Pediatric Focused Safety Review
Lexapro
Pediatric Advisory Committee Meeting
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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:** Escitalopram (Lexapro)
- **Original FDA approval date:** August 14, 2002
- **Therapeutic Category**: Selective Serotonin Reuptake Inhibitor (SSRI)
- **Indications**
  - **Acute and Maintenance Treatment of Major Depressive Disorder (MDD)** in adults and **adolescents 12 - 17 years**
  - Acute treatment of Generalized Anxiety Disorder (GAD) in adults
- **Dose:** *Varies by indication*
  - MDD: initial dose 10 mg/day; recommended dose 10 mg/day; maximum dose 20 mg/day (for adults and adolescents 12-17 years)
  - GAD: initial dose 10 mg/day; recommended dose 10 mg/day; no maximum dose labeled (for adults only)
- **Formulations:**
  - Oral tablets: 5 mg, 10 mg, and 20 mg
  - Oral solution: 1 mg/mL
- **Sponsor:** Forest Labs

Background Information

- **Best Pharmaceuticals for Children Act (BPCA) labeling change:**
  - Major Depressive Disorder: March 19, 2009
    - Section 1.1, Section 2.1 (for ages 12 to 17 years)

- **PAC Meeting May 2011 - recommendations:**
  - OSE Review: no labeling changes were recommended, continue routine pharmacovigilance; the committee agreed
  - The committee highlighted the difficulty of conducting studies in various subgroups of the pediatric population

- **Pediatric Research Equity Act (PREA) labeling change:***
  - Major Depressive Disorder: October 31, 2014
    - Section 8.4

*Initiated Current Review

Major Depressive Disorder in Children

- A 26-week, open-label, flexible-dose 10-20 mg/day, multicenter, long-term study **to evaluate safety and tolerability** (7 to 11 years)
  - N=118 (safety population consisting of all patients who took at least one dose of escitalopram)
- No formal statistical efficacy analysis was conducted
- Safety and effectiveness have not been established in patients younger than 12 years old with MDD

*This study initiated the current review and presentation.

Labeling: Warnings and Precautions

Section 5 Warnings and Precautions

- 5.1 Clinical Worsening and Suicide Risk **(includes children and adolescents)**
- 5.2 Serotonin Syndrome
- 5.3 Discontinuation of Treatment with Lexapro
- 5.4 Seizures
- 5.5 Activation of Mania/Hypomania
- 5.6 Hyponatremia
- 5.7 Abnormal Bleeding
- 5.8 Interference with Cognitive and Motor Performance
- 5.9 Angle Closure Glaucoma
- 5.10 Use in Patients with Concomitant Illness

Labeling: Adverse Reactions - Pediatric (continued)

Section 6 Adverse Reactions

6.1 Clinical Trials Experience

Incidence of Adverse Reactions in Placebo-Controlled Clinical Trials (Major Depressive Disorder; Pediatrics; 6 – 17 years)

- The overall profile of adverse reactions in pediatric patients was generally similar to that observed in adult studies.
- The following adverse reactions were reported at an incidence of at least 2% for Lexapro and greater than placebo: back pain, urinary tract infection, vomiting, and nasal congestion.

Labeling: Pediatric Clinical Studies – Efficacy

Section 14 Clinical Studies (Pediatrics)

- 14.1 Major Depressive Disorder
  - The efficacy of escitalopram as an acute treatment for major depressive disorder in adolescent patients was established in an 8-week, flexible-dose, placebo-controlled study that compared Lexapro 10-20 mg/day to placebo in outpatients 12 to 17 years of age who met DSM-IV criteria for MDD.
    - The primary outcome was change from baseline to endpoint in the Children's Depression Rating Scale - Revised (CDRS-R).
    - Lexapro showed statistically significant greater mean improvement compared to placebo on the CDRS-R.
  - The efficacy of Lexapro in the acute treatment of major depressive disorder in adolescents was established, in part, on the basis of extrapolation from the 8-week, flexible-dose, placebo-controlled study with racemic citalopram 20-40 mg/day.

