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

Pediatric Postmarketing Pharmacovigilance and Drug Utilization Review

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Product Name:	Cymbalta (duloxetine)
Pediatric Labeling Approval Date:	October 16, 2014
Application Type/Number:	NDA 21427
Applicant/Sponsor:	Eli Lilly and Company
OSE RCM #:	2017-618

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EXECUTIVE SUMMARY

In accordance with the Food and Drug Administration Amendments Act (FDAAA) and 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 duloxetine in pediatric patients.

Duloxetine was first approved in 2004 and is indicated for major depressive disorder (MDD), generalized anxiety disorder (GAD), diabetic peripheral neuropathic pain (DPNP), fibromyalgia, and chronic musculoskeletal pain. The pediatric labeling change prompting this review was the October 16, 2014 approval for the treatment of GAD in pediatric patients, ages 7 – 17 years.

This review serves as an update to a previous Pediatric Advisory Committee presentation in March 2015. The Division of Pharmacovigilance (DPV) searched the FDA Adverse Event Reporting System (FAERS) database for reports of duloxetine received from August 1, 2014 to March 31, 2017. DPV reviewed all serious pediatric cases reported with the use of duloxetine. There were no fatal cases, and a total of eight non-fatal cases in the case series. All the serious adverse events reported to FDA were labeled events that are well characterized, or they were symptoms of the disorder being treated. There were no new safety signals identified, no increased severity or frequency of any labeled adverse events and there were no deaths directly associated with duloxetine.

Drug utilization patterns were assessed to capture pediatric utilization of duloxetine and to provide context for the adverse event reports submitted to the FAERS database. The outpatient retail utilization data showed that pediatric patients 0 – 17 years of age accounted for 1% (approximately 69,000 patients) of the total patients who received dispensed duloxetine prescriptions from August 2014 through March 2017, cumulative. Approximately 99% of pediatric patients who received dispensed duloxetine prescriptions were 7 – 17 years of age. Patients 6 years or younger accounted for 1% of pediatric patients who received dispensed duloxetine prescriptions from outpatient retail pharmacies.

Based on office-based physician surveys, GAD (ICD10 F41.1) was the only diagnosis associated with duloxetine use in patients 6 years or younger. In pediatric patients 7 – 17 years of age, chronic pain syndrome (ICD10 G89.4) was the top diagnosis associated with duloxetine use, followed by MDD, single episode, in partial remission (ICD10 F32.4) and GAD.

Overall, the pediatric utilization of duloxetine was small, and no new patterns of FAERS cases or trends suggestive of new or unexpected adverse events attributable to the use of duloxetine were identified. DPV recommends no labeling changes at this time, and will continue to monitor adverse events associated with the use of duloxetine.

1 INTRODUCTION

1.1 PEDIATRIC REGULATORY HISTORY

Product Information and Dosing:

Cymbalta® (duloxetine) was approved on August 3, 2004. It is a serotonin and norepinephrine reuptake inhibitor (SNRI). It is indicated for the treatment of major depressive disorder (MDD), generalized anxiety disorder (GAD), diabetic peripheral neuropathic pain (DPNP), fibromyalgia, and chronic musculoskeletal pain. The only approved pediatric indication is for GAD. Cymbalta® is available as delayed release capsules in 20mg, 30mg, and 60mg.[1] The starting, target, and maximum doses are listed in **Table 1.1** along with the dosing schedule for each indication and age group.

Table 1.1. Recommended doses for duloxetine by indication and age

Indication	Starting Dose	Target Dose	Maximum Dose
MDD	40mg/day to 60mg/day	Acute treatment: 40mg/day (20mg twice daily) to 60mg/day (once daily or as 30mg twice daily); Maintenance Treatment: 60mg/day	120mg/day
GAD Adults Elderly Children and adolescents (7 to 17 years of age)	 60mg/day 30mg/day 30mg/day	 60mg/day (once daily) 60mg/day (once daily) 30mg/day (once daily)	 120mg/day 120mg/day 120mg/day
DPNP	60mg/day	60mg/day (once daily)	60mg/day
Fibromyalgia	30mg/day	60mg/day (once daily)	60mg/day
Chronic musculoskeletal pain	30mg/day	60mg/day (once daily)	60mg/day

