

**Pediatric Focused Safety Review
Lexapro
Pediatric Advisory Committee
Meeting
September 20, 2018**

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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.

Major Depressive Disorder in Children

Safety

- Primary Safety Endpoints: AE recording, physical examinations, clinical laboratory evaluations, electrocardiograms, vital signs, and Columbia–Suicide Severity Rating Scale
- Overall escitalopram well tolerated with no new patterns of AEs and no new safety concerns related to long-term treatment in pediatric patients 7 - 11 years old
- Safety Results:
 - No deaths were reported
 - Two patients (1.7%) reported SAEs: mania (1), suicidal ideation (1)
 - Nine patients (7.6%) had AEs that led to discontinuation. The most frequent cause of discontinuation was psychiatric disorders (7 patients)
 - The most commonly reported TEAEs were gastrointestinal (31% of patients) and nervous system disorders (29% of patients)
 - Most were mild in severity

AEs = Adverse Events; SAEs = Serious Adverse Events;
TEAEs = Treatment-Emergent Adverse Events

Labeling: Boxed Warning, Dosage and Administration



Boxed Warning

Increased risk of suicidal thinking and behavior in children, adolescents, and young adults taking antidepressants for major depressive disorder (MDD) and other psychiatric disorders. Lexapro is not approved for use in pediatric patients less than 12 years of age (5.1).

Section 2 Dosage and Administration

2.1 Major Depressive Disorder

- Adolescents 12 – 17 years
 - Initial: 10 mg once daily
 - Recommended: 10 mg once daily
 - Maximum: 20 mg once daily



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



Section 6 Adverse Reactions

6.1 Clinical Trials Experience

Clinical Trial Data Sources (Pediatrics; 6 – 17 years old)

Adverse events were collected in 576 pediatric patients (286 Lexapro, 290 placebo) with major depressive disorder in double-blind placebo-controlled studies. Safety and effectiveness of Lexapro in pediatric patients less than 12 years of age has not been established.

Adverse Events Associated with Discontinuation of Treatment (Major Depressive Disorder; Pediatrics; 6 – 17 years old)

- Adverse events were associated with discontinuation of 3.5% of 286 patients receiving Lexapro and 1% of 290 patients receiving placebo.
- Insomnia was the most common adverse event associated with discontinuation (1% Lexapro, 0% placebo)

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: Use in Specific Populations, Clinical Pharmacology



Section 8 Use in Specific Populations

- 8.4 Pediatric Use
 - The safety and effectiveness of Lexapro have not been established in pediatric (younger than 12 years of age) patients with major depressive disorder. In a 24-week, open-label safety study in 118 children (aged 7 to 11 years) who had major depressive disorder, the safety findings were consistent with the known safety and tolerability profile for Lexapro.
 - Decreased appetite and weight loss have been observed in association with the use of SSRIs.
 - Regular monitoring of weight and growth should be performed in children and adolescents treated with an SSRI such as Lexapro.

Section 12 Clinical Pharmacology (Pediatrics)

- 12.3 Pharmacokinetics
 - In a single dose study of 10 mg escitalopram, AUC of escitalopram decreased by 19%, and C_{max} increased by 26% in healthy adolescent subjects (12 to 17 years of age) compared to adults. Following multiple dosing of 40 mg/day citalopram, escitalopram elimination half-life, steady-state C_{max} and AUC were similar in patients with MDD (12 to 17 years of age) compared to adult patients. No adjustment of dosage is needed in adolescent patients.

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.

Labeling: Pediatric Clinical Studies – Efficacy (continued)



Section 14 Clinical Studies (Pediatrics)

- 14.1 Major Depressive Disorder
 - Two additional flexible-dose, placebo-controlled MDD studies did not demonstrate efficacy.
 - Although maintenance efficacy in adolescent patients has not been systematically evaluated, maintenance efficacy can be extrapolated from adult data along with comparisons of escitalopram pharmacokinetic parameters in adults and adolescent patients.



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.



Characteristics of Pediatric Case Series with Escitalopram (n=12)

- **Gender**
 - Male (n=3)
 - Female (n=9)
- **Ages**
 - 6 to < 12 years (n=3)
 - 12 to < 17 years (n=9)
- **Serious Outcomes**
 - Hospitalized (n=1)
 - Disability (n=1)
 - Other serious (n=10)
 - There were no deaths in our case series

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

- 11-year-old male previously well maintained on “Lexapro” and “Abilify” for MDD and GAD. “Depressive symptoms” returned within 3 days of receiving a new “Lexapro” prescription. “These worsened over the next 2 weeks up to and including suicidal ideation.” Lot numbers were requested but unavailable from pharmacy. Reporter stated pharmacy said they have had no other complaints.
- 11-year-old female “becomes depressed with...anything but brand”
- 14-year-old female experienced “increase in depression with generic also some nausea”

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?



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