



FDA CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF ANESTHESIA AND ANALGESIA PRODUCTS

Summary Review for Regulatory Action

Date	November 4, 2010
From	Bob A. Rappaport, M.D. Director Division of Anesthesia and Analgesia Products
Subject	Division Director Summary Review
NDA #	22-516
Applicant Name	Eli Lilly and Co.
Date of Submission	March 15, 2009
PDUFA Goal Date	March 15, 2010
Proprietary Name / Established (USAN) Name	Cymbalta Duloxetine HCl
Dosage Forms / Strength	20 mg, 30 mg and 60 mg Delayed-release capsules
Proposed Indication	For the management of Chronic Pain
Action:	Approval

Material Reviewed/Consulted	
OND Action Package, including:	
Medical Officer Review	Anjelina Pokrovnichka, M.D.
Statistical Review	Yongman Kim, Ph.D.; Dionne Price, Ph.D.; Thomas Permutt, Ph.D.
Pharmacology Toxicology Review	N/A
CMC Review/OBP Review	N/A
Microbiology Review	N/A
Clinical Pharmacology Review	N/A
DDMAC	Mathilda Fienkeng, Pharm.D.
DSI	Susan Liebenhaut, M.D., Tejashri Purohit-Sheth, M.D.
CDTL Review	Ellen Fields, M.D., M.P.H.
OSE/DPV I	Laurelle Cascio, Pharm.D.; Ida-Lina Diak, Pharm.D.; Mark Avigan, M.D.;
OSE/DMEPA	N/A
OSE/DAEA	N/A
OSE/DRISK	Jessica Diaz, R.N.; Shawna L Hutchins Pharm.D.; Claudia Karwoski, Pharm.D.
OSE/DEPI	Rajdeep K. Gill, Pharm.D.; Laura Governale, Pharm, D.

OND=Office of New Drugs
DDMAC=Division of Drug Marketing, Advertising and Communication
OSE= Office of Surveillance and Epidemiology
DMEDP=Division of Medication Error Prevention
DSI=Division of Scientific Investigations
DRISK= Division of Risk Management
DAEA=Division of Adverse Event Analysis
CDTL=Cross-Discipline Team Leader
DEPI= Division of Epidemiology
DPV I=Division of Pharmacovigilance I

1. Introduction

Cymbalta is a selective serotonin and norepinephrine reuptake inhibitor that was initially approved for the treatment of major depressive disorder and for the treatment of the pain associated diabetic peripheral neuropathy (DPN) in 2004. This was followed by approvals for generalized anxiety disorder (2004) and maintenance treatment of major depressive disorder (2007). In 2008, an additional indication for the management of fibromyalgia (FM) was approved. Eli Lilly has now submitted a new application for the management of chronic pain. This application has been submitted as a Type 6 NDA, as the approved application is held by the Division of Psychiatry Products (DPP). The referenced application is NDA 21-427. Duloxetine is theorized to provide analgesia by potentiating descending inhibitory pain pathways from the brain to the spinal cord.

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2. Background

The applicant has submitted studies in patients with chronic low back pain (CLBP) and pain due to osteoarthritis (OA) to supplement their previous approvals for DPN and FM in support of a general chronic pain indication. The paradigm for what should constitute an appropriate set of studies of different painful conditions to support a broad, (or at least broader than what currently exists for non-opioid, non-NSAID analgesics), indication has been controversial and in flux for many years. I will discuss the basis for this controversy in Section 12, below. At a Pre-IND meeting in 2005, the applicant proposed a development program resulting in a CLBP indication. The division recommended that a broader indication be sought, and informed the applicant that they could achieve that broader indication by studying chronic pain in two separate pain populations, and that one study in each of those populations would be sufficient, in combination with their already approved DPN indication, to achieve the level of evidence necessary for the approval of a general chronic pain indication. In 2007, the division informed the sponsor that their proposal to study CLBP and the pain of OA would be sufficient to support their proposed chronic pain indication.

The applicant submitted their first NDA for the management of chronic pain in May, 2008, but it was subsequently withdrawn by the applicant after they were informed by the division that, based on our preliminary review of the submitted studies, they did not appear to have demonstrated efficacy in the single OA study that, in addition to their two CLBP studies, was needed to support the proposed general chronic pain indication. The current application was then submitted on May 15, 2009, and includes an additional study in OA.

