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

Pediatric Postmarketing Pharmacovigilance and Drug Utilization Review

Date:	November 22, 2017
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Product Name:	Lexapro (escitalopram)
Pediatric Labeling Approval Date:	October 31, 2014
Application Type/Numbers:	NDA 21323/044 and 21365/032
Applicant/Sponsor:	Forest Labs
OSE RCM #:	2017-678

TABLE OF CONTENTS

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 with a serious outcome and drug utilization data for Lexapro (escitalopram) in pediatric patients.

Escitalopram was first approved in 2002 and is indicated for the acute and maintenance treatment of major depressive disorder in adults and in adolescents 12 to 17 years of age. Escitalopram is also approved for the acute treatment of generalized anxiety disorder in adults.

This review serves as an update to a previous Division of Pharmacovigilance (DPV) pediatric review in preparation for the May 2011 Pediatric Advisory Committee meeting. DPV reviewed all domestic, unlabeled, serious pediatric cases reported with the use of escitalopram in the FDA Adverse Event Reporting System (FAERS) database received from October 14, 2010 to March 31, 2017. There were no fatal cases and a total of 12 non-fatal cases in the case series. There were no new safety signals identified, no increased severity or frequency of any labeled adverse event.

Drug utilization patterns were assessed to capture pediatric use of escitalopram and to provide context for the adverse event reports submitted to the FAERS database. Pediatric patients 0-16 years accounted for approximately 3- 4% of the total patients annually and doubled in terms of patient utilization from approximately 148,500 patients to 290,000 patients during the study period from April 2011 through March 2017.

Pediatric utilization of escitalopram approximately doubled during the examined six-year period; however, no new patterns of FAERS cases or trends suggestive of new or unexpected adverse events attributable to the use of escitalopram were identified.

DPV recommends no labeling changes at this time, and will continue to monitor adverse events associated with the use of escitalopram.

1 INTRODUCTION

1.1 PEDIATRIC REGULATORY HISTORY

Lexapro® (escitalopram) was approved on August 14, 2002. It is a selective serotonin reuptake inhibitor (SSRI). It is indicated for the acute and maintenance treatment of major depressive disorder (MDD) and the acute treatment of generalized anxiety disorder (GAD). The only approved pediatric indication is for MDD in adolescents 12 to 17 years old. Escitalopram is available as delayed release capsules in 5mg, 10mg, and 20mg. It is also available as an oral solution 1mg/mL.[1] The initial, target, and maximum doses are listed in **Table 1.1** along with the dosing schedule for each indication and age group.

Table 1.1 Initial, recommended, and maximum doses of escitalopram by indication and age

Indication	Dose
MDD	
Adolescents	Initial: 10mg once daily Recommended: 10mg once daily Maximum: 20mg once daily
Adults	Initial: 10mg once daily Recommended: 10mg once daily Maximum: 20mg once daily
GAD	
Adults	Initial: 10mg once daily Recommended: 10mg once daily

On March 19, 2009, escitalopram was approved for the treatment of MDD in adolescents 12 to 17 years old. Safety and effectiveness have been established in adolescents 12 to 17 years old for the treatment of MDD. Maintenance efficacy is supported from extrapolation of data from adult studies along with comparisons with racemic citalopram pharmacokinetic parameters in adults and adolescents. Safety and effectiveness have not been established in pediatric patients less than 12 years old with MDD. Safety and effectiveness have not been established in pediatric patients less than 18 years of age with GAD. Adverse events were generally similar to those observed in adults.

The approval letter dated March 19, 2009, contained a postmarketing commitment to conduct a long-term safety study: an open-label, 24-week safety study with escitalopram in children 7 to11 years old with MDD. On March 12, 2014, the Sponsor submitted the final study report. The study enrolled 118 children 7 to 11 years old. Efficacy was not established in this study and no new safety concerns were identified.

1.2 HIGHLIGHTS OF LABELED SAFETY ISSUES

WARNING: Suicidality and Antidepressant Drugs

See full prescribing information for complete 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).

