Cross-Discipline Team Leader and Division Director Summary Review for Regulatory Action

Date	(electronic stamp)
From	Pamela Horn, MD, Cross-Discipline Team Leader Naomi Lowy, MD, Deputy Division Director
Subject	Cross-Discipline Team Leader and Division Director Summary Review
NDA # and Supplement #	21427 s052
Applicant	Eli Lilly and Company
Date of Submission	June 20, 2019
PDUFA Goal Date	April 20, 2020
Proprietary Name	Cymbalta
Established or Proper Name	duloxetine
Dosage Form/ Strengths	Oral (delayed-release capsules) / 20 mg, 30 mg, 60 mg
Applicant Proposed Indication(s)/Population(s)	No new indication proposed by Applicant
Action or Recommended Action:	*Approval*
Approved/Recommended Indication(s)/Population(s) (if applicable)	*Treatment of Juvenile Fibromyalgia Syndrome in adolescents 13-17 years old*

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	**Nancy Baxi, MD**
Statistical Review	**Yan Zhou, PhD**
QT-IRT Review	**Christine Garnett, PharmD**
OPDP	**L. Shenee Toombs, PharmD** **Sam Skariah, PharmD**
OSI	**John Lee, M.D.** **Phillip Kronstein, M.D.** **Kassa Ayalew, M.D., M.P.H.**

DPMH consult review	**Ndidi Nwokorie, MD** **Mona Khurana, MD** **John J. Alexander, MD, MPH**
DP consult review	**Jean Kim, MD**

OND=Office of New Drugs
OPDP=Office of Prescription Drug Promotion
OSI=Office of Scientific Investigations
DPMH=Division of Maternal and Pediatric Health
DP=Division of Psychiatry
QT-IRT= QT-Interdisciplinary Review Team

1. Benefit-Risk Assessment

Benefit-Risk Assessment Framework

Benefit-Risk Integrated Assessment

The Applicant submitted the results of a single adequate and well-controlled study (Study HMGW) that evaluated the efficacy and safety of Juvenile Fibromyalgia Syndrome (JFS) in pediatric patients aged 13 to 17. This study was required under the Pediatric Research Equity Act (PREA) and was deferred until after approval of the fibromyalgia indication in adults.

JFS, also referred to as Juvenile Primary Fibromyalgia Syndrome (JPFS), is the name for the syndrome of fibromyalgia in children. Like fibromyalgia in adults, JFS is a challenging disease to manage with unknown etiology. Typical symptoms include chronic widespread musculoskeletal pain, fatigue, and non-restorative sleep. There is very little published literature on JFS with gaps and uncertainties about all aspects of JFS including cause, natural history, prevalence, treatment, and impact. The pathophysiology is unknown, although the current working theory is that genetics and psychological factors appear to play a part in central sensitization leading to chronic pain, similar to adults. Studies show that JFS has a significant effect on quality of life, including poorer physical and psychosocial functioning, more pain, greater anxiety and depressive symptoms, more school absenteeism, and more medical visits/utilization compared to those without JFS. Studies also indicate there may be an increase in suicidal thoughts and behaviors in those afflicted with JFS. Additionally, JFS appears to persist into adulthood.

Standard of care treatment involves a multidisciplinary step-wise approach, using non-pharmacologic therapies such as exercise and cognitive behavioral therapy as first-line and with pharmacologic therapies additive to non-pharmacologic therapies. There are no FDA-approved drugs for JFS, and drugs that are

used off-label include gabapentin, pregabalin, selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs) and opioids. Of note, nonsteroidal anti-inflammatory drugs (NSAIDs) and opioids are not generally considered effective. There are no clear delineations on what therapies will work best for whom. For both of the two other drugs approved for fibromyalgia in adults (pregabalin and milnacipran), their respective studies in pediatric populations were either underpowered or could not recruit. Therefore, JFS is also challenging to treat because of a lack of approved pharmacologic options.

Study HMGW consisted of a 13-week double-blind phase with a primary efficacy endpoint of reduction in average pain score on the Brief Pain Inventory (BPI), followed by a 26-week open-label phase to collect additional safety data. The study showed a numerical improvement in pain in the duloxetine treatment group compared to placebo using the prespecified Mixed-Effects Model Repeated Measures (MMRM) analysis. This analysis was not agreed-upon as an acceptable method of imputing missing data during protocol development by the Division, and these concerns were conveyed to the company in multiple communications before the study was completed.