On October 16, 2014, Cymbalta® was approved for the treatment of GAD in children and adolescents 7 to 17 years of age. The safety and efficacy for GAD in 7 to 17 years of age was demonstrated in one 10-week, placebo-controlled trial (n=272). Safety and effectiveness in pediatric patients less than seven years have not been established. The most frequently observed

adverse reactions in the pediatric trials included nausea, headache, weight reduction, and abdominal pain. Weight and height should be regularly monitored in children and adolescents treated with duloxetine. The average steady-state duloxetine concentration was about 30% lower in children and adolescents relative to adults.

A Written Request was issued on June 23, 2006 to assess the safety and efficacy of Cymbalta® as a treatment for MDD in children (7 to 11 years) and adolescents (12 to 17 years). The studies did not demonstrate efficacy and did not result in a pediatric indication for Cymbalta® for the treatment of MDD. The safety findings were consistent with the known safety and tolerability profile for duloxetine. There were no new or unexpected adverse events in the pediatric subjects, compared to the safety profile in adults.

The approved prescribing information for Cymbalta® includes the following language regarding pediatric use and the negative pediatric controlled trials of Cymbalta® in MDD:[1]

USE IN SPECIFIC POPULATIONS
8.4 Pediatric Use
Generalized Anxiety Disorder — In pediatric patients aged 7 to 17 years, efficacy was demonstrated in one 10 week, placebo-controlled trial. The study included 272 pediatric patients with GAD of which 47% were 7 to 11 years of age. CYMBALTA demonstrated superiority over placebo as measured by greater improvement in the Pediatric Anxiety Rating Scale (PARS) for GAD severity score *[see Clinical Studies (14.2)]*. The safety and effectiveness in pediatric patients less than 7 years of age have not been established.

Major Depressive Disorder — Efficacy was not demonstrated in two 10-week, placebo-controlled trials with 800 pediatric patients with MDD, age 7 to 17. Neither CYMBALTA nor an active control (indicated for treatment of pediatric depression) was superior to placebo. The safety and effectiveness in pediatric patients less than 7 years of age have not been established.

The most frequently observed adverse reactions in the clinical trials included nausea, headache, decreased weight, and abdominal pain. Decreased appetite and weight loss have been observed in association with the use of SSRIs and SNRIs. Perform regular monitoring of weight and growth in children and adolescents treated with an SNRI such as CYMBALTA *[see Adverse Reactions (6.11)]*.

Use of CYMBALTA in a child or adolescent must balance the potential risks with the clinical need *[see Boxed Warning and Warnings and Precautions (5.1)]*.

1.2 HIGHLIGHTS OF LABELED SAFETY ISSUES FOR CYMBALTA

WARNING: SUICIDAL THOUGHTS AND BEHAVIORS

See full prescribing information for complete boxed warning.

- **Increased risk of suicidal thinking and behavior in children, adolescents, and young adults taking antidepressants (5.1)**
- **Monitor for worsening and emergence of suicidal thoughts and behaviors (5.1)**

---------- CONTRAINDICATIONS ----------

- Serotonin Syndrome and MAOIs: Do not use MAOIs intended to treat psychiatric disorders with CYMBALTA or within 5 days of stopping treatment with CYMBALTA. Do not use CYMBALTA within 14 days of stopping an MAOI intended to treat psychiatric disorders. In addition, do not start CYMBALTA in a patient who is being treated with linezolid or intravenous methylene blue (4)