----------**CONTRAINDICATIONS**----------

- Serotonin Syndrome and MAOIs: Do not use MAOIs intended to treat psychiatric disorders with Lexapro or within 14 days of stopping treatment with Lexapro. Do not use Lexapro within 14 days of stopping an MAOI intended to treat psychiatric disorders. In addition, do not start Lexapro in a patient who is being treated with linezolid or intravenous methylene blue (4.1).
- Pimozide: Do not use concomitantly (4.2).
- Known hypersensitivity to escitalopram or citalopram or any of the inactive ingredients (4.3).

----------WARNINGS AND PRECAUTIONS----------

- Clinical Worsening/Suicide Risk: Monitor for clinical worsening, suicidality and unusual change in behavior, especially, during the initial few months of therapy or at times of dose changes (5.1).
- Serotonin Syndrome: Serotonin syndrome has been reported with SSRIs and SNRIs, including Lexapro, both when taken alone, but especially when co-administered with other serotonergic agents (including triptans, tricyclic antidepressants, fentanyl, lithium, tramadol, tryptophan, buspirone, amphetamines, and St. John's Wort). If such symptoms occur, discontinue Lexapro and initiate supportive treatment. If concomitant use of Lexapro 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 (5.2).
- Discontinuation of Treatment with Lexapro: A gradual reduction in dose rather than abrupt cessation is recommended whenever possible (5.3).
- Seizures: Prescribe with care in patients with a history of seizure (5.4). □Activation of Mania/Hypomania: Use cautiously in patients with a history of mania (5.5). □Hyponatremia: Can occur in association with SIADH (5.6).
- Abnormal Bleeding: Use caution in concomitant use with NSAIDs, aspirin, warfarin or other drugs that affect coagulation (5.7).
- Interference with Cognitive and Motor Performance: Use caution when operating machinery (5.8).
- Angle Closure Glaucoma: Angle closure glaucoma has occurred in patients with untreated anatomically narrow angles treated with antidepressants. (5.9)
- Use in Patients with Concomitant Illness: Use caution in patients with diseases or conditions that produce altered metabolism or hemodynamic responses (5.10).

----------**ADVERSE REACTIONS**----------

Most commonly observed adverse reactions (incidence ≥ 5% and at least twice the incidence of placebo patients) are: insomnia, ejaculation disorder (primarily ejaculatory delay), nausea, sweating increased, fatigue and somnolence, decreased libido, and anorgasmia (6.1).

----------DRUG INTERACTIONS----------

Concomitant use with SSRIs, SNRIs or Tryptophan is not recommended (7.2). Use caution when concomitant use with drugs that affect Hemostasis (NSAIDs, Aspirin, Warfarin) (7.6).

2 DRUG UTILIZATION DATA

2.1 METHODS AND MATERIALS

Proprietary drug utilization databases were used to conduct these analyses. Detailed descriptions and limitation of the databases are included in Appendix A.

2.1.1 *Data Sources Used*

Sales Distribution Data

The QuintilesIMS, National Sales Perspectives™ database was used to obtain the nationally estimated number of units (packages) sold for escitalopram from manufacturers to all U.S. channels of distribution for 2016. The sales distribution data represent the amount of product sold from manufacturers to pharmacies and other setting of care; it does not reflect what is being sold to or administered to patients directly.

Outpatient Retail Settings

The IMS Health Total Patient Tracker (TPT) database was used to provide the nationally estimated number of patients who received a dispensed prescription for escitalopram from U.S. outpatient retail pharmacy settings stratified by patient age (0-16 years and 17 years and older) from April 2011 through March 2017, annually.

The inVentiv Health, LLC., Treatment Answers™ database, an office-based physician survey database, was used to determine the top diagnoses associated with the use[1] of escitalopram, stratified by patient age (0-16 years and 17 years and older), 2016.

2.2 RESULTS

2.2.1 Determining Settings of Care

Sales data for escitalopram by the number of packages sold from manufacturers to all U.S. settings of distribution indicated that approximately 79% of sales were to outpatient retail

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

pharmacies, 11% to non-retail settings and 10% to mail-order/specialty pharmacies during 2016. Accordingly, only U.S. outpatient retail pharmacy utilization patterns were examined for escitalopram. Data from mail-order/specialty pharmacies and non-retail settings, such as clinics and hospitals, were not included in this review.

