Pediatric Focused Safety Review:

Symbyax (olanzapine and fluoxetine hydrochloride)

Pediatric Advisory Committee Meeting
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Mona Khurana, MD

Division of Pediatric and Maternal Health
Office of New Drugs

Center for Drug Evaluation and Research
Food and Drug Administration

Outline

- Background Information
- Relevant Safety Labeling
- Pediatric Studies
- Pediatric Labeling Changes
- Drug Use Trends
- Adverse Events
- Summary

Background Information: Symbyax (olanzapine and fluoxetine HCl)

- **Drug:** Symbyax (olanzapine and fluoxetine HCl)
- **Formulation:** 3 mg/25 mg, 6 mg/25 mg, 6 mg/50 mg, 12 mg/25 mg, 12 mg/50 mg capsules*
- **Indication**: Oral treatment of bipolar depression in adults and pediatric patients 10 years of age and older and for treatment-resistant depression (TRD) in adults
- **Drug Category:** Anti-depressant
- **Sponsor: Eli Lilly and Company**

HCl: hydrochloride
*mg olanzapine/mg equivalent fluoxetine HCl

Background Information: Symbyax (olanzapine and fluoxetine HCl)

- **Original market approval:** December 24, 2003
- **New dosage form approved:** April 9, 2007
  - PREA requirements
    - Deferred safety and efficacy study in patients 10 years to 17 years of age with bipolar depression
    - Partial waiver to study patients less than 10 years of age
- **PREA labeling changes:** July 26, 2013
  - Safety and effectiveness established in patients 10 to 17 years of age
  - PREA PMR fulfilled (initiator for this presentation)

Relevant Safety Labeling: Symbyax (olanzapine and fluoxetine HCl)

WARNINGS: SUICIDAL THOUGHTS AND BEHAVIORS; AND INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS

See full prescribing information for complete boxed warning.

- **Increased risk of suicidal thinking and behavior in children, adolescents, and young adults taking antidepressants. SYMBYAX is not approved for use in children less than 10 years of age (5.1, 8.4, 17.2).**
- **Monitor for worsening and emergence of suicidal thoughts and behaviors (5.1, 17.2).**
- **Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. SYMBYAX is not approved for the treatment of patients with dementia-related psychosis (5.2, 5.19, 17.3).**

Relevant Safety Labeling: Symbyax (olanzapine and fluoxetine HCl)

Section 4 Contraindications

4.1 Monoamine Oxidase Inhibitors

4.2 Other Contraindications

- **Pimozide**
- **Thioridazine**

Relevant Safety Labeling: Symbyax (olanzapine and fluoxetine HCl)

Section 5 Warnings and Precautions

5.1 Suicidal Thoughts and Behaviors in Children, Adolescents, and Young Adults
5.2 Increased Mortality in Elderly Patients with Dementia-Related Psychosis
5.3 Neuroleptic Malignant Syndrome (NMS)
5.4 Metabolic Changes
5.5 Serotonin Syndrome
5.6 Angle-Closure Glaucoma
5.7 Allergic Reactions and Rash
5.8 Activation of Mania/Hypomania
5.9 Tardive Dyskinesia
5.10 Orthostatic Hypotension
5.11 Leukopenia, Neutropenia, and Agranulocytosis

Relevant Safety Labeling: Symbyax (olanzapine and fluoxetine HCl)

Section 5 Warnings and Precautions

5.12 Dysphagia
5.13 Seizures
5.14 Abnormal Bleeding
5.15 Hyponatremia
5.16 Potential for Cognitive and Motor Impairment
5.17 Body Temperature Dysregulation
5.18 QT Prolongation
5.19 Use in Patients with Concomitant Illness
5.20 Hyperprolactinemia
5.21 Concomitant Use of Olanzapine and Fluoxetine Products
5.22 Long Elimination Half-Life of Fluoxetine
5.23 Discontinuation Adverse Reactions

