentions (95% CI; 95,000 – 225,000).(data not shown)

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 B for a description of the FAERS database.

3 The term *drug uses* refers to mentions of a drug in association with a diagnosis during an office-based patient visit. 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 prescription being generated. Rather, the term indicates that a given drug was mentioned during an office visit with a physician.

Table 3.1.1 FAERS Search Strategy	
Date of Search	September 2, 2015
Time Period of Search	January 1, 2004* - June 30, 2015
Search Type	Quick Query
Product Name(s)	Symbyax
Search Parameters	All ages, all outcomes, worldwide

** Symbyax was approved on December 24, 2003, but became available in 2004.*

3.2 RESULTS

3.2.1 Total number of FAERS reports by Age

Table 3.2.1: Number of adult and pediatric FAERS reports* from January 1, 2004 to June 30, 2015 with Symbyax

	All reports (US)	Serious† (US)	Death‡ (US)
Adults (≥ 17 years)	355(347)	325(317)	54(50)
Pediatrics (0 to <17 years)	22(22)	18(18)	4(4)

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

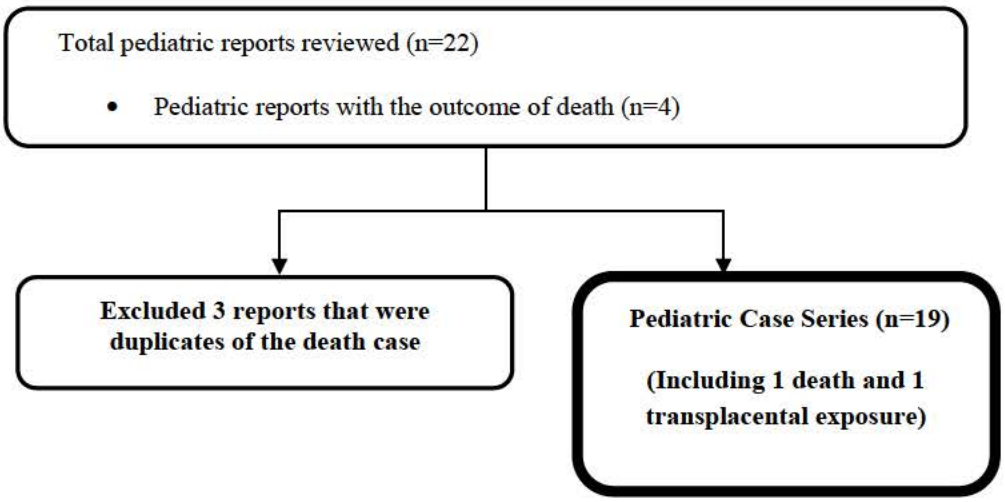
† *Serious adverse drug experiences per regulatory definition (CFR 314.80) include outcomes of death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, and other serious important medical events.*

‡ *Does not include null age death reports*

3.2.2 Selection of Pediatric Cases in FAERS

We identified 22 pediatric reports (See Table 3.2.1). **Figure 3.2.2** below explains the specific selection of cases to be summarized in **Sections 3.3-3.5.**

Figure 3.2.2 Selection of Pediatric Cases with Symbyax



3.2.3 Characteristics of Pediatric Case Series

Appendix C 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 Symbyax (N=19)

Age (n=19)	0 - < 1 month	1
	1 month - <2 years	1
	2- < 6 years	0
	6- <12 years	6
	12- < 17 years	11
Sex (n=19)	Male	11
	Female	8
Country (n=18)	United States	18
Reported Reason for Use	Depression[†]	7
	Aggression	2
	Bipolar Disorder	2
	Oppositional/ Defiant Disorder	1
	Mood Disorder	1
	Unknown	6
Serious Outcome[‡] (n=16)	Death	1
	Hospitalized	8
	Other serious	7

† Includes manic depression, bipolar depression, and major depressive disorder
‡ Serious adverse drug experiences per regulatory definition (CFR 314.80) include outcomes of death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, and other serious important medical events. Reports may have more than one outcome.