2.2.2 Patient Data

Table 1 shows the nationally estimated number of patients who received dispensed prescriptions for escitalopram, from U.S. outpatient retail pharmacies, stratified by patient age from April 2011 through March 2017, annually.

Overall, the number of patients who received a dispensed prescription for escitalopram gradually increased from approximately 4.3 million in the 12-month period ending March 2012 to 7.2 million in the 12-month period ending March 2017. Pediatric patients 0-16 years accounted for approximately 3- 4% of the total patients annually over the examined time period and nearly doubled from approximately 148,500 patients to 290,000 pediatric patients during the study period.

Table 1 **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

2.2.3 Diagnosis Data

Table 2 shows the top diagnoses associated with the use of escitalopram according to U.S. office-based physician survey database, stratified by patient age, for 2016. Approximately 2% of escitalopram mentions were for patients 0-16 years old. Major depressive disorder (ICD-10 Code F329) and generalized anxiety disorder (ICD 10 Code F411) were recorded as top

diagnoses for both the 0-16 years and 17 years and older age groups. Approximately 95% of total oral escitalopram mentions were for patients 17 years or older.

Caution is advised in interpreting projected annual mentions below 100,000 as the sample size is very small with correspondingly large confidence intervals.

Table 2 Top Diagnoses Associated with the Use of Escitalopram According to U.S. Office-Based Physician Surveys, Stratified by Patient Age, 2016.

	2016 Uses (thousands)	2016 Share(%) Uses	95% Confidence Interval (thousands)
Total Market	**11,386**	***100%***	**10,792-11,981**
0-16 years	**223**	***2.0%***	**140-306**
F329 Major depressive disorder, single episode, unspecified	**82**	***37.0%***	**32-133**
F411 Generalized anxiety disorder	**40**	***17.8%***	**5-75**
F331 Major depressive disorder, recurrent, moderate	**28**	***12.7%***	**<0.5-58**
F939 Childhood emotional disorder, unspecified	**21**	***9.5%***	**<0.5-47**
F419 Anxiety disorder, unspecified	**11**	***5.1%***	**<0.5-30**
All Others*	**40**	***18.0%***	**5-75**
17 years and older	**10,817**	***95.0%***	**10,237-11,396**
F329 Major depressive disorder, single episode, unspecified	**3,331**	***30.8%***	**3,009-3,652**
F411 Generalized anxiety disorder	**1,474**	***13.6%***	**1,261-1,688**
F419 Anxiety disorder, unspecified	**991**	***9.2%***	**815-1,166**
F320 Major depressive disorder, single episode, mild	**539**	***5.0%***	**410-669**
F321 Major depressive disorder, single episode, moderate	**534**	***4.9%***	**405-663**
All Others*	**3,947**	***36.5%***	**3,597-4,297**
Unspecified Age**	**347**	***3.1%***	**243-451**

* The *All others* category is an aggregate of all other ICD-10 codes per patient age group.
** Unspecified Age represents drug use mentions that were not specified in terms of patient age.
Source: inVentiv Health Research and Insights, TreatmentAnswers ™ with Pain Panel, January 2016 to December 2016. Extracted June 2017.
Source File: PDDA 2017-678_escitalopram_BPCA_6-26-2017.xlsx
inVentiv Health Research & Insights LLC., recommends caution interpreting projected annual occurrences or mentions below 100,000 as the sample size is very small with correspondingly large confidence intervals.

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.

Table 3.1.1 FAERS Search Strategy	
Date of Search	May 1, 2017
Time Period of Search	October 14, 2010* - March 31, 2017
Search Type	Quick Query
Product Name(s)	Lexapro
Search Parameters	All ages, all outcomes, worldwide

Table 3.1.1 FAERS Search Strategy

** Lexapro was previously presented to the PAC in May 2011. This review serves as an update to the December 2010 review.[2]*

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 October 14, 2010 to March 31, 2017 with Escitalopram

	All reports (U.S.)	Serious† (U.S.)	Death‡ (U.S.)
Adults (≥ 17 years)	7255(3934)	6380(2555)	999(699)
Pediatrics (0 to <17 years)	703(424)	645(371)	74(56)