Coincidentally, during the review process, a workshop was held at which academic experts in pain medicine and analgesic clinical trial design were asked to provide a consensus position on the number and types of studies that would be appropriate to allow extrapolation of efficacy from one painful condition to other painful conditions, based on the available scientific data. The division had decided to convene the workshop in order to address certain basic scientific and clinical questions that had arisen during the preparation of a draft guidance document for industry on the development of analgesic drug products. At that workshop in December, 2009, the experts concluded that an extensive series of clinical trials in nociceptive, neuropathic and visceral pain conditions, a number of which would need to be replicated, would be necessary to support extrapolation to a broad chronic pain population. They based this conclusion on the paucity of existing data that would support being able to extrapolate efficacy from one painful condition to another and the fact that, in light of the toxicities associated with many analgesic drug products, it is essential that we be sure an analgesic will work before we support more widespread use. However, they did feel that, within certain categories of chronic pain, (e.g., chronic pain due to peripheral neuropathic disorders, chronic pain due to non-rheumatologic musculoskeletal disorders), the findings of efficacy in two adequate and well-controlled trials of one disorder could be extrapolated to a second disorder with the support of only one additional trial in that second disorder. The division initially informed the sponsor that the application would be taken to an advisory committee meeting to discuss the proposed indication, for the management of chronic pain, as this would have been the first non-opioid/non-NSAID analgesic product with a general pain indication. However, the meeting

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was canceled as further internal discussion became necessary due to concerns raised regarding the hepatotoxicity of Cymbalta by Dr. Marc Stone, a clinical reviewer in DPP. A decision regarding the overall risk-benefit profile of Cymbalta for the management of chronic pain could not be made without a clear understanding of its hepatotoxic potential.

Based on the outcomes of the workshop, and after further internal deliberation, it became clear that the present program from Lilly would not be adequate to support a general chronic pain indication. We decided that an indication for the management of chronic musculoskeletal pain could be more appropriately supported by the applicant's findings of efficacy in CLBP and the pain of OA. As this indication would still result in a much greater level of prescribing of Cymbalta, and coupled with the concerns regarding the drug's potential to cause hepatotoxicity that may be greater than comparable products, the division decided to reschedule an advisory committee meeting. Although doing so would result in our missing the PDUFA goal date, we felt it was critical to address the ramifications of a broadened indication in a public meeting, even if it was not as broad as that originally sought, considering the likely much wider use of Cymbalta that would ensue.

The indication "for the management of chronic musculoskeletal pain" would be in addition to the previously approved indications for DPN and FM. This is the indication that was ultimately presented to the advisory committee members. The committee was asked, based on this expanded indication, whether the benefits of the drug would outweigh its risks. They were not asked additional questions regarding the specific wording for the indication as we had already decided on the appropriate category for this application by that time. Further discussion of the advisory committee's deliberations and of the divisions decisions regarding the indication follow in Sections 9 and 11 below.

3. CMC

There are no new CMC issues for this previously approved formulation of Cymbalta. The Environmental Impact of the new indication was determined to be acceptable.

4. Nonclinical Pharmacology/Toxicology

No new non-clinical pharmacology or toxicology data was included in this submission.

5. Clinical Pharmacology/Biopharmaceutics

No new clinical pharmacology or biopharmaceutics data was included in this application.

6. Clinical Microbiology

No clinical microbiology data were necessary for this application.

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7. Clinical/Statistical-Efficacy

The applicant submitted five clinical trials in support of efficacy, HMEP and HMFG in OA patients, and HMEN, HMEO and HMGC in CLBP patients. The five trials had a number of features in common. The subjects had to have had a diagnosis of chronic pain for at least three months and a baseline score of four or greater on an eleven-point Likert scale measuring pain intensity. Subjects with major depressive disorder were excluded. In the CLBP trials, patients with neurological deficits or clinical evidence of either spinal stenosis or radiculopathy were excluded in an attempt to focus on non-neuropathic back pain. The subjects were permitted to remain on their regular doses of NSAIDs, provided that they had been using them at the time of enrollment, and randomization was stratified by NSAID use.