A MMRM analysis utilizes a missing at random assumption (i.e., the probability of missing depends only on the observed data before patients dropped out and thus the statistical response profiles of dropouts are similar to those of completers) for patients who were discontinued. However, this assumption is unlikely to be true for those who discontinued due to lack of efficacy or an adverse event.

A multiple imputation method that the Division finds acceptable showed a statistically significant treatment effect on the primary efficacy endpoint. The Division's method is preferred because this imputation method assumes that patients who drop out do not contribute any treatment benefit. The Applicant-submitted reanalysis results conducted with the ANCOVA method were consistent with the statistical reviewer's and are the most suitable analyses for the primary efficacy endpoint in this trial.

The Applicant did not propose an indication for JFS because they concluded that the study had not demonstrated efficacy. However, because the analysis that employed an acceptable method for handling missing data demonstrated a statistically significant treatment effect, the Division concludes that study HMGW demonstrated efficacy and therefore supports the addition of an indication for JFS.

Cymbalta has been approved in the US since 2004 and has been studied in over 30,000 adults and 822 pediatric patients. Study HMGW provided data from 149 additional pediatric patients for the pediatric safety database, and review of the safety data revealed no new safety signals in adolescents. The most common adverse events noted in this study that had a higher incidence in the duloxetine group compared to placebo were nausea, headache, vomiting, decreased appetite, somnolence, nasopharyngitis, and viral gastroenteritis. There was one seizure in the open-label period of the study. The safety experience in study HMGW is generally consistent with the safety experience that has been observed in other patient populations as described in the product prescribing information. A key safety concern with duloxetine is the increased risk of suicidal ideation and behavior in children and young adults, which is highlighted in a boxed warning in the prescribing information. There was a higher incidence of suicidal ideation or behavior observed in prospective assessments conducted in Study HMGW in the duloxetine group compared to the placebo group that was comparable to other pediatric duloxetine studies

and consistent with current labeling. As a result, additional risk mitigation beyond the information provided in the prescribing information is not warranted at this time.

There is an unmet medical need for an approved drug for JFS. Efficacy was demonstrated in Study HMGW and the safety findings are consistent with the known risks of duloxetine. The benefit-risk profile is favorable, and the Division recommends approval of duloxetine for JFS in the pediatric population 13 years through 17 years of age.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• JFS is characterized by widespread musculoskeletal pain, tender points, fatigue, non-restorative sleep, headaches, and often irritable bowel syndrome and subjective soft tissue swelling. • The cause is unknown, although central sensitization is thought to be a main feature in pathophysiology, and risk factors seem to include genetic predisposition and psychological conditions. • There is very little published literature; available literature shows a significant quality of life impact and that JFS can persist into adulthood. • JFS appears to be similar to adult fibromyalgia in most respects. • JFS predominantly affects females, with a mean age of onset of 12 years. The prevalence seems to be 1-6% of children. • There is no gold standard for diagnostic criteria or treatment.	• JFS has a substantial impact on quality of life that may have long-term impacts into adulthood. • JFS is challenging to diagnose and treat.
Current Treatment Options	• As in adult fibromyalgia, a multi-modal approach should be taken to treatment, including non-pharmacologic management with cognitive-behavioral therapy, exercise, and physical therapy. • Medications may be added, particularly for treating certain aspects of fibromyalgia, such as pain and sleep disturbance. • There are no approved drugs for JFS. • Off-label use of drugs used include gabapentin, pregabalin, SNRIs, SSRIs, and TCAs. Opioids are used but are not generally recommended. • Pregabalin, milnacipran, and duloxetine are approved for treatment of fibromyalgia in adults.	• There are no approved drugs to treat JFS. The safety and effectiveness of the other two drugs approved to treat fibromyalgia in adults has not been established in the treatment of JFS. • There is an unmet medical need for a medication to treat JFS.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• In a study of pediatric patients ages 12 through 17 years with JFS, pregabalin-treated patients had a numerically greater improvement on pain compared to placebo, but it did not reach statistical significance. These findings are described in the pediatric use section of the Lyrica prescribing information along with a statement that the safety and effectiveness in pediatric patients has not been established. • A study of milnacipran in JFS patients terminated early. The pediatric use section of the prescribing information states that the safety and effectiveness in pediatric patients has not been established.	
Benefit	• Study HMGW showed a numerical improvement in pain in the duloxetine treatment group compared to placebo using the prespecified Mixed-Effects Model Repeated Measures (MMRM) analysis. During the development of the protocol, this analysis was not agreed upon by the Division as an acceptable method of imputing missing data. With the sNDA submission, a reanalysis by the FDA using a multiple imputation method that the Division finds acceptable showed a statistically significant treatment effect on the primary efficacy endpoint. This acceptable method attributes unfavorable pain scores to patients who discontinued the study for reasons likely to be associated with a poor outcome on pain. • The point estimate on the treatment effect represents a change of approximately 0.8 points on the 11-point pain scale. This is within the range observed in the Cymbalta adult fibromyalgia studies. • All responder analyses conducted as secondary analyses support a finding of efficacy on the primary analysis including: -30% reduction in pain responders: 52.2% duloxetine vs. 36.3% placebo -50% reduction in pain responders: 40.0% duloxetine vs. 24.2% placebo	• The benefit of duloxetine in the treatment of JFS was demonstrated in study HMGW. • The benefit is similar to the benefit observed in the duloxetine fibromyalgia trials in adults.
Risk and Risk Management	• The safety database in pediatric patients for Cymbalta is 822 patients, ages 7 to 17 years, who were exposed to duloxetine in 4 clinical trials (three studies in patients with MDD and one study in patients with generalized anxiety disorder [GAD]). • Study HMGW had a safety database of 149 patients, ages 13 to 17 years,	• Additional risk mitigation beyond the information provided in the prescribing information is not warranted at this time.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	who were exposed to duloxetine. • Overall, safety findings of duloxetine in Study HMGW were consistent with the known safety and tolerability profile of duloxetine in adults and prior pediatric studies, and no new safety signals were identified in the pediatric studies. • There was a higher incidence of suicidal ideation or behavior observed in prospective assessments conducted in Study HMGW in the duloxetine group compared to the placebo group that was comparable to other pediatric duloxetine studies and consistent with current labeling.	