Pediatric Studies: Symbyax (olanzapine and fluoxetine HCl)

- 8-week, multi-center, randomized, double-blind, placebo-controlled, forced dose-titration trial (ages 10 to 17 years, n=255)
  - 51% male, mean age 14.7 years
  - Symbyax treatment resulted in greater mean reduction in the Children's Depression Rating Scale-Revised (CDRS-R) total score at Week 8 compared to placebo (28.4 points vs. 23.4 points; p=0.003)
  - Overall safety profile similar to that seen in adults

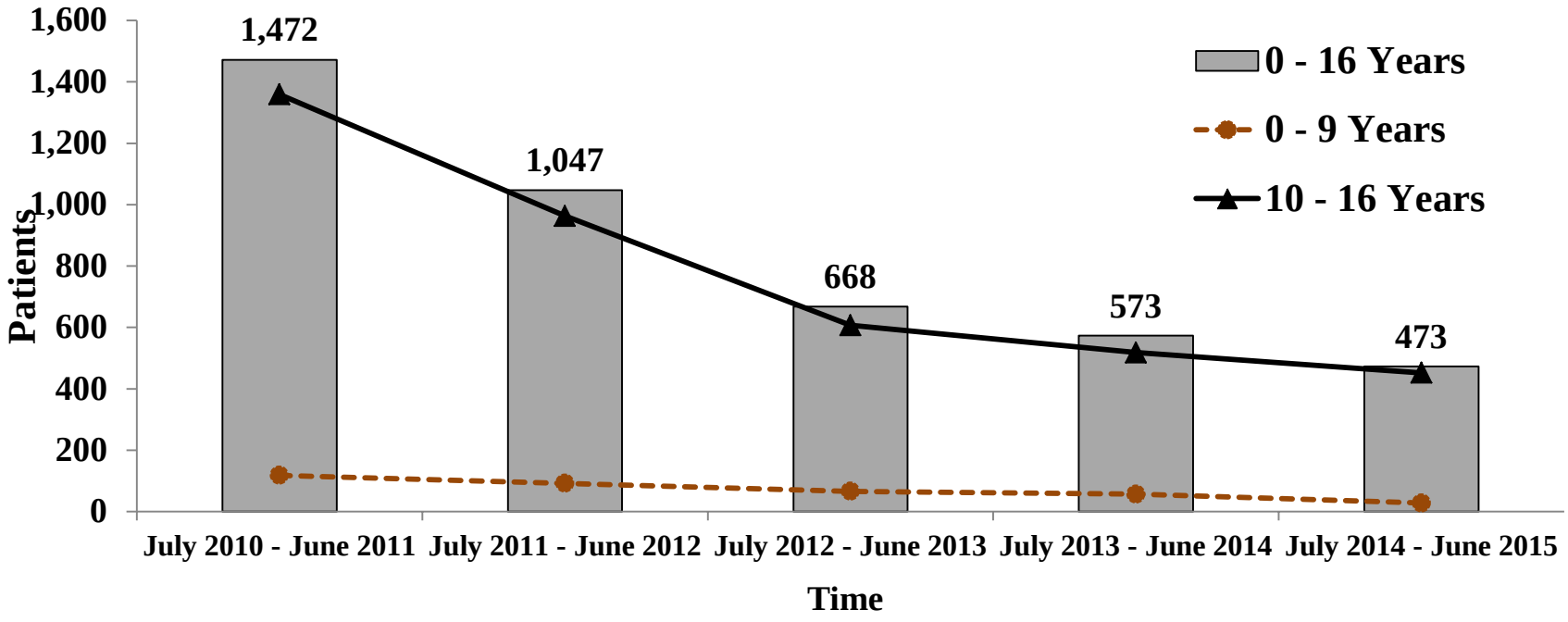
Pediatric Labeling Changes: Symbyax (olanzapine and fluoxetine HCl)