The following summary of the individual studies has been reproduced from pages 3 and 4 of Dr. Fields' review:

Study HMEP was a 13-week, double-blind, placebo-controlled, international, multi-center trial investigating the safety and efficacy of duloxetine in patients with osteoarthritis knee pain. In the study, 231 patients were randomized to duloxetine 60mg (n = 111) or placebo (n = 120). At Week 7, patients initially randomized to duloxetine 60mg were re-randomized to either duloxetine 60mg or duloxetine 120mg. The primary efficacy variable was the change from baseline to Week 13 in the weekly mean of the 24-hour average pain. Secondary efficacy measures included Patient Global Impression of Improvement (PGI-I) and Western Ontario and McMaster Universities (WOMAC) physical function subscale.

Study HMEN was a 13-week, double-blind, placebo-controlled, international, multi-center trial investigating the safety and efficacy of duloxetine in patients with chronic low back pain. In the study, 236 patients were randomized to duloxetine 60mg (n = 115) or placebo (n = 121). At Week 7, patients who were randomized to duloxetine 60mg and did not meet a response criterion defined as at least 30% reduction in pain scores had their dose increased to 120mg. The primary efficacy outcome was the pain severity as measured by the BPI 24-hour average pain scores from baseline to Week 13. Secondary efficacy measures included Clinical Global Impression of Severity (CGI-Severity) and Roland-Morris Disability Questionnaire (RMDQ-24).

Study HMEO was a 13-week, double-blind, placebo-controlled, international, multi-center trial investigating the safety and efficacy of duloxetine in patients with chronic low back pain. In the study, 404 patients were randomized to duloxetine 20 mg (n=59), duloxetine 60mg (n=116), duloxetine 120mg (n=112), or placebo (n=117). The primary efficacy variable was the change from baseline to Week 13 in the weekly mean of the 24-hour average pain. Secondary efficacy measures included Patient Global Impression of Improvement (PGI-I) and Roland-Morris Disability Questionnaire (RMDQ-24). This study failed to show efficacy of duloxetine in the treatment of CLBP.

Study HMFG was a 13-week, double-blind, placebo-controlled, international, multi-center trial investigating the safety and efficacy of duloxetine in patients with osteoarthritis knee pain. In the study, 256 patients were randomized to duloxetine 60mg (n=128) or placebo (n=128). At Week 7, patients who were randomized to duloxetine 60mg and did not meet response criterion defined as at least 30% reduction in pain scores had their dose increased to 120mg. The primary efficacy outcome was the pain severity as measured by the BPI 24-hour average pain scores from baseline to Week 13. Secondary efficacy measures included the patient reported outcomes such as Patient Global Impression of Improvement (PGI-I) and Western Ontario and McMaster Universities (WOMAC) physical function subscale.

Study HMGC was a 12-week, double-blind, placebo-controlled, international, multi-center trial investigating the safety and efficacy of duloxetine in patients with chronic low back pain. In the study, 401 patients were randomized to duloxetine 60mg (n=198) or placebo (n = 203). The primary efficacy outcome was the pain severity as measured by the BPI 24-hour average pain scores from baseline to Week 12. Secondary efficacy measures included the patient reported outcomes such as Patient Global Impression of Improvement (PGI-I) and Roland-Morris Disability Questionnaire (RMDQ-24).

The primary efficacy outcome for each of the studies was the change in pain severity from baseline to Week 13 (Week 12 for GMGC). In studies HMFG, HMEP and HMEN, this analysis was based on the combined 60 mg and 120 mg QD dosages compared to placebo. A mixed-model repeated measures analysis was employed as the primary statistical analysis and additional analyses were performed with ANCOVA methodology using a variety of imputation strategies including LOCF, BOCF, and a modified BOCF in which BOCF was used to impute missing data from dropouts due to loss of efficacy or adverse events and LOCF was used to impute missing data from dropouts due to other reasons, e.g., lost to follow up. The primary analysis was performed on a modified intent-to-treat (mITT) population which was defined as all patients who were randomized and who had baseline scores and at least one post-baseline observation.