2. Background

Duloxetine is a selective serotonin and norepinephrine uptake inhibitor (SSRNI) approved for major depressive disorder (MDD), diabetic peripheral neuropathic pain (DPNP), fibromyalgia (FM), chronic musculoskeletal pain in adults, and generalized anxiety disorder (GAD) in both adults and children aged 7-17. It has been approved in the United States since 2004 under the trade name Cymbalta.

Duloxetine was approved for fibromyalgia in adults on June 13, 2008. Juvenile Fibromyalgia Syndrome (JFS), also referred to as Juvenile Primary Fibromyalgia Syndrome and Juvenile Fibromyalgia Pain Syndrome, like fibromyalgia in adults, is a condition of chronic, diffuse musculoskeletal pain with fatigue and nonrestorative sleep. Also, like fibromyalgia in adults, JFS has a strong female predominance. The average age of onset is 12 years old. Because JFS occurs in adolescents, a post-marketing requirement (PMR) under the Pediatric Research Equity Act (PREA) to study the adolescent patient population was included in the approval of fibromyalgia in adults. Supplement 52, the subject of this review, contains a clinical study report for one efficacy study in adolescents between the ages of 13-17 with JFS. Patients were treated with a starting dose of 30 mg a day and a target dose of 60 mg a day, if tolerated, which is the same as the recommended adult dosing regimen for fibromyalgia.

The two other drugs approved for treatment of fibromyalgia in adults are Lyrica (pregabalin) and Savella (milnacipran hydrochloride). In the pediatric use section of both products, it states that the safety and effectiveness in pediatric patients has not been established. In the Lyrica label it also states that in a study of pediatric patients ages 12 through 17 years with JFS, pregabalin-treated patients had a numerically greater improvement on pain compared to placebo, but it did not reach statistical significance. The publicly reported treatment effect in the pregabalin JFS study on a primary endpoint of change from baseline to week 15 on the average daily pain score on an 11-point numeric rating scale was a decrease of -0.66 (point estimates of -1.60 for the pregabalin group and -0.94 for the placebo group).

3. Product Quality

Not applicable

4. Nonclinical Pharmacology/Toxicology

Not applicable

5. Clinical Pharmacology

Not applicable

6. Clinical Microbiology

Not applicable

7. Clinical/Statistical-Efficacy

The original pediatric plan proposal submitted by the Sponsor was for a randomized, double-blind, placebo-controlled trial with approximately 100 patients per treatment arm.

The study protocol was submitted to IND 63615 in December 2010. The Division communicated to the Sponsor in 2011 that the proposed mixed-model repeated measures (MMRM) strategy is not acceptable for the primary analysis. A MMRM analysis utilizes a missing at random assumption (i.e., the probability of missing depends only on the observed data before patients dropped out and thus the statistical response profiles of dropouts are similar to those of completers) for patients who were discontinued. However, this assumption is unlikely to be true for those who discontinued due to lack of efficacy or an adverse event.