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

- Hepatotoxicity: Hepatic failure, sometimes fatal, has been reported in patients treated with CYMBALTA. CYMBALTA should be discontinued in patients who develop jaundice or other evidence of clinically significant liver dysfunction and should not be resumed unless another cause can be established. CYMBALTA should not be prescribed to patients with substantial alcohol use or evidence of chronic liver disease (5.2)
- Orthostatic Hypotension, Falls and Syncope: Cases have been reported with CYMBALTA therapy (5.3)
- Serotonin Syndrome: Serotonin syndrome has been reported with SSRIs and SNRIs, including with CYMBALTA, 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 CYMBALTA and initiate supportive treatment. If concomitant use of CYMBALTA 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 (5.4)
- Abnormal Bleeding: CYMBALTA may increase the risk of bleeding events. Patients should be cautioned about the risk of bleeding associated with the concomitant use of CYMBALTA and
  NSAIDs, aspirin, or other drugs that affect coagulation (5.5, 7.4)
- Severe Skin Reactions: Severe skin reactions, including erythema multiforme and Stevens-Johnson Syndrome (SJS), can occur with CYMBALTA. CYMBALTA should be discontinued at the first appearance of blisters, peeling rash, mucosal erosions, or any other sign of hypersensitivity if no other etiology can be identified. (5.6)
- Discontinuation: May result in symptoms, including dizziness, headache, nausea, diarrhea, paresthesia, irritability, vomiting, insomnia, anxiety, hyperhidrosis, and fatigue (5.7)
- Activation of mania or hypomania has occurred (5.8)
- Angle-Closure Glaucoma: Angle-closure glaucoma has occurred in patients with untreated anatomically narrow angles treated with antidepressants. (5.9)

- Seizures: Prescribe with care in patients with a history of seizure disorder (5.10)
- Blood Pressure: Monitor blood pressure prior to initiating treatment and periodically throughout treatment (5.11)
- Inhibitors of CYP1A2 or Thioridazine: Should not administer with CYMBALTA (5.12)
- Hyponatremia: Cases of hyponatremia have been reported (5.13)
- Glucose Control in Diabetes: In diabetic peripheral neuropathic pain patients, small increases in fasting blood glucose, and HbA_{1c} have been observed (5.14)
- Conditions that Slow Gastric Emptying: Use cautiously in these patients (5.14)
- Urinary Hesitation and Retention (5.15)

---------- ADVERSE REACTIONS ----------

- Most common adverse reactions (≥5% and at least twice the incidence of placebo patients): nausea, dry mouth, somnolence, constipation, decreased appetite, and hyperhidrosis (6.3).

2 DRUG UTILIZATION DATA

2.1 METHODS AND MATERIALS

2.1.1 Data Sources Used

Proprietary databases available to the Agency were used to conduct the drug utilization analyses in this review (see Appendix A for full database descriptions and limitations).

The QuintilesIMS, National Sales Perspectives™ database was used to determine the settings of distribution for duloxetine based on the volume of packages sold from the manufacturer to the various settings of care in 2016.

The QuintilesIMS, Total Patient Tracker (TPT) database was used to provide national estimates of unique patients who received dispensed prescriptions for duloxetine, stratified by patient age (0-6, 7-17, and 18+ years), from August 2014 through March 2017, cumulative.

The inVentiv Health Research & Insights LLC., TreatmentAnswers™ , with pain panel database was used to provide the diagnoses associated with the use of duloxetine, stratified by patient age (0-6, 7-17, and 18+ years), as reported by U.S. office-based physician surveys from August 2014 through March 2017, cumulative.

2.2 RESULTS

2.2.1 Determining Settings of Care

Based on the QuintilesIMS, National Sales Perspectives™ database, approximately 87%, 7%, and 6% of duloxetine bottles were distributed to outpatient retail pharmacies[2], non-retail settings[3], and mail-order/specialty settings, respectively, in 2016.[4] As a result, we examined duloxetine utilization patterns in the outpatient retail pharmacy setting. Data from non-retail and mail-order/specialty settings were not included in the analysis.

2.2.2 Number of Patients

Table 2.2.2. National estimates of unique patients*, stratified by patient age, who received dispensed prescriptions for duloxetine from U.S. outpatient retail pharmacies, cumulative August 2014 through March 2017**

	August 2014 through March 2017 (cumulative)	
	N	%
Total Patients on Duloxetine	**6,869,621**	***100.0%***
0 - 17 years	68,981	*1.0%*
0 - 6 years	656	*1.0%*
7 - 17 years	68,421	*99.2%*
18+ years	6,765,389	*98.5%*
Unknown Age	94,017	*1.4%*

Source: QuintilesIMS, Total Patient Tracker™. August 2014 through March 2017. Data extracted May 2017.
File: TPT 2017-617 duloxetine BPCA age 5-17-2017.xls

*Patient subtotals may not sum exactly because patients aged over the examined time. For this reason, summing patients across age groups is not advisable and will result in overestimates of patient counts. Moreover, the sum of the percentages will be greater than 100% because patients are double counted across age groups.