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

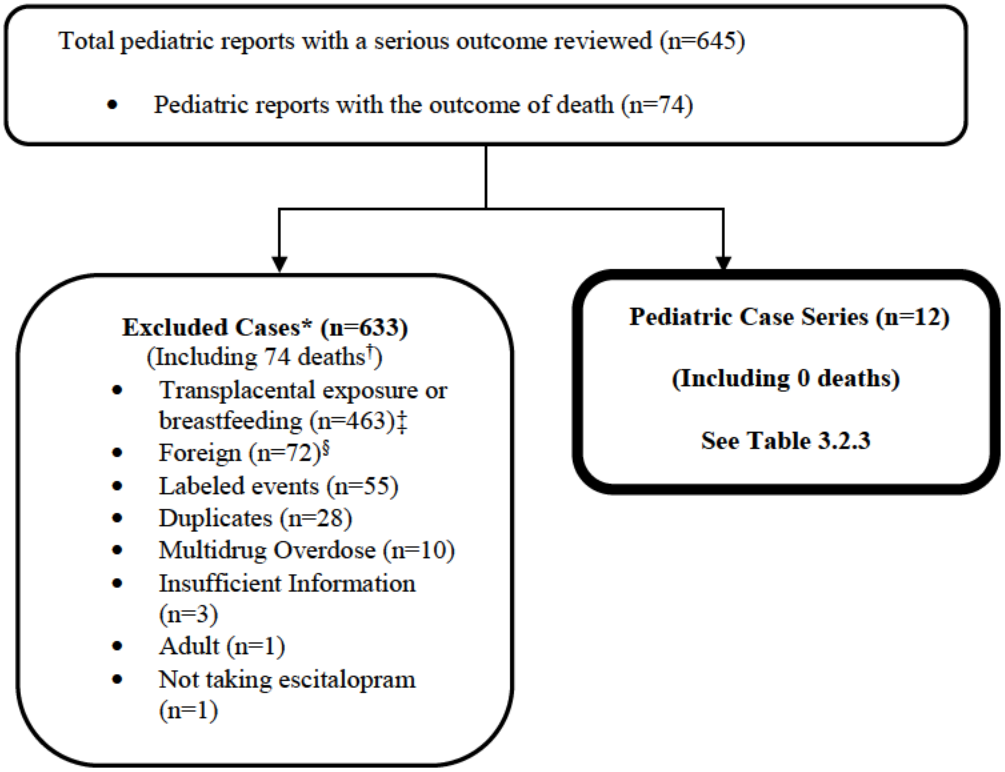
† For the purposes of this review, the following outcomes qualify as serious: ***death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, required intervention, and other serious important medical events.***

‡ Does not include null age death reports

3.2.2 Selection of Serious Pediatric Cases in FAERS

We identified 645 pediatric reports with a serious outcome (See Table 3.2.1). See **Figure 3.2.2** below for the specific selection of cases to be summarized in **Sections 3.3 and 3.4.**

Figure 3.2.2 Selection of serious pediatric cases with escitalopram



* DPV reviewed these cases, but they were excluded from the case series for the reasons listed above.
† The deaths included: 1) transplacental exposure, 2) completed suicide, or 3) multidrug overdose.
‡ There is a pregnancy registry for antidepressants run by Massachusetts General Hospital (https://womensmentalhealth.org/clinical-and-research-programs/pregnancyregistry/antidepressants/).
§No new signals were identified from the foreign cases.

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 FAERS Case Series with Escitalopram (N=12)

Age	6- <12 years	3
	12- < 17 years	9
Sex	Male	3
	Female	9
Country	United States	12
Reported Reason for Use	Depression	6
	Anxiety*	3
	Obsessive-Compulsive Disorder (OCD)	1
	Unknown	2

Table 3.2.3 Characteristics of Pediatric FAERS Case Series with Escitalopram (N=12)		
Serious Outcome†	Hospitalized	1
	Disability	1
	Other serious	10

***** Including social anxiety disorder

† For the purposes of this review, the following outcomes qualify as serious: death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, required intervention, and other serious important medical events.