The Division reiterated the disagreement on the MMRM strategy after receiving a response from the Sponsor that they still planned to use the MMRM strategy.

Study HMGW was a Phase 3b, multicenter, randomized, placebo-controlled trial in pediatric patients 13 to 17 years of age diagnosed with JFS. The study design included a 13-week parallel, randomized, double-blind, placebo-controlled treatment period of duloxetine 30/60 mg once daily. Patients were randomized in a 1:1 ratio at the beginning of the treatment period to receive either duloxetine or placebo. Upon completion of the 13-week double-blind period, patients entered a 26-week, open-label extension phase of duloxetine 30/60 mg daily. There was a 1-week drug taper period who completed or discontinued on duloxetine 60 mg daily. The prespecified primary efficacy endpoint was change from baseline to Week 13 in Brief Pain Inventory (BPI) average pain score (24-hour average pain severity).

Subject eligibility was determined based on the Yunus and Masi diagnostic criteria for JFS. At the time that Study HMGW began, these criteria were appropriate given that the ACR 2010 criteria had not yet been validated in pediatric patients. The study results can be expected to be generalizable as it appears that the Yunus and Masi criteria are still used at least as often as the ACR 2010 to diagnose JFS in current practice.

The trial completed in December 2017. The Applicant randomized close to the originally-planned number of 100 patients per arm (91 patients in the duloxetine group and 93 patients in the placebo group). The disposition of patients is reproduced in Table 5 from the joint clinical/statistical review:

Table 1: Patient Disposition, Double-Blind Phase

Primary Reason for Discontinuation	DLX (N=91) n %	PLA (N=93) n %	Total (N=184) n %
Completed DB treatment phase	74 (81.3)	75 (80.7)	149 (81)
Reasons for discontinuation for DB Treatment phase			
Overall	17 (18.7)	18 (19.4)	35 (19)
Adverse event	5 (5.5)	1 (1.1)	6 (3.3)
Lack of efficacy	1 (1.1)	3 (3.2)	4 (2.2)
Lost to follow-up	2 (2.2)	3 (3.2)	5 (2.7)
Parent/caregiver decision	2 (2.2)	4 (4.3)	6 (3.3)
Protocol violation	4 (4.4)	3 (3.2)	7 (3.8)
Withdrawal by subject	3 (3.3)	4 (4.3)	7 (3.8)

Abbreviations: DB = double-blind; DLX = duloxetine; PLA = placebo
Source: Statistical reviewer's analysis

A higher proportion of patients discontinued due to adverse events in the duloxetine group compared to the placebo group and a higher proportion of patients discontinued due to lack of efficacy in the placebo group compared to the duloxetine group. Other reasons for discontinuation were reported for 12% of the duloxetine group and 15% of the placebo group.

The results of the primary efficacy variable were numerically in favor of duloxetine but with a p-value of 0.052, using a pre-specified Mixed-Effects Model Repeated Measures (MMRM) analysis that was not agreed-upon by the Division. However, the FDA re-analysis done with multiple imputation (MI) methods to impute missing data did show statistical significance. The Division's method is preferred because this imputation method assumes that patients who drop out do not contribute any treatment benefit.

During development of the protocol, the Division disagreed with the company's proposed analysis based on MMRM. Nevertheless, the company insisted on their proposed analysis against our advice. Because our imputation method was proposed during the protocol development stage, before data unblinding, we do not consider these analyses to be post hoc.

Following an Information Request, The Applicant-submitted reanalysis results conducted with the ANCOVA method (see Table 10 from the joint clinical/statistical review) were consistent with the statistical reviewer's results, shown below. The Division considers this the most suitable method for imputing missing data for the primary endpoint.