DSM-IV=Diagnostic and Statistical Manual of Mental Disorders, 4th Edition

Nationally estimated number of patients* who received prescriptions for escitalopram from U.S. outpatient retail pharmacies, stratified by patient age (0-16 years, 17 years and older)**, April 2011 through March 2017, annually

Age Group	April 2011-March 2012		April 2012-March 2013		April 2013-March 2014	
	Patients	Share (%)	Patients	Share (%)	Patients	Share (%)
Grand Total	4,328,282	*100%*	4,359,109	*100%*	5,036,199	*100%*
0 - 16 years	148,512	*3.4%*	153,529	*3.5%*	187,244	*3.7%*
17 years and older	4,190,901	*96.8%*	4,217,615	*96.8%*	4,863,216	*96.6%*
Unknown Age	85	*0.0%*	72	*0.0%*	9,904	*0.2%*

Age Group	April 2014-March 2015		April 2015-March 2016		April 2016-March 2017	
	Patients	Share (%)	Patients	Share (%)	Patients	Share (%)
Grand Total	5,886,074	*100%*	6,538,033	*100%*	7,229,459	*100%*
0 - 16 years	224,370	*3.8%*	273,624	*4.2%*	288,446	*4.0%*
17 years and older	5,645,656	*95.9%*	6,214,649	*95.1%*	6,888,170	*95.3%*
Unknown Age	65,853	*1.1%*	120,202	*1.8%*	90,154	*1.2%*

Source: IMS Health, Total Patient Tracker™. April 2011 – March 2017.
Extracted June 2017. File: TPT 2017-678 escitalopram BPCA 6-22-2017.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

FDA Adverse Event Reporting System (FAERS)
Pediatric Case Selection
October 14, 2010 to March 31, 2017

Total pediatric reports with a serious outcome reviewed (n=645)
Pediatric reports with the outcome of death (n=74)

Excluded Cases* (n=633)
(Including 74 deaths†)

- Transplacental exposure or breastfeeding (n=463)‡
- Foreign (n=72)§
- Labeled events (n=55)
- Duplicates (n=28)
- Multidrug Overdose (n=10)
- Insufficient Information (n=3)
- Adult (n=1)
- Not taking escitalopram (n=1)

Pediatric Case Series
(n=12)
Including 0 deaths

* DPV reviewed these cases, but they were excluded from the case series for the reasons listed.
† The deaths included reports of: 1) transplacental exposure, 2) completed suicide, or 3) multidrug overdose.
‡ There is a pregnancy registry for antidepressants run by Massachusetts General Hospital
§ No new signals were identified from the foreign cases.

Non-Fatal Serious Unlabeled Pediatric Adverse Events (n= 12)

- Lack of efficacy: Product substitution issue, product quality issue (n=5)
- Homicidal ideation (n=4)
- One event each for the following:
  - Chronic Fatigue Syndrome/ Postural Orthostatic Tachycardia Syndrome
  - Non-alcoholic steatohepatitis
  - Neuromuscular instability

There is no discernible pattern for the previously unlabeled events.

Lack of efficacy: Product substitution issue, product quality issue (continued)

- 15-year-old female refilled escitalopram with a "new generic version" and developed "anxiety and behavior dysregulation similar to what she exhibited prior to treatment." Her "symptoms improved significantly" with brand Lexapro.
  - This was the only case that provided any tablet identifying information
- 16-year-old female with history of bipolar disorder switched from brand to generic due to insurance. She "went manic within 2 days" and had "violent outbursts mood swings and insomnia." She switched back to brand and "felt better within 3 days."

Homicidal ideation

- Two cases: a 16-year-old male and a 17-year-old female. The cases lacked clinical information
  - Escitalopram was being used off-label for obsessive compulsive disorder in the first case. The reason for use was not reported in the second case
- Two cases: Both 15-year-old females. The patients had complicated psychiatric and histories (post-traumatic stress disorder, oppositional defiant disorder, etc.). Both had reported noncompliance with prescribed medication regimens and medical appointments

Summary: Pediatric Safety Review

- The escitalopram 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?

Summary: Pediatric Safety Review

- FDA recommends posting pediatric reviews without new risks or potential safety signals on the web in the future.
- What are the Committee's thoughts about web posting future reviews without new risks or potential safety signals, such as this current review?


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