3.3 SUMMARY OF FATAL PEDIATRIC ADVERSE EVENT CASES (N=0)

There were no fatal reports in our case series.

3.4 SUMMARY OF NON-FATAL PEDIATRIC SERIOUS ADVERSE EVENT CASES (N=12)

3.4.1 Product substitution issue, Product quality issue (n=5)

Four of the five product substitution or product quality issue cases reported a return or increase in symptoms "up to and including suicidal ideation" when switching brands of escitalopram. The patients were aged 11, 11, 14, and 15 years respectively. The action taken with escitalopram and outcome of events were not reported in these four cases. The fifth case reported a 16-year-old female with a history of bipolar disorder who "went manic within 2 days" and "had violent outbursts mood swings and insomnia" when she was switched to generic escitalopram. She "felt better within 3 days" after switching back to brand name escitalopram. Only one of the five cases reported identifying information for the escitalopram tablet; for the other 4 cases, it is not certain whether the patient was exposed to the innovator product or a particular generic product. Lot numbers were not reported in any of the cases.

Reviewer Comments: Escitalopram is labeled with a Warning & Precaution for "worsening of… depression and/or the emergence of suicidal ideation and behavior or unusual changes in behavior." The labeling states, "All patients being treated with antidepressants for any indication should be monitored appropriately and observed closely for clinical worsening, suicidality, and unusual changes in behavior, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases." Escitalopram also contains a warning for activation of mania/hypomania and states "Lexapro should be used cautiously in patients with a history of mania." Due to the lack of identifying information such as lot numbers or tablet imprints in all but one of the above cases, we are unable to determine the manufacturer(s) for the reported generic escitalopram used in these cases.

Generally for all innovator and generic drug products, it is extremely difficult in most cases to attribute lack of efficacy to a particular product, including a reported switch from an innovator product to a generic product. It is important to note that 'lack of effect' and related preferred terms are the most common group of adverse events reported for all cases submitted to FAERS. The preferred term 'lack of effect' alone accounts for approximately 6% to 7% of all adverse event terms reported in FAERS cases. Thus, this group of AE terms has a markedly high background rate, and is experienced or suspected by many patients. This largely reflects the heterogeneity and complexity of medical conditions, as well as the variability of clinical responses to therapeutic products among individuals. Many conditions are not fully amenable to treatments, and many are chronic, episodic, and progressive. Because of these and other factors, it is typically not possible to attribute reported lack of effectiveness to a generic product substitution or other product characteristics. On the other hand, there are rare cases in which there is a clearly identified product quality problem, lack of bioequivalence, therapeutic inequivalence between innovator and generic products, or other unique situations.

In our experience in investigating reported lack of effect with generic products, in close collaboration with OGD, the vast majority of such analyses indicate that there is no evidence of product quality problems, bioequivalence, or therapeutic inequivalence between a particular generic product and the relevant innovator product. We expect to find reports of lack of effect and related AEs for virtually any product, for the reasons discussed above.

For psychiatric conditions such as depression, other mood disorders, etc., these disorders are typically episodic, chronic, and often do not respond fully to even ideal courses of medication and other treatment. Thus, we expect that many patients with these conditions will experience relapse of symptoms, despite treatment, as part of the natural history of the disorders. There are certain types of products that theoretically might pose greater risk of problems with therapeutic inequivalence or bioinequivalence; typically these include products with a narrow therapeutic index, modified-release products, and products with other complex features. Escitalopram does not pose these particular risks; it is not a narrow therapeutic index drug, and it is an immediate-release formulation.