Table 2: Reviewer's Sensitivity Analysis Using Multiple Imputation With Baseline Used for Imputation for Certain Discontinued Patients, Change From Baseline in BPI Average Pain Score at Visit 8 (Week 13), Double-Blind Phase, All Randomized Patients

ANCOVA* Analysis for BPI Average Pain Score at Visit 8 (Week 13) Between Treatment Comparison

DSC Reasons Considered**	Treatment	N	LS Mean Change (SE)	LS Mean Change Difference (SE)	95% CI for Difference	p-Value
LOE/AE/PD	DLX	90	-1.70 (0.26)	-0.75 (0.33)	(-1.41, -0.09)	0.025
	PLA	91	-0.95 (0.25)			
LOE/AE/PCD	DLX	90	-1.69 (0.26)	-0.78 (0.33)	(-1.43, -0.13)	0.020
	PLA	91	-0.91 (0.25)			
Any Reason	DLX	90	-1.61 (0.26)	-0.84 (0.33)	(-1.48, -0.19)	0.012
	PLA	91	-0.77 (0.25)			

Abbreviations: AE = adverse event; ANCOVA = Analysis of Covariance; BPI = Brief Pain Inventory; DLX = duloxetine; DSC = discontinuation; LOE = lack of efficacy; LS = least square; N = number of patients with baseline and non-missing or imputed value at Visit 8 (Week 13); PCD = Patient or Parent/Caregiver Decision; PD = Patient Decision; PLA = placebo

* ANCOVA Model: Change=Treatment + Pooled Investigator + Baseline

** Missing Visit 8 (Week 13) data for patients discontinuing for the reasons listed here are imputed according to the distribution of baseline BPI average pain (using all patients). Missing Visit 8 values for other patients imputed based on patient randomized treatment along with available non-missing BPI average pain collected including the baseline assessment.

Source: Statistical reviewer's analyses

These results demonstrate the efficacy of duloxetine in the treatment of JPFS and support the benefit in the age 13-17 pediatric population.

8. Safety

There was adequate exposure experience both in terms of numbers of pediatric patients and duration of exposure in the safety database from study HMGW. There were 149 adolescent subjects exposed to duloxetine overall in study HMGW; 80 patients had exposure for at least six months. There were no new safety signals identified and adverse events (AEs) observed were consistent with the known safety profile of duloxetine.

There were no deaths in Study HMGW. There were two serious adverse events (SAEs) during the double-blind period in the duloxetine group (appendicitis and suicidal ideation) and none in the placebo group.

In the open-label extension period of the study there was one SAE each of appendicitis, generalized tonic-clonic seizure, affective disorder, intentional overdose, suicidal ideation, intentional self-injury, and auditory hallucination and two SAEs of suicide attempt.

The patient who had a seizure in the open-label period of this study had no known risk factors for or history of seizure disorder. The prescribing information includes an adequate warning about seizures in the Warnings and Precautions section.

There were few discontinuations due to adverse events during the double-blind phase. In the duloxetine group the AEs reported were nausea, somnolence, anxiety, depressed mood and suicidal behavior and in the placebo there was one discontinuation due to diarrhea. These adverse events are consistent with the known safety profile of duloxetine.

With respect to the psychiatric adverse events reported in study HMGW, the consult response from the Division of Psychiatry contains the following assessment and conclusions (SI/B means suicidal ideation or behavior):
"Fibromyalgia is known to have significant comorbidity with MDD, anxiety, and other psychiatric conditions. Several cohort studies (including ones done in Spain,[1] in Denmark,[2] and in Taiwan[3] with national registries) also note possible increased risk of SI/B (including completed suicide) for people with fibromyalgia, especially given its association with known SI/B risk factors other than psychiatric illness, such as chronic pain and insomnia.[4]

Per the C-SSRS data, the number of SI/B events in this pediatric fibromyalgia study was numerically higher on drug than on placebo during the DB phase at roughly 7% drug to 3(or 4 if including NSIB)% placebo, or over a 2:1 ratio, despite not being statistically significant. This trend seems to correlate with prior ones seen in pediatric antidepressant studies for both MDD and other psychiatric indications; several metaanalyses indicate a slightly higher rate of SI/B events on drug versus placebo, usually in the 1.5 to 2 times increased risk range overall—although these analyses did not prospectively use the C-SSRS.[5]"

"It is difficult to say whether the overall SI/B event trends for this single study are necessarily worse than the trends seen in other duloxetine or other pediatric antidepressant studies; the ratio of SI/B (including NSIB) events on C-SSRS on drug versus placebo (7% versus 4%) seem numerically higher for this pediatric study than the original adult fibromyalgia studies (discussed in the next section), but comparable to other pediatric duloxetine studies (overall exposure-based rate around 5 to 6%, see pediatric ISS section on page 13; crude SI/B rate in the pediatric MDD studies of 17% for both arms, see page 12 of this review). Again, the difference between drug and placebo was not statistically significant within the DB phases.
Also, this new study utilized prospective monitoring with the C-SSRS, and studies prior