As per the following summary reproduced from page 5 of Dr. Fields' review, there were a number of features of the applicant's statistical review with which the clinical and statistical reviewers did not agree:

As stated by Dr. Kim in his review, there were a number of issues related to the statistical analyses specified by the Applicant. The MMRM analysis method is not appropriate for chronic pain trials because it assumes dropouts occur at random, and utilizes data from patients who withdrew early from the trial, potentially assigning good pain scores to subjects who withdrew due to adverse events. In contrast, subjects who withdraw before the end of the study should be treated as non-responders, and no benefit should be assigned based on the pain scores prior to dropout. Analysis methods that impute missing data conservatively, such as BOCF and mBOCF are the preferred methods for these types of trials. In addition, Dr. Kim conducted the analyses using the ITT population which consisted of all patients who were randomized and had baseline scores, regardless of whether they had a post-baseline observation, in contrast to the method described by the Applicant.

As noted above, Study HMEO failed to show efficacy, even by the applicant's protocol-specified analyses. For each of the other four studies, the following results of the applicant's analysis, as well as Dr. Kim's analysis and his continuous responder curve analysis, are reproduced from pages 6 through 13 of Dr. Fields' review:

HMEP:

Applicant's Primary Efficacy Analysis: HMEP (mITT)

LS Mean Change (SE) from Baseline to Week 13 in weekly mean of 24-hour average pain	Placebo (N=119)	DLX60-120mg (N=108)	P-value
MMRM*	-2.1 (0.16)	-2.9 (0.17)	<0.001
ANCOVA/BOCF**	-1.8 (0.19)	-2.2 (0.20)	0.086

*P-value calculated from MMRM model with terms for treatment, week, treatment*week, site, NSAID use, baseline, week*baseline.

**P-value calculated from ANCOVA model with terms for treatment, site, NSAID use, and baseline score as covariate.

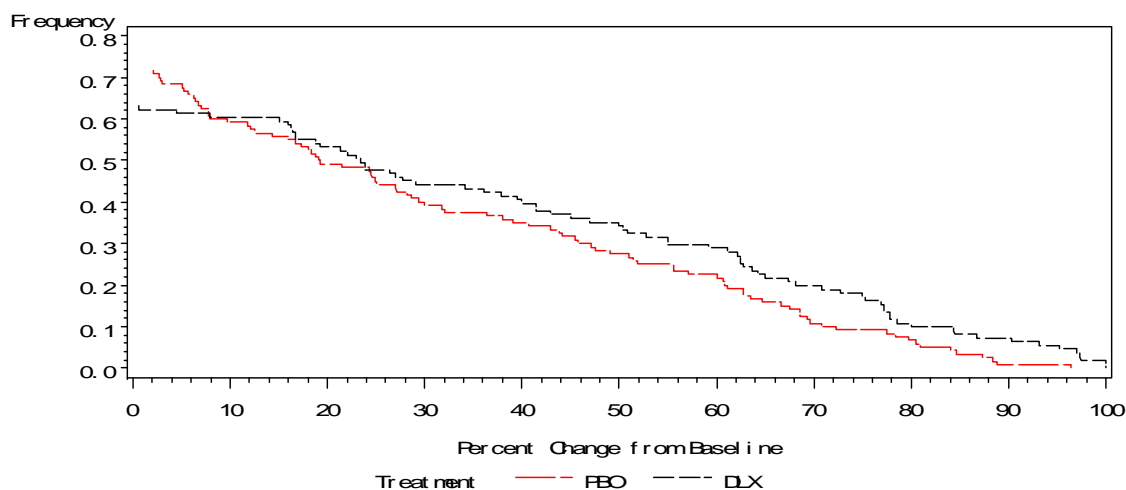
Note: mITT population excluded patients with no post-baseline observations.

Reviewer's Primary Efficacy Analysis: HMEP (ITT)

LS Mean Change (SE) from Baseline to Week 13 in weekly mean of 24-hour average pain	Placebo (N=120)	DLX60-120mg (N=111)	P-value
ANCOVA/BOCF*	-1.7 (0.19)	-2.0 (0.19)	0.412
ANCOVA/mBOCF*	-1.9 (0.13)	-2.5 (0.14)	0.002

*P-value calculated from ANCOVA model with terms for treatment, site, NSAID use, and baseline score as covariate.

Cumulative Improvement in Pain from Baseline



HMEN:

Applicant's Primary Efficacy Analysis: HMEN (mITT)

LS Mean Change (SE) from Baseline to Week 13 in BPI 24-hour average pain	Placebo (N=115)	DLX60-120mg (N=109)	P-value
MMRM*	-1.5 (0.21)	-2.3 (0.22)	0.004
ANCOVA/BOCF**	-1.3 (0.20)	-1.9 (0.20)	0.019
ANCOVA/mBOCF**	-1.4 (0.21)	-1.9 (0.21)	0.041

*P-value calculated from MMRM model with terms for treatment, week, treatment*week, site, NSAID use, baseline, week*baseline.