As noted above, there is no product-identifying information for 4 of the 5 products cited in the cases above. In addition, there were no other informative features of the case for interpreting the adverse events. Another general problem is that reporters often misattribute generic products, which greatly complicates an attempted analysis of reported therapeutic failure.[3,4]

3.4.2 Homicidal ideation (n=4)

Four cases of homicidal ideation were reported in our case series, including two cases that also reported concurrent suicidal ideation, which is a labeled event. The first case is a 16-year-old male who was started on escitalopram for OCD. The patient's mother reported that

"her son began to have suicidal thoughts and had thoughts of hurting his family" after switching from brand Lexapro to generic escitalopram. The manufacturer of the generic escitalopram was not reported. Generic escitalopram was discontinued and brand Lexapro was resumed. The suicidal thoughts and thoughts of hurting his family resolved. No additional clinical information was provided. The second case is a 17-year-old female who reported mania, had thoughts of suicide, and started "to plan the murders of [her] mother, brother, and classmates" an unknown time after starting escitalopram for an unspecified indication following a shooting at her school. Escitalopram was discontinued, and "almost immediately the thoughts went away." After discontinuing escitalopram, she started bupropion and also experienced mania and similar thoughts of suicide. Her past medical history and concomitant medications, if any, were not reported. No additional clinical information was provided.

The last two cases were both 15-year-old females with complicated psychiatric or medical histories. The first case had a history of posttraumatic stress disorder (PTSD), MDD, and oppositional defiant disorder, and was admitted to a psychiatric hospital for "worsening aggressive behavior, which included homicidal threats." She had a history of noncompliance with her medication regimen and psychiatric appointments. The outcome and the action taken with escitalopram were not reported. The second case "became fixed upon the idea she could kill someone and 'get away with it'" after switching to escitalopram from fluoxetine for an unspecified indication. She tried to suffocate a friend with her hands and was described as "having a 'glazed over look in her eyes'." Escitalopram was discontinued, and the symptoms did not improve. She was started on antipsychotics; however, her mother "remained convinced" her problems were due to "hormonal problems." Oral contraceptives were started and the patient's emotional and behavioral problems stabilized. She self-discontinued her antipsychotics and remained free of neuropsychiatric symptoms for 17 months following her initial visit.

Reviewer's Comments: Aggression collectively refers to, unless otherwise specified, suicide, homicide, and other forms of violence. The difference between these forms of violence is their intended target. Escitalopram is labeled in Section 5, Warnings and Precautions, for "anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, and mania." However, many other factors have also been reported in the literature to increase aggression: current or past suicidal or homicidal thoughts and behavior, psychiatric diagnoses, psychosocial issues, history of childhood trauma, family history, behavioral features (i.e., impulsiveness, agitation), cognitive features (i.e., loss of executive function, thought constriction ["tunnel vision"], polarized thinking, close-mindedness), demographics, and additional features such as access to firearms or history of substance abuse.[5,6] Therefore, based on the limited clinical information in the first two cases we are unable to make an assessment. Additionally, identifying information such as the manufacturer, lot number, and batch number was not reported in the first case. The second case is confounded by a shooting at the reporter's school. Contagion in mass killings and school shootings has been reported in the literature.[7] Finally, the complicated medical histories in the last two cases make it difficult to make an assessment.

3.4.3 Chronic fatigue syndrome (CFS), postural orthostatic tachycardia syndrome (POTS) (n=1)

A 16-year-old female reported she "developed Postural Orthostatic Tachycardia Syndrome and/or Orthostatic intolerance" while taking escitalopram for anxiety. She "was also diagnosed with Chronic Fatigue Syndrome." The symptoms became so severe she "had to be medicated for them." She reported, "Once I stopped taking the Escitalopram, I stopped fainting, I was no longer dizzy, and I was not suffering from chronic fatigue." She took escitalopram for approximately five years and "was diagnosed with chronic fatigue about 1 year into the treatment, and the POTS about 2 years into it." Further clinical details were not provided. The outcome was not reported.

Reviewer's Comments: Although escitalopram is labeled for fatigue in Section 6, Adverse Reactions, CFS requires three criteria according to the 1994 case definition currently used by the Centers for Disease Control and Prevention: 1) The individual has had severe chronic fatigue for 6 or more consecutive months and the fatigue is not due to ongoing exertion or other medical conditions associated with fatigue (these other conditions need to be ruled out by a doctor after diagnostic tests have been conducted); 2) The fatigue significantly interferes with daily activities and work; and 3) The individual concurrently has 4 or more of the following 8 symptoms: post-exertion malaise lasting more than 24 hours, unrefreshing sleep, significant impairment of short-term memory or concentration, muscle pain, pain in the joints without swelling or redness, headaches of a new type, pattern, or severity, tender lymph nodes in the neck or armpit, a sore throat that is frequent or recurring.[8] Escitalopram is also labeled for tachycardia in Section 6.2, Post-Marketing Experience. Despite the positive dechallenge, due to the lack of clinical information and long latency between the initiation of escitalopram and development of CFS and POTS we are unable to determine a causal association.