**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 old (16 years and 11 months).

2.2.3 Diagnoses Data

Table 2.2.3. Diagnoses associated with the use of duloxetine by patient age as reported by U.S. office-based physician surveys, cumulative August 2014 through March 2017

	August 2014 through March 2017 (cumulative)		
	Uses	95% CI	%
Duloxetine	**15,121,000**	**14,425,000 - 15,817,000**	***100.0%***
0-6 years	8,000	<500 - 24,000	*0.1%*
F411 Generalized anxiety disorder	8,000	<500 - 24,000	*100.0%*
7-17 years	53,000	12,000 - 94,000	*0.4%*
G894 Chronic pain syndrome	17,000	<500 - 40,000	*31.5%*
F324 Major depressv disorder, single episode, in partial remis	11,000	<500 - 29,000	*20.0%*
F411 Generalized anxiety disorder	9,000	<500 - 27,000	*17.6%*
F329 Major depressive disorder, single episode, unspecified	9,000	<500 - 25,000	*16.1%*
F39 Unspecified mood [affective] disorder	5,000	<500 - 18,000	*9.9%*
R51 Headache	3,000	<500 - 12,000	*4.8%*
18+ years	14,119,000	13,446,000 - 14,791,000	*93.4%*
Unknown Age	942,000	768,000 - 1,116,000	*6.2%*

Source: inVentiv Health Research and Insights, LLC., TreatmentAnswers™. August 2014 through March 2017. PDDA_2017-617_duloxetine_BPCA_ICD10_dx4_6-29-2017.xls

*Diagnosis data are not directly linked to dispensed prescriptions, but are obtained from surveys of a sample of 3,200 office-based physicians reporting on patient activity during one day per month. Because of the small sample sizes with correspondingly large confidence intervals, the drug use mentions <100,000 are too low to provide reliable national estimates for the diagnoses and therefore, preclude meaningful interpretation of data trends.

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	April 12, 2017
Time Period of Search	August 1, 2014* - March 31, 2017
Search Type	Quick Query
Product Name(s)	Duloxetine, Duloxetine Hydrochloride
Search Parameters	All ages, all outcomes, worldwide

** Duloxetine was previously presented to the Pediatric Advisory Committee (PAC) in March 2015. This review serves as an update to the previous review.*

3.2 RESULTS

3.2.1 Total number of FAERS reports by Age

Table 3.2.1 Total Adult and pediatric FAERS reports* August 1, 2014 to March 31, 2017 with duloxetine.

	All reports (U.S.)	**Serious† (U.S.)**	**Death (U.S.)**
Adults (≥ 18 years)	2248 (1464)	1697 (946)	399 (297)
Pediatrics (0 - <18 years)	40 (25)	**33‡ (18)**	0 (0)

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

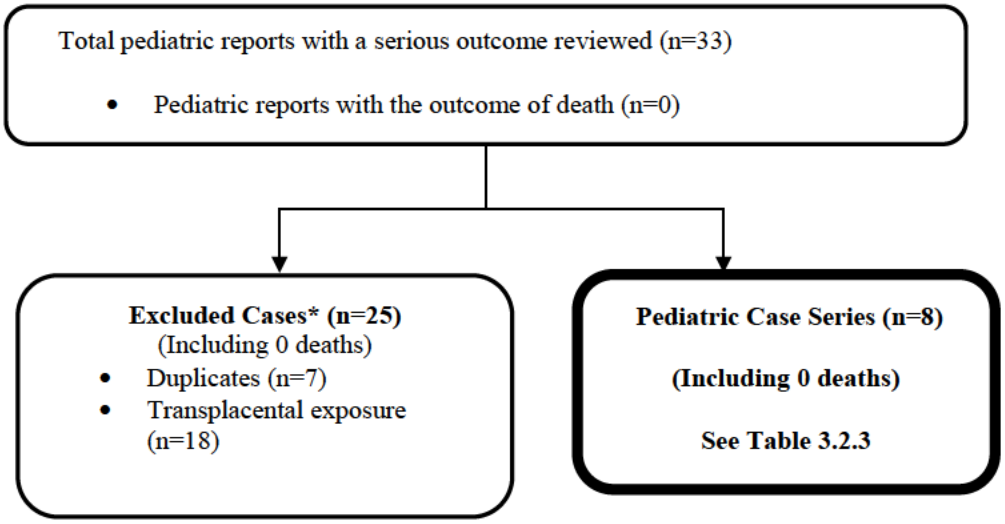
† For the purposes of this review, the following outcomes qualify as serious: death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, required intervention, and other serious important medical events.