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[1] Calandre EP, et al. Suicide Attempts and Risk of Suicide in Patients with Fibromyalgia: A Survey in Spanish Patients. Rheumatology 2011;50:1889-1893.
[2] Dreyer L, et al. Mortality in a Cohort of Danish Patients with Fibromyalgia. Arthritis and Rheumatism 2010;62(10):3101-3108.
[3] Lan C, et al. Increased Risk of a Suicide Event in Patients with Primary Fibromyalgia and in Fibromyalgia Patients with Concomitant Comorbidities. Medicine 2016;95(44):1-9.
[4] Jimenez-Rodriguez I, et al. Suicidal Ideation and the Risk of Suicide in Patients with Fibromyalgia: A Comparison with Non-Pain Controls and Patients Suffering from Low-Back Pain. Neuropsychiatric Disease and Treatment 2014;10: 625-630.
[5] Hammad et al. Suicidality in Pediatric Patients Treated with Antidepressant Drugs. Arch Gen Psychiatry 2006;63:332-339.

to 2009 (including the original adult fibromyalgia studies) did not routinely conduct this type of monitoring. Accordingly, detected SI/B events (particularly SI) would be expected to be higher than previously observed. Finally, background rates of SI/B would likely be higher for an adolescent population with fibromyalgia due to the aforementioned risk factors of high background psychiatric comorbidity, chronic pain, insomnia, and adolescence-related psychosocial stressors. Psychosocial stressors were reflected in many of the narratives for this study, even if most of the SI/B cases did not have a known prior psychiatric history.

Given the overall context of the similar, small numerical increase in SI/B events on drug versus placebo during prior pediatric antidepressant trials, the worrisome case of new-onset psychosis and agitation post-drug initiation, and the known background psychiatric risk and comorbidity for patients with fibromyalgia, it seems that the same risks discussed in the existing boxed warning for antidepressants apply to this population and this study. However, the SI/B AEs do not appear to constitute a unique risk that requires additional or different labeling language; the existing boxed warning, mania activation warning, and postmarketing experience section should cover these issues."

I concur with the assessment and conclusion that the same risks discussed in the existing boxed warning, mania activation warning apply to the JFS population and that the findings do not constitute a unique risk that requires changes to the existing language in the prescribing information.

The following Table 22 from the joint clinical/statistical review summarizes AEs in the double-blind period of study HMGW:

Table 3: Common Adverse Events Study HMGW Double-Blind Phase and Open-Label Phase (Incidence of ≥5% in the Duloxetine Treatment in the Double-Blind Phase)

Preferred Term*	Duloxetine, DBP N=91 n(%)	Placebo, DBP N=93 n(%)	Duloxetine, OLP N=74 n(%)
Nausea	23 (25)	14 (15)	32 (21)
Headache	13 (14)	10 (11)	11 (7)
Vomiting	14 (15)	5 (5)	12 (8)
Decreased appetite	14 (15)	3 (3)	14 (9)
Somnolence	8 (9)	3 (3)	5 (3)
Nasopharyngitis	8 (9)	2 (2)	7 (5)
Upper respiratory infection	6 (7)	2 (2)	10 (7)
Fatigue	5 (5)	2 (2)	6 (4)
Gastroenteritis viral	5 (5)	0 (0)	5 (3)

Abbreviations: DBP = double-blind phase; OLP = open-label phase
*Of note, dizziness also occurred at a >5% incidence in the Duloxetine phase (9%); however, it occurred at a higher rate (10%) in the placebo arm.
Source: Adapted from CSR Table HMGW.12.11

The incidence of nausea, vomiting, and decreased appetite were higher in this study compared to what is labeled in pediatric Major Depressive Disorder and Generalized Anxiety Disorder studies in the duloxetine-treated group. The incidence of weight loss (a decrease of ≥3.5% from baseline occurred in 15% of the duloxetine-treated group compared to 5% of the placebo

group) was similar to what has been labeled for other pediatric populations. There was also a higher incidence in the duloxetine group compared to the placebo group of nasopharyngitis, upper respiratory infection and viral gastroenteritis, the relatedness and significance of which is unknown.

The serum transaminase and CPK elevation findings are consistent with the current prescribing information. The joint clinical/statistical review includes the following assessment of liver tests:
There were no Hy's Law cases. The highest ALT elevation (ALT >5X ULN) appears to be related to viral hepatitis infection and resolved. The incidence of elevated ALT in the open-label phase is higher than what is noted on the label, but it is unclear why this might be. No serious or significant AEs appear to be attributable to the liver tests, however.