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

A seven year old male patient of an incarcerated mother, with a history of possible previous sexual molestation, impulse control disorder, enuresis, aggression, and self-injurious behavior committed suicide. During the first visit of a court ordered psychiatric evaluation in August 2008, the physician reported "there was no suicidal ideation, plan, or intent expressed by the patient." Therapy sessions were recommended, but drug therapy was not started at that time. Over the course of the next few months, the patient demonstrated inappropriate behavior towards other classmates, as well as self-injurious behavior. At the next appointment, the patient presented as "hyperverbal with loud speech, inability to sit still, and increased impulsivity." Vyvanse (lisdexamfetamine dimesylate) 30mg daily was initiated with noticeable improvement in focus, concentration, mood, sleep and appetite. In January 2009, the patient "was having anxiety, crying fits and obsessions with hair twirling." A month later Lexapro (escitalopram) 5mg daily was added to his medication regimen and therapy was increased from once a week to twice a week. Later that month, the patient's behavior "worsened, as exemplified by lying, stealing, and throwing scissors in class." These behaviors reportedly started after beginning visits with his mother in jail. In March 2009, the behaviors again worsened as he "threatened younger siblings, poor eye contact, flat affect, and impulsive behaviors returned with fair judgment and insight." Lexapro was discontinued and Symbyax 3mg/25mg daily was initiated to "decrease the threatening and aggressive behaviors and impulsivity." In late March 2009, the patient presented with a new foster parent with whom he had been living with for two weeks and the patient stated "I have anger problems." Vyvanse was increased to 50mg daily and Symbyax was continued. This was the last time the patient was seen by the physician and according to the physician "at no time during treatment with this physician did the patient express any suicidal ideation, plan or intent." A month later, the patient "locked himself in the bathroom of his foster home and hanged himself with a detachable shower hose following an argument with his foster father's son."

Reviewer's Comments: The patient had an extensive medical and psychosocial history. The patient's behavior had been observed to be worsening for a few months preceding the initiation of Symbyax despite previous treatment with Vyvanse and Lexapro and twice weekly therapy sessions and continued worsening after initiation of Symbyax leading to the patient's demise. Vyvanse is indicated for the treatment of attention deficit hyperactivity disorder in children as young as six years old. Lexapro is not approved for use in pediatric patients less than 12 years

of age. Lexapro has a boxed warning for increased risk of suicidal thinking and behavior in children, adolescents and young adults taking antidepressants for major depressive disorder (MDD) and other psychiatric disorders.

3.4 SUMMARY OF TRANSPLACENTAL EXPOSURE ADVERSE EVENTS CASES (N=1)

A male patient was born full term to a mother who had taken fluoxetine and Symbyax 6mg/50mg during pregnancy. The total daily fluoxetine dosage during pregnancy varied from 60mg to 120mg. No start date or indication for Symbyax was reported. The mother experienced pregnancy induced hypertension. No further pregnancy issues or complications were reported. At birth the patient was cyanotic and diagnosed with respiratory distress syndrome. He was intubated. He was also diagnosed with transposition of the great vessels. He underwent arterial switch procedure and left diaphragm placation. After discharge he was reported to have no other problems. On an unknown date, he was also found to have trivial right pulmonary artery stenosis. Fluoxetine was continued after the pregnancy. It is unknown if Symbyax was continued.

Reviewer's Comment: Symbyax is pregnancy category C. The Symbyax label states neonates exposed to fluoxetine, and other SSRIs and SNRIs late in the third trimester have developed complications arising immediately upon delivery (respiratory distress, cyanosis, apnea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycemia, hypotonia, hypertonia, hyperreflexia, tremor, jitteriness, irritability, and constant crying) requiring prolonged hospitalization, respiratory support, and tube feeding.

3.5 SUMMARY OF NON-FATAL PEDIATRIC ADVERSE EVENT CASES (N=17)

3.5.1 Psychiatric Disorders (N=4)

Labeled Events

Suicide Attempt (n=1)

A 16 year old female patient who was taking Symbyax for Bipolar I Disorder tried to commit suicide by taking an overdose of Symbyax. She was hospitalized. The action taken with Symbyax and the outcome was not reported.

Reviewer's Comments: The Symbyax label contains a boxed warning for suicidal thoughts and behaviors. The events were consistent with the known risk in the labeling.