- **8.4 Pediatric Use**
  - Safety and efficacy established in patients 10 years to 17 years of age
  - Recommended starting dose of 3/25 mg* daily
  - Safety and efficacy for bipolar I depression have not been established in patients below 10 years of age
  - Safety and efficacy for TRD have not been established in patients below 18 years of age
  - Must balance potential risks with clinical need *[see Boxed Warning and Warnings and Precautions (5.1)].*

* mg olanzapine/mg equivalent fluoxetine HCl

Pediatric Drug Utilization: Symbyax (olanzapine and fluoxetine HCl)

National estimates of pediatric patients (0-9, 10-16 years), who received dispensed prescriptions for combination olanzapine/fluoxetine products from U.S. outpatient retail pharmacies July 2010-June 2015, annually



Source: IMS Health, Vector One®: Total Patient Tracker. Data extracted January 2016

Top Prescribing Specialty & Diagnoses: Symbyax (olanzapine and fluoxetine HCl)

July 2010- June 2015

Top Prescribing Specialties[1]

Psychiatry (33%)
Family practice (23%)
Pediatric specialists (less than 1%)

Diagnosis Data[2]

According to an office-based physician survey database, there were no diagnosis codes associated with the use of combination olanzapine/fluoxetine in pediatric patients 0-16 years of age

[1]IMS Health, Health National Prescription Audit (NPA). July 2010 – June 2015. Extracted January 2016
[2]Encuity Research, LLC.,TreatmentAnswers with Pain™ July 2010 – June2015. Extracted January 2016.

Adverse Events: Symbyax (olanzapine and fluoxetine HCl)

(January 1, 2004* - June 30, 2015)

	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*

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

Adverse Events:
Symbyax (olanzapine and fluoxetine HCl)

Selection of Pediatric FAERS Cases

Total Pediatric Reports Reviewed (n=22)
Pediatric reports with fatal outcome (n=4)

Excluded Reports (n=3)*
3 duplicate fatal cases

Pediatric Case Series (n=19)
1 fatal report
18 non-fatal reports
- 1 transplacental exposure

*Reviewed prior to exclusion

Labeled Adverse Events: Symbyax (olanzapine and fluoxetine HCl)

5 Warnings and Precautions

5.1 Suicidal Thoughts and Behaviors in Children, Adolescents and Young Adults (n=3*)

5.4 Metabolic Changes (n=1)

5.7 Allergic Reactions and Rash (n=1)

5.8 Activation of Mania/Hypomania (n=2)

5.9 Tardive Dyskinesia (n=1)

5.10 Orthostatic Hypotension (n=2)

5.13 Seizures (n=3)

6 Adverse Reaction

Dystonia (n=1) Edema (n=1) Somnolence (n=1)

8 Use in Special Populations

8.1 Pregnancy (n=1)

10 Overdosage (n=1**)

* Includes single fatal case

** Intentional overdose by an adolescent for whom the drug was not prescribed

Fatal Adverse Event: Symbyax (olanzapine and fluoxetine HCl)

- Completed suicide in 7 year old male with impulse control disorder, aggression, and self-injurious behavior with worsening behavior on lisdexamfetamine dimesylate and escitalopram treatment that continued to deteriorate after starting Symbyax

Transplacental Exposure: Symbyax (olanzapine and fluoxetine HCl)

- Maternal fluoxetine and Symbyax 6 mg/50 mg* use for unspecified duration
- Full term male requiring intubation at birth for cyanosis and respiratory distress
- Diagnosed with transposition of great vessels
  - Insufficient characterization of exposure to assess causality

*mg olanzapine/mg equivalent fluoxetine HCl

Summary:
Symbyax (olanzapine and fluoxetine HCl)

- This concludes the pediatric focused safety review
- No new pediatric safety signals were identified
- FDA recommends continuing ongoing surveillance
- Does the Committee concur?

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