The QT-IRT reviewed the QT interval data from study HMGW. The following assessment from the joint clinical/statistical reviews summarizes the conclusions from the consult response:
The QT-IRT team's review showed that a thorough QT (TQT) study had been done under IND (b) (4) *and that no QT prolongation was noted at duloxetine doses of 160 mg and 200 mg BID, and concluded that the cases above did not represent a concerning signal, especially given the prior negative TQT study.*

The following summarizes the assessment of withdrawal symptoms in the study from the joint clinical/statistical review:
Of the 77 patients that were in the taper phase of Study HMGW, 10% reported one or more AEs, all of whom were tapering from 60 mg to 30 mg. Dizziness was reported in 4% of patients, and headache, paresthesia, and somnolence were reported in 1% of patients each. These findings are consistent with current labeling.

I concur with the clinical reviewer's conclusion that no new safety signals were identified in the study and the AEs observed are consistent with the known safety profile of duloxetine.

9. Advisory Committee Meeting

There was no advisory committee meeting held for this application.

10. Pediatrics

DPMH was consulted to provide labeling language for subsection 8.4 to reflect the results of the efficacy and safety trial for Cymbalta in pediatric patients 13-17 years of age with juvenile fibromyalgia syndrome.

As noted in their review, Pediatric Use subsection and other appropriate sections of labeling must include a description of the pediatric use information. The information must include what is known and unknown about the use of the drug, differences in safety and efficacy in the pediatric population compared to adults, and any limitations of use in that pediatric population. When evidence supports the use of a drug for a pediatric indication, all relevant sections of

labeling which include: Indications and Usage, Dosage and Administration, Adverse Reactions, Use in Specific Populations, Clinical Pharmacology, and Clinical Studies, as well as any other sections that may be appropriate must include pediatric use information. (21CFR 201.57(c)(9)(iv)(B), (C), and (D)).

The DPMH Labeling review focused primarily on the following sections: Highlights, 1 (Indications and Usage), 2 (Dosage and Administration), 6 (Adverse Reactions), 8.4 (Use in Specific Populations - Pediatric Use), 12 (Clinical Pharmacology), and 14 (Clinical Studies).

11. Other Relevant Regulatory Issues

Two clinical study sites were selected for inspection, one in Texas and one in Argentina. The inspection of the Argentina site was completed with no problems noted.

For the Texas site, the Clinical Investigator (Dr. Irwin Russell) was not available at this address (professionally retired), and the location was also not accessible for inspection (business/legal constraints). Efforts to conduct the inspection at a near-by records storage facility (b) (4) with limited remote and in-person assistance by Dr. Russell, was complicated by the logistic demands of the recently-mandated public health measures to contain the COVID-19 pandemic. The need for this inspection in supporting the sNDA review was revisited, and it was determined that the assessment of the application could proceed without this inspection. Accordingly, this inspection was deemed not mission-critical and was cancelled with review division concurrence on March 25, 2020.