Mania (n=2)

Two female patients experienced mania while taking Symbyax. They were both hospitalized. Both cases, one reported by a health care professional and the other a consumer, attributed the

manic episode to be medication related. Concomitant medications were not reported for one patient. The consumer, whose relationship to the patient was not stated, reported multiple concomitant medications including Lexapro, Trileptal, Abilify, Focalin XR, clonidine, and trazodone. It is unknown if Symbyax was continued in either patient. One patient was reportedly treated with quetiapine fumarate and olanzapine and she improved and was transferred from the hospital to a residential treatment facility. The outcome of the other patient was not reported.

Reviewer's Comments: The Symbyax label contains a Warning and Precaution for activation of mania/hypomania. Insufficient information was provided in the cases to be able to make an assessment. The events were consistent with the known risks in the labeling.

Psychotic Disorder (n=1)

A 14 year old male was taking Symbyax and Strattera for unknown indications. The doses and duration of treatment were not provided. During the course of therapy he "became more psychotic." The action taken with either of the medication was not reported. The outcome is unknown.

Reviewer's Comments: Insufficient information was provided in the cases to be able to make an assessment. The case is also confounded by the concomitant use of Strattera, which is labeled for treatment emergent psychotic or manic symptoms, e.g., hallucinations, delusional thinking, or mania.

3.5.2 Nervous System Disorders (N=7)

Labeled Events

Seizure (n=3)

Three cases of seizure were reported. In all three cases the patient had no prior history of seizure. Laboratory and test results were reported as normal in all three patients. In one case it was reported the nurse suspected the seizure was due to an accidental overdose when she did a pill count and found less pills than expected in the bottle. In another case, the seizure was unwitnessed and a description of the seizure was not provided. The reporting physician questioned whether the patient was exhibiting attention seeking behavior. In the above two cases the Symbyax was continued/re-started and further seizures were not reported. A third case reported the patient experienced a seizure one day after initiating Symbyax. Symbyax was discontinued and the patient had not experienced any further seizures.

Reviewer's Comments: The Symbyax label contains a Warning and Precaution for seizures. The events were consistent with the known risk in the labeling.

Dizziness (n=2)

Two cases of dizziness were reported. One case lacked sufficient information to be able to make an assessment. The second case involved a 16 year old female with a history of "three to four episodes of dizziness and passing out." She began taking Symbyax 6mg/25mg for the treatment of bipolar depression and experienced another episode of dizziness and passing out. Symbyax was discontinued and monotherapy with fluoxetine was initiated. The patient experienced another episode while on fluoxetine. The patient was being referred to neurology. Fluoxetine was continued.

Reviewer's Comments: Symbyax is labeled for dizziness. One case lacked sufficient detail to make an assessment. The other case was confounded due to a history of dizziness and passing out prior to initiating Symbyax and a subsequent episode while taking fluoxetine.

Tardive Dyskinesia (n=1)

A 13 year old male had been taking Vyvanse (lisdexamfetamine dimesylate) for one year and OROS paliperidone for 9 months bipolar disorder. The patient developed mood swings and was switched from OROS paliperidone to Symbyax. Subsequently, he experienced "tongue rolling, involuntary movements of the eyes, stiff breathing, arms and legs twitching (involuntary)" after the switch. At the time he had only taken 11 doses of Symbyax. Symbyax was also discontinued after the development of these symptoms. The outcome is unknown.

Reviewer's Comments: The case reported the event as "tardive dyskinesia or withdrawal dyskinesia due to the OROS paliperidone." The events could also be consistent with dystonia. Symbyax contains language in the Adverse Reactions section of labeling regarding dystonia. The label also contains a Warning and Precaution for tardive dyskinesia. The events were consistent with the known risk in the labeling.

Eye Movement Disorder, Musculoskeletal Stiffness, Neuromyopathy, Tongue Paralysis (n=1)

A 13 year old female experienced "uncontrollable eye movements, head and neck became contorted, rapid tongue thrusting and 'made strange animal noises'" one day after initiating Aripiprazole 5mg daily for impulse control disorder and Symbyax 6mg/25mg daily for oppositional defiant disorder. The patient was taken to the emergency room and both medications were discontinued. No treatment was provided. Two weeks later it was reported "all the symptoms 'pretty much dissipated.'"