3.4.4 Non-alcoholic steatohepatitis (n=1)

Gracious et al. reported a 17-year-old female with bipolar disorder, anxiety disorder, panic disorder, a recent concussion, social and educational problems, and attention deficit hyperactivity disorder (ADHD) had "poorly controlled symptoms, including sleep dysregulation, mood cycling with irritable mixed mania, extreme agitation, restlessness, and distractibility." She was overweight, and she continued to gain weight due to an inactive lifestyle, poor eating habits, adverse effects of medications, and daily stressors. Unspecified pharmacologic and non-pharmacologic interventions to help her lose weight were tried but were unsuccessful. She had been taking escitalopram, cetirizine, clonazepam, lorazepam, oxcarbazepine, aripiprazole, lithium, bupropion, docusate, acetylcestine, methylphenidate, and clonidine at the time of her first abnormal aspartate aminotransferase (AST) and alanine aminotransferase (ALT) although the exact dates of initiation could not be determined from the case. Her AST and ALT gradually became elevated over nine months. Approximately two years later she was referred to a liver specialist because of persistent elevated AST and ALT levels. She was diagnosed with nonalcoholic steatohepatitis (NASH) with stage 3-4 fibrosis. An ultrasound "showed fatty infiltration of the liver and mild splenomegaly." Other laboratory tests were all within normal limits except for an insulin level of 30.4 (range 9.1-21.7 uU/mL). A liver biopsy revealed "severe steatosis, choric steatohepatitis with mild

inflammatory activity, minimal ballooning injury, and periportal and early bridging fibrosis (NASH activity score 5/8, stage 3)." The action taken with escitalopram was unknown and the outcome was not reported.[9]

Reviewer's Comments: The case is confounded by multiple concomitant medications known to cause weight gain such as aripiprazole, oxcarbazepine, lithium, and clonidine and to cause elevations in hepatic enzymes such as aripiprazole and oxcarbazepine. "Weight-gain–inducing psychotropics (including the mood stabilizers lithium and sodium valproate or certain antidepressants)" were identified by the authors as risk factors for nonalcoholic fatty liver disease (NAFLD) and NASH.[9] Escitalopram is also labeled in Section 6.2, Post-Marketing Experience, for fulminant hepatitis, hepatic failure, hepatic necrosis, and hepatitis.

3.4.5 Neuromuscular Disorder (N=1)

The last case, reported in the literature by Rhea, was a 15-year-old male who was found via genetic testing to be a poor metabolizer of CYP2D6, and experienced "neuromuscular instability" while taking escitalopram. The unspecified symptoms were so severe and "became unbearable" that escitalopram was discontinued. His depression returned and escitalopram was restarted. The escitalopram dose was titrated to 20 mg but he "decompensated and experienced intense suicidal ideation." Escitalopram was discontinued a second time. He was started on sertraline for depression and anxiety and mirtazapine to "improve sleep continuity." Genetic testing result showed that the patient "possessed variations in SLC6A4 and CYP450 enzymes and may be at an even greater risk for side effects and/or intolerability with SSRIs due to a combination of altered signaling at the target site (SLC6A4) and altered blood levels of medications related to impaired metabolism." He eventually improved after additional changes to his medication regimen based on the result of his genetic testing and "restarted his college coursework and reengaged in social activities."[10]

Reviewer's Comment: The patient's reported symptoms are likely related to well-known adverse events consistent with an activation syndrome; these include akathisia, restlessness, or psychomotor agitation that are quite common adverse reactions with escitalopram and other SSRIs as well as other antidepressants. Such adverse events are often more common in patients with anxiety disorders, as was the case with this patient. If the patient had CYP2D6 poor metabolizer status, this would increase his risk of these and other adverse reactions related to escitalopram.