‡See Figure 3.2.2

3.2.2 Selection of Serious Pediatric Cases in FAERS

We identified 33 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 Duloxetine



* DPV reviewed these cases, but they were excluded from the case series for the reasons listed above

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 Duloxetine (N=8)

Age (n=8)	12- < 17 years	8
Sex	Male	2
	Female	6
Country	United States	7
	Foreign	1
Reported Reason for Use	Depression	4
	Chronic Pain	1
	Mood Disorder NOS	1
	Schizoaffective Disorder, Depressive Type	1
	Unknown	1
Serious Outcome*	Hospitalized	3
	Disability	1
	Other serious	4

* 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

There were no pediatric deaths.

3.4 SUMMARY OF NON-FATAL PEDIATRIC SERIOUS ADVERSE EVENT CASES

There were eight non-fatal, serious adverse events reported. All the events were labeled and no new or unexpected adverse events were identified.

3.4.1 *Suicidal ideation/suicidal behavior/suicide attempt (n=4)*

There were four cases reporting the PTs *Suicidal ideation, Suicide attempt,* and/or *Suicidal behavior*. A 14-year-old male developed suicidal ideation after switching from one brand of generic duloxetine to another for the treatment of depression. When he switched back, his symptoms resolved. A 16-year-old female tried to commit suicide by multiple drug overdose with a synthetic cannabinoid, nutmeg, and multiple other non-prescription and prescription drugs including duloxetine. A 17-year-old female with a history of schizoaffective disorder (depressive type), and suicide ideation and attempts was started on duloxetine after experiencing only partial improvement of her symptoms while on fluoxetine and risperidone. After two months on duloxetine, "she became irritable and talkative, had increased goal-directed activities, multiple planning, decreased sleep need, and aggression along with subjective low mood, suicide ideation, and worthlessness." Duloxetine was discontinued. Her therapy was switched to clonazepam and lamotrigine along with risperidone, and her symptoms gradually resolved. The fourth patient was a 14-year-old female with a complicated medical history due to chronic pain. She was taking multiple opioid and non-opioid drugs including duloxetine, had two spinal cord stimulators implanted, and was also using "holistic medicine." All were unsuccessful at treating her pain and she developed "debilitating fatigue and depression with occasional thoughts of suicide." She was referred to the (b) (6). She "made drastic improvements…and once again was able to function independently" at the conclusion of the three-week program. She was successfully titrated off all her narcotic medications at discharge. At her six-month follow-up, "depression and anxiety were in the nonclinical range" and she was taking only trazodone at bedtime for sleep.

Reviewer's Comments: Duloxetine has a Boxed Warning for suicidal thoughts and behaviors. The Warnings and Precautions section of 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." Duloxetine also has a Warning and Precaution for Activation of Mania/Hypomania. Symptoms such as irritability, being talkative, increased activity, and decreased sleep may be signs of activation of mania. Three of the patients were using duloxetine off-label (depression, schizoaffective disorder [depressive type], multi-drug overdose), and the reason for use was

unknown for the last patient. The events are consistent with the known risk in the labeling for duloxetine and no increased severity was observed in these cases.

3.4.2 *Condition aggravated (n=1)*

A 17-year-old female experienced a return of depressive symptoms while weaning herself off of duloxetine. The reason for weaning was not reported. At the time of the report, she was still taking duloxetine at an unknown dose and the event was ongoing.

Reviewer's Comments: The case contains limited information and we are unable to make an assessment.