12. Labeling

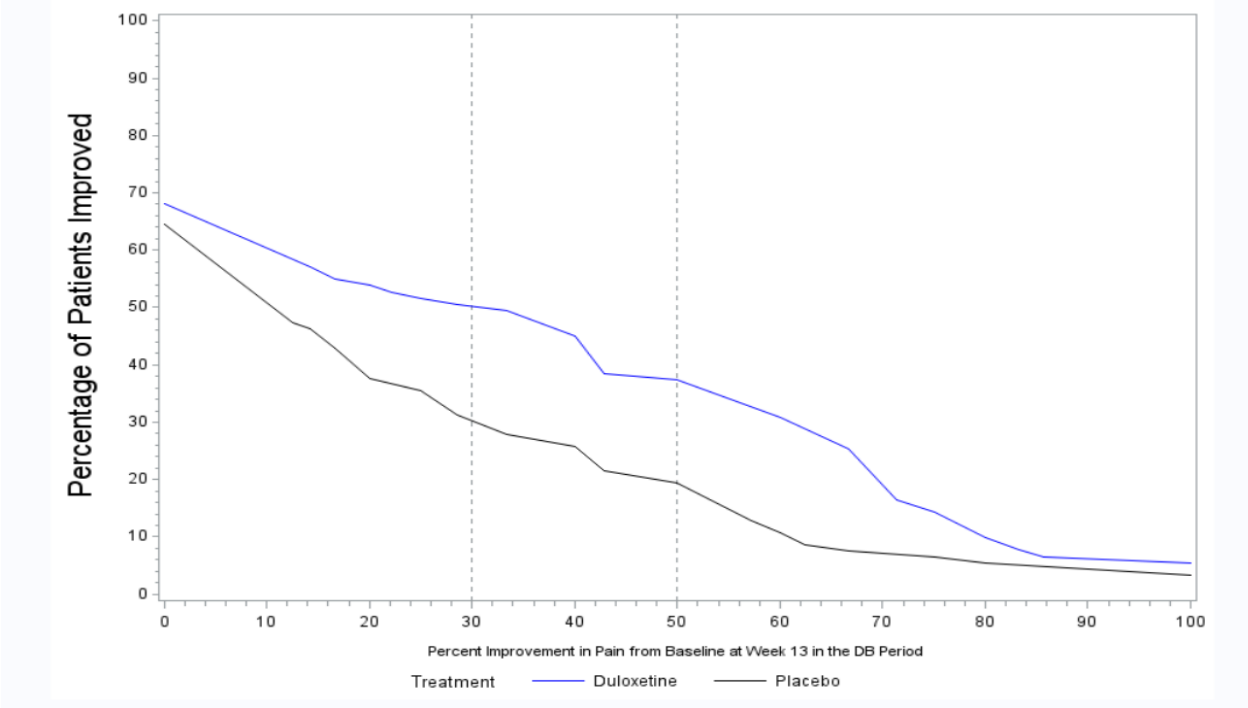
The proposed revised prescribing information submitted with the supplement contained a single paragraph in section 8.4 Pediatric Use stating that efficacy was not demonstrated in the HMGW clinical trial in adolescents and the safety results were consistent with the known safety profile of duloxetine. Based on the review of study HMGW, the Division sent an information request (IR) to the Applicant on 2/21/2020 asking that the Applicant submit revised labeling that reflects an indication (section 1) for Juvenile Pediatric Fibromyalgia Syndrome in adolescent patients 13-17 years of age. The IR further stated that all relevant sections of the Prescribing Information should be updated accordingly, including the following sections: (1) Indications and Usage, (2) Dosage and Administration, (6) Adverse Reactions, (8) Use in Specific Populations (8.4 Pediatric Use), and (14) Clinical Studies.

The Applicant responded to the IR with an updated proposed label that included information pertaining to the treatment of JFS in all but section (1) Indications and Usage. The Division revised the label with input from labeling experts within the Office of New Drugs, including a revised section 1 that states that Cymbalta is indicated for the treatment of Fibromyalgia in adults and pediatric patients 13 years of age and older.

The Applicant accepted the Division's suggested revisions, including the addition of JFS to section 1.

The graphical representation in Figure 3 from the joint clinical/statistical review is suitable for inclusion in labeling to provide information on the observed treatment effect that is most easily interpreted by prescribers and is consistent with the figures depicting the treatment effect observed in fibromyalgia trials in adults in the current prescribing information.

Figure 1: Percent Improvement in BPI Average Pain from Baseline at Week 13



Source: Statistical reviewer's analysis

Section (6) Adverse Reactions includes a list of the most frequently observed adverse reactions in all pediatric populations as well as a table of the adverse reactions observed in the JFS study alone.

In addition to the revisions made related to the Supplement 52, the Division suggested changes and edits to the label to clarify specific language and to update language to be consistent with current best practices. This Review does not include a comprehensive list of changes that were made, but two specific examples of changes along with their rationale are described here:

- In INDICATIONS AND USAGE, ages were added to the indications and (b) (4) were removed. This was done for the following reasons: to ensure a consistent message about pediatric use information in labeling (especially Sections 1 and 2 and subsection 8.4), to provide clarity to healthcare practitioners on the pediatric conditions of use of CYMBALTA, to be consistent with the recommendations in the draft guidance for industry: *Indications*

and Usage Section of Labeling for Human Prescription Drug and Biological Products - Content and Format (July 2018).

- In ADVERSE REACTIONS, we proposed deletion of a sentence in second paragraph which read, [redacted (b) (4)]. This was done for the following reasons: [redacted (b) (4)], and it is inconsistent with the definition of an adverse reaction included in labeling as per 21 CFR 201.57(c)(7).

13. Postmarketing

- Postmarketing Risk Evaluation and Mitigation Strategies

A REMS is not recommended at this time.

- Other Postmarketing Requirements and Commitments

No PMRs or PMCs are recommended at this time.

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/s/

PAMELA J HORN
04/20/2020 12:11:37 PM

NAOMI N LOWY
04/20/2020 12:13:41 PM