Reviewer's Comments: Symbyax contains language in the Adverse Reactions section of labeling regarding dystonia. This case of dystonia is consistent with oculogyric crisis, a well-known type of dystonia caused by antipsychotic medications.

3.5.3 Skin and Subcutaneous Tissue Disorder (N=2)

Labeled Events

Urticaria, Compulsions, Weight Increased, Drug Ineffective, Feeling Abnormal, Pain in Extremity, Skin Warm, Swelling, Tremor (n=1)

A 6 year old female began taking Symbyax 6mg/25mg daily for the treatment of possible manic depression. The dose was increased to twice daily because it was not effective. The patient reportedly gained 14 pounds in two weeks and was a compulsive eater after initiating Symbyax. Approximately two week after initiating Symbyax, she woke up with a rash described as welts which "looked like cigarette burns" around her neck and "had the shakes." Symbyax was discontinued. A day later the rash spread to her entire body and it was reported her "skin felt like it was on fire" and "she was so swollen she could not see her hands and feet." The patient was treated in the emergency room with steroids and released, but was admitted two days later to the hospital for worsening of the rash. The swelling resolved, but the rash continued "especially when the patient became upset" for another week. Afterwards, the patient developed pain in the area that had been swollen and pain in the hands, legs, and feet. The patient had also experienced a rash while taking chlorpromazine leading to the discontinuation of it.

Reviewer's Comments: The Symbyax label contains a Warning and Precaution for allergic reactions and rash. The events were consistent with the known risk in the labeling.

Edema (n=1)

An eight year old female taking Symbyax 6mg/25mg for the treatment of severe disruptive behavior and bipolar disorder developed severe edema and was hospitalized. The edema was primarily of her abdomen. Symbyax was discontinued and the edema resolved.

Reviewer's Comments: Edema is labeled in Adverse Reactions as one of the most common adverse reactions in adults. The events were consistent with the known risk in the labeling.

3.5.4 Investigations (N=1)

Labeled Events

Weight Increased (n=1)

A 14 year old male taking Symbyax 6mg/25mg for an unknown indication experienced a 100 pound weight gain over one year. The Symbyax was discontinued. The outcome was not reported.

Reviewer's Comments: The Symbyax label contains a Warnings and Precaution for weight gain.

3.5.5 Injury Poisoning and Procedural Complications (N=3)

Labeled

Dyspnea, Exposure During Breast Feeding, Maternal Exposure During Pregnancy (n=1)

A four month old male was born premature. The mother was reported to be on Focalin XR while pregnant. The baby spent time in the neonatal intensive care after birth and had breathing problems requiring administration of a surfactant, but "has been doing fine" since coming home. He is currently being weaned off breast milk and "no symptoms are noted." Upon follow-up, a second suspect medication, Symbyax, was reported. But, no further details regarding Symbyax were provided by the reporter.

Reviewer's Comments: The case contains insufficient information to make an assessment. The time period during which the mother took Symbyax was unclear.

Unlabeled

Overdose (n=1)

A 15 year old female took 28 capsules of her boyfriend's Symbyax 6mg/25mg. It was reported the patient "became very psychotic, delusional, had 'burns' around her eyes, was very combative, and was taken to the hospital." The patient also developed hypotension. Treatment information and the outcome were not provided. The patient was admitted to the psychiatric ward. No additional information was provided at the time of reporting.

Medication Error (n=1)

A 13 year old male was taking atomoxetine 80mg daily. His dose of atomoxetine was decreased to 60mg. When he went to the pharmacy to pick up the prescription for the new dose, he mistakenly received Symbyax 6mg/25mg instead. The patient took the incorrect medication for three weeks and the mistake was noticed when the next refill was picked up and it looked different from what he had been taking. While taking the Symbyax the patient was "subdued." The Symbyax was discontinued and the patient received the correct medication. No additional information was reported.

Reviewer's Comments: Somnolence is labeled as an adverse event occurring in at least 2% of patients during a pediatric clinical trial for Symbyax in bipolar depression.

4 DISCUSSION

This review focused on all pediatric adverse events spontaneously reported with Symbyax®. DPV reviewed 19 pediatric cases (reported from January 1, 2004 to June 30, 2015). Among these, there was one fatal report and 18 non-fatal reports, including one case of transplacental exposure. Due to the limited number of case reports for each event, it was difficult to draw any conclusions. In addition, drug utilization showed a decrease in the use of combination olanzapine and fluoxetine among adult and pediatric patients. The possible causes for the decline in use are not clear at this time.