3.4.3 *Elevated liver transaminases, weight increased (n=1)*

A 17-year-old male was taking duloxetine for an unspecified mood disorder. Concomitant medications included lamotrigine, benztropine, and aripiprazole. He experienced an approximate 4.5 kg weight gain over 12 months. Liver function tests were performed "because of weight gain in conjunction with atypical antipsychotic use." They demonstrated an alanine aminotransferase (ALT) of 79 and aspartate aminotransferase (AST) of 54. At the time, he had been taking lamotrigine for 8 months, and duloxetine, aripiprazole, and benztropine for 14 months. Aripiprazole and benztropine were discontinued, but the action taken with lamotrigine and duloxetine was not reported. One month later, ALT had declined to 44 (normal: less than 40 U/L) and AST was normal at 29. Gamma-glutamyl transpeptidase (GGTP) was normal at 25 (normal: 8-78 U/L). The patient's primary care physician ordered a ceruloplasmin, which was found to be low (18 mg/dL; range: 21-53 mg/dL). This was possibly indicative of Wilson's disease. Because of the concern that Wilson's disease might be related to the patient's psychiatric symptoms and might require differing treatment, the patient was referred to the pediatric gastroenterology department and to the ophthalmology department. An eye examination was negative for Keyser-Fleischer rings. An ultrasound of the liver and spleen showed a normal liver with spleen size at the upper limits of normal for his age, and the liver biopsy demonstrated the presence of steatosis without inflammation or fibrosis. One week after the liver biopsy, the patient's ALT was 36 and his AST was 30. Recommendations were made for exercise and diet with a goal of weight loss.

Reviewer's Comments: Duloxetine has hepatotoxicity in the Warnings and Precautions section, and it states, "CYMBALTA should be discontinued in patients who develop jaundice or other evidence of clinically significant liver dysfunction and should not be resumed unless another cause can be established." Aripiprazole is labeled for hepatic enzyme increased in Section 6.1 Clinical Trials Experience. The temporal relationship between the discontinuation of aripiprazole and benztropine and the decrease in AST/ALT suggest a causal relationship with these two drugs. The causal relationship with duloxetine is unclear because the action taken with duloxetine was not reported. The events are consistent with the known risk in the labeling for duloxetine and no increased severity was observed in this case.

3.4.4 *Rash (n=1)*

A 16-year-old female experienced a "body-wide, extremely itchy red rash" after five doses of duloxetine 60 mg. The rash was accompanied by "mild chest pains" and "a bit of trouble with swallowing." She was treated with steroids, hydroxyzine, and intravenous (IV) omeprazole. The rash resolved. The action taken with duloxetine was not reported.

Reviewer's Comments: Duloxetine has severe skin reactions in the Warnings and Precautions section, and it states, "CYMBALTA should be discontinued at the first appearance of blisters, peeling rash, mucosal erosions, or any other sign of hypersensitivity if no other etiology can be identified." Rash is also labeled in Section 6.12 Postmarketing Spontaneous Reports. The events are consistent with the known risk in the labeling for duloxetine and no increased severity was observed in this case.

3.4.5 *Headache (n=1)*

One case of headache was reported in a 17-year-old female with a history of Crohn's disease, drug-induced lupus, depression, secondary adrenal insufficiency, anxiety, and amplified pain syndrome. She was started on duloxetine and fluoxetine for depression during a previous hospital admission in addition to being on multiple concomitant medications. The patient began experiencing tremors. Serotonin syndrome was suspected and both antidepressants were discontinued, but "duloxetine would later be restarted at half the dose." The patient developed a headache described as "throbbing with a pulse (8 out of 10) and with migraneous features (photophobia and nausea)." She was admitted to the hospital for management including head computerized tomography ("which was unremarkable"), hydromorphone, IV fluids, IV ketorolac, IV divalproex, and IV magnesium. She had no previous history of headaches. The patient was discharged with "significant improvement" of her headache.