4 DISCUSSION

This review serves as an update to a previous DPV pediatric review in preparation for the May 2011 Pediatric Advisory Committee meeting.

Drug utilization patterns were assessed to capture pediatric use of escitalopram and to provide context for the adverse event reports submitted to the FAERS database. Findings from this review should be interpreted in the context of the known limitations of the databases used. We estimated that escitalopram was distributed primarily to the outpatient setting based on the IMS Health, IMS National Sales Perspectives™. Accordingly this review was focused on outpatient

retail pharmacy utilization. Pediatric patients 0-16 years accounted for approximately 3- 4% of the total patients annually and doubled in terms of patient utilization from approximately 148,500 patients to 290,000 patients during the study period from April 2011 through March 2017. These data are based on dispensed prescription claims, and do not undergo chart validation for accuracy of abstracted information from prescription level data. Furthermore, our analyses were only focused on the outpatient retail setting and might not apply to other settings of care such as inpatient setting and clinics where escitalopram may be used.

DPV reviewed all domestic, unlabeled, serious pediatric cases reported with the use of escitalopram in the FAERS database received from October 14, 2010 to March 31, 2017. There were no fatal cases and a total of 12 non-fatal cases in the case series. There were no new safety signals identified, no increased severity or frequency of any labeled adverse event.

5 CONCLUSION

Pediatric utilization of escitalopram approximately doubled during the examined six-year period; however, no new patterns of FAERS cases or trends suggestive of new or unexpected adverse events attributable to the use of escitalopram were identified.

6 RECOMMENDATIONS

DPV recommends no labeling changes at this time, and will continue to monitor adverse events associated with the use of escitalopram.

7 REFERENCES

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8 APPENDICES

8.1 APPENDIX A. DRUG UTILIZATION DATABASE DESCRIPTIONS/LIMITATIONS

QuintilesIMS, 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.

QuintilesIMS, Total Patient Tracker™ (TPT):

Total Patient Tracker (TPT) 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 2.1 billion prescription claims per year.

inVentiv Health Research & Insights, LLC., TreatmentAnswers™

inVentiv Health Research & Insights, 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.

The term "drug uses" to refer to mentions of a drug in association with a diagnosis during a patient visit to an office-based physician. This term may be duplicated by the number of diagnoses for which the drug is mentioned. It is important to note that a "drug use" does not necessarily result in a prescription being generated. Rather, the term indicates that a given drug was mentioned during an office visit.

Indications for use were obtained using a monthly survey of 3,200 office-based physicians. Although these data are helpful to understand how drug products are prescribed by physicians, the small sample size and the relatively low usage of these products limits the ability to identify trends in the data. In general, physician survey data are best used to identify the typical uses for the products in clinical practice, and outpatient prescription data are best used to evaluate utilization trends over time. Results should not be overstated when nationally projected estimates of annual uses or mentions fall below 100,000 as the sample size is very small with correspondingly large confidence intervals.

Given that statistical accuracy increases as the projected number of records increase, data below 100,000 projected mentions or occurrences may not represent national level trends, because results below this threshold represent insufficient raw physician responses prior to applied projection factors. Data below 100,000 (mentions or occurrences) do not

represent sufficient portion of the population and is not representative of actual physician prescribing habits at a national level. In general, this physician survey database is most appropriate to identify the typical uses for a product in office-based physician's clinical practice. Therefore, the patient exposure estimates reported in this review may not apply to other settings of care or other specialty offices in which these products may be prescribed or dispensed.

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=12)

FAERS Case #	Version #	Manufacturer Control #
7795437	1	(Blank)
9036764	1	(Blank)
9199756	1	(Blank)
10771526	1	US-ACTAVIS-2015-01217
11926821	1	US-SUN PHARMACEUTICAL INDUSTRIES LTD-2016US-109945
11780981	1	US-HETERO LABS LTD-1044689
12577815	1	(Blank)
11276872	1	(Blank)
10076559	1	(Blank)
8537218	1	US-FRI-1000029754
11603151	1	(Blank)
11761478	1	US-GLAXOSMITHKLINE-US2015GSK165203

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/s/

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