5 CONCLUSION

The vast majority of adverse events reported to FDA were labeled events that are well characterized in the labeling for olanzapine, fluoxetine, and combination of olanzapine and fluoxetine. There is no evidence from these data that there are new or unexpected pediatric safety concerns with this drug at this time.

6 RECOMMENDATIONS

Based on the data summarized in this review, DPV recommends no labeling changes at this time and a return to routine pharmacovigilance monitoring. DPV will continue to monitor adverse events associated with the use of Symbyax.

7 REFERENCES

1. Symbyax® [package insert]. Indianapolis, IN. Eli Lilly and Company. December 2014.

2. Symbyax. New Pediatric Labeling Information Database – Detail. http://www.accessdata.fda.gov/scripts/sda/sdDetailNavigation.cfm?sd=labelingdatabase&id=14CE032259A21B7DE053564DA8C071F2&rownum=1 Accessed 11/17/15.

8 APPENDICES

8.1 APPENDIX A. DRUG UTILIZATION DATABASE DESCRIPTIONS/LIMITATIONS

IMS Health, IMS 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.

The findings from this review should be interpreted in the context of the known limitations of the databases used. Based on the IMS Health, IMS National Sales Perspectives™ database, we estimated that about 81% of all combination olanzapine and fluoxetine bottles were distributed to outpatient retail pharmacy 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.

IMS, Vector One® : Total Patient Tracker (TPT)

The IMS, Vector One® : Total Patient Tracker 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 1.9 billion prescription claims per year, representing over 158 million unique patients. Since 2002 Vector One® has captured information on over 15 billion prescriptions representing over 356 million unique patients.

IMS, National Prescription Audit

The National Prescription Audit (NPATM) measures the “retail outflow” of prescriptions, or the rate at which drugs move out of retail pharmacies, mail service houses, or long-term care facilities into the hands of consumers via formal prescriptions in the U.S. The NPA audit measures what is dispensed by the pharmacist. Data for the NPA audit is a national level estimate of the drug activity from retail pharmacies. NPA™ receives over 2.7 billion prescription claims per year, captured from a sample of the universe of approximately 57,000 pharmacies throughout the U.S. The pharmacies in the database account for most retail pharmacies and represent nearly 86% of retail prescriptions dispensed nationwide. The type of

pharmacies in the sample are a mix of independent, retail, chain, mass merchandisers, and food stores with pharmacies, and include prescriptions from cash, Medicaid, commercial third-party and Medicare Part-D prescriptions.

Encuity Research, LLC., TreatmentAnswers™

Encuity Research, 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.

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

FDA Adverse Event Reporting System (FAERS)

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

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

8.3 APPENDIX C. FAERS CASE NUMBERS, FAERS VERSION NUMBERS AND MANUFACTURER CONTROL NUMBERS FOR THE PEDIATRIC CASE SERIES WITH DRUG (N=19)

FAERS Case #	Version #	Manufacturer Control #
10612928	3	US-ELI_LILLY_AND_COMPANY-US201411010114
5961330	2	PHEH2006US00673
4211459	1	USA040360730
6994961	2	SPV1-2009-00850
5877163	1	USA050597126
5764125	2	USA040978710
4211458	1	USA040362367
7027153	1	N/A
5764124	1	USA040259392
6861635	1	US-JNJFOC-20081204676
6883177	1	US-BRISTOL-MYERS SQUIBB COMPANY-13953914
4211979	1	USA040670710
5742319	1	USA040979040
7323861	1	US-ELI_LILLY_AND_COMPANY-US201003002138
4217867	1	USA040977121
5693230	2	USA040772576
5664215	3	USA040361534
6070684	1	US200601005326
6800760	1	N/A

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/s/

COURTNEY M SUGGS
02/18/2016

TRAVIS W READY
02/18/2016

RAJDEEP K GILL
02/18/2016
drug use data cleared by data vendors

GRACE CHAI
02/19/2016

IDA-LINA DIAK
02/19/2016

CINDY M KORTEPETER
02/19/2016

ROBERT L LEVIN
02/19/2016