Reviewer's Comments: Duloxetine has serotonin syndrome in the Warnings and Precautions section, and it states, "Treatment with CYMBALTA and any concomitant serotonergic agents, should be discontinued immediately if" symptoms of serotonin syndrome occur. Symptoms of serotonin syndrome may include tremors. Duloxetine also has warnings for headache in Section 5.7 for Discontinuation of Treatment with CYMBALTA and 5.13 Hyponatremia. Headache is also labeled in Section 2.7 Discontinuing CYMBALTA, Section 6 Adverse Reactions (multiple mentions), and Section 8.4 Pediatric Use. The temporal relationship between the initiation of duloxetine and the onset of the headache was not reported in this case. The case stated duloxetine was later restarted at a lower dose, but further information on the restart was not reported. The events are consistent with the known risk in the labeling for duloxetine and no increased severity was observed in this case.

4 DISCUSSION

This review serves as an update to a previous PAC presentation in March 2015. DPV searched the FAERS database for reports of duloxetine received from August 1, 2014 to March 31, 2017.

DPV reviewed all serious pediatric cases reported with the use of duloxetine. There were no fatal cases, and a total of eight non-fatal cases in the case series. All the serious adverse events reported to FDA were labeled events that are well characterized, or they were symptoms of the disorder being treated. There were no new safety signals identified, no increased severity or frequency of any labeled adverse events and there were no deaths directly associated with duloxetine.

The outpatient retail utilization data showed that approximately 69,000 pediatric patients 0-17 years of age (1% of total patients) received dispensed duloxetine prescriptions from August 2014 through March 2017, cumulative. Although the data showed duloxetine use in patients under 7 years of age, this use cannot be validated due to the lack of access to patient medical records. Furthermore, our analyses only focused on the outpatient retail setting and might not apply to other settings of care such as mail-order/specialty pharmacies where duloxetine may be dispensed.

Based on office-based physician surveys, duloxetine use in patients 6 years or younger was primarily for GAD while chronic pain syndrome was the top diagnosis associated with duloxetine use in patients 7-17 years of age. The diagnoses data were obtained from surveys of a sample of 3,200 office-based physicians with 115 pain specialists reporting on patient activity during one day per month; therefore, these data are not directly linked to dispensed prescriptions. Because of the small sample sizes with correspondingly large confidence intervals, the drug use mentions <100,000 are too low to provide reliable national estimates for the diagnoses and therefore, preclude meaningful interpretation of data trends.

5 CONCLUSION

Overall, the pediatric utilization of duloxetine was small, and no new patterns of FAERS cases or trends suggestive of new or unexpected adverse events attributable to the use of duloxetine were identified.

6 RECOMMENDATIONS

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

7 REFERENCES

1. Cymbalta [package insert]. Eli Lily and Company; October 2016.

2. Retail settings include chain drug stores, independent drug stores, mass merchandisers, and food stores.

3. Non-retail settings include clinics, non-federal hospitals, federal facilities, HMOs, long-term care facilities, home health care, and other miscellaneous settings.

4. QuintilesIMS, National Sales Perspectives™. 2016. Data extracted April 2017. File: NSP 2017-617 duloxetine BPCA channel 4-18-2017.xlsx

8 APPENDICES

8.1 APPENDIX A. DRUG UTILIZATION DATABASE DESCRIPTIONS/LIMITATIONS

QuintilesIMS, National Sales Perspectives™: Retail and Non-Retail

The QuintilesIMS, 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 QuintilesIMS sales distribution 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. The amount of product purchased by these non-federal hospital channels of distribution may be a possible surrogate for use, if we assume the facilities purchase drugs in quantities reflective of actual patient use.

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.

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 Case #	Version #	Manufacturer Control #
11170302	2	US-AUROBINDO-AUR-APU-2015-04784
10522863	1	ADR-2014-01858
10897849	1	PHHY2015US024395
12364402	1	(Blank)
10510599	1	JPI-P-034176
11767616	1	US-GLAXOSMITHKLINE-US2015GSK165352
11659582	1	TW-ACTAVIS-2015-22980
11705729	2	US-JNJFOC-20151101934

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/s/

COURTNEY M SUGGS
07/07/2017

TRACY M PHAM
07/07/2017

RAJDEEP K GILL
07/07/2017
drug use data has been cleared by data vendors

VICKY C CHAN
07/07/2017

GRACE CHAI
07/10/2017

CINDY M KORTEPETER
07/11/2017