**P-value calculated from ANCOVA model with terms for treatment, site, NSAID use, and baseline score as covariate.

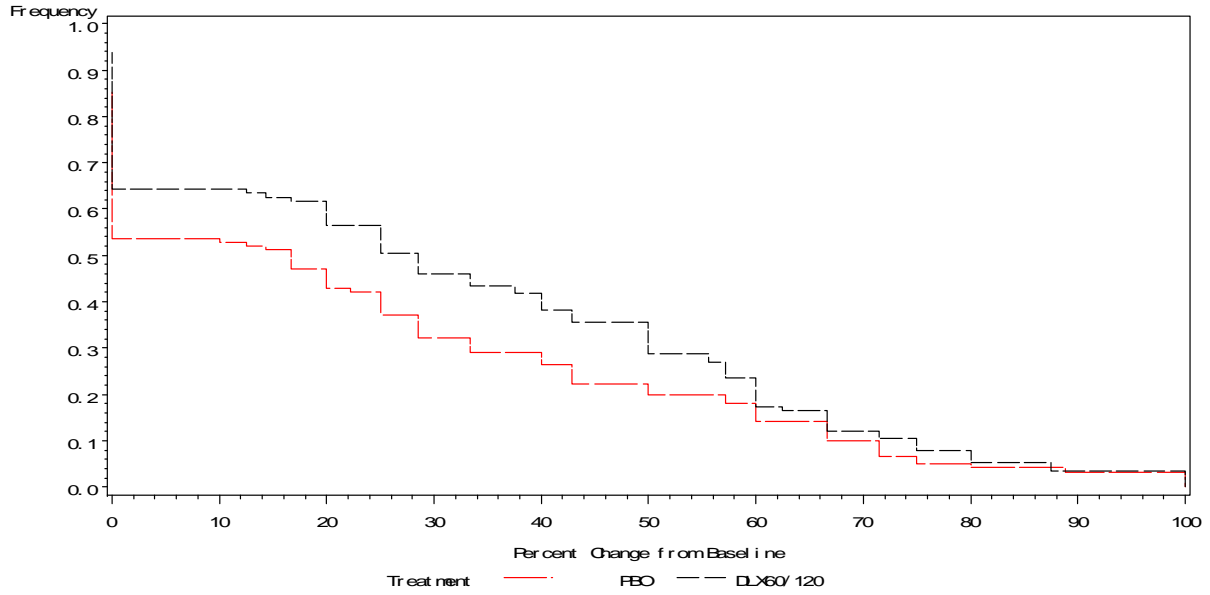
Note: mITT population excluded patients with no post-baseline observations.

Reviewer's Primary Efficacy Analysis: HMEN (ITT)

LS Mean Change (SE) from Baseline to Week 13 in BPI 24-hour average pain	Placebo (N=121)	DLX60-120mg (N=115)	P-value
ANCOVA/BOCF*	-1.2 (0.19)	-1.9 (0.19)	0.009
ANCOVA/mBOCF*	-1.2 (0.20)	-1.8 (0.20)	0.020

*P-value calculated from ANCOVA model with terms for treatment, site, NSAID use, and baseline score as covariate.

Reviewer’s Continuous Responder Analysis on Primary Efficacy Variable: HMEN (ITT)



Note: P-value of **0.018** is generated by van der Waerden test.

HMFG:

Applicant’s Primary Efficacy Analysis: HMFG (mITT)

LS Mean Change (SE) from Baseline to Week 13 in BPI 24-hour average pain	Placebo (N=127)	DLX60-120mg (N=121)	P-value
MMRM*	-1.9 (0.18)	-2.7 (0.20)	<0.001
ANCOVA/BOCF**	-1.6 (0.19)	-2.2 (0.20)	0.013
ANCOVA/mBOCF**	-1.6 (0.19)	-2.3 (0.20)	0.005

*P-value calculated from MMRM model with terms for treatment, week, treatment*week, site, NSAID use, baseline, week*baseline.

**P-value calculated from ANCOVA model with terms for treatment, site, NSAID use, and baseline score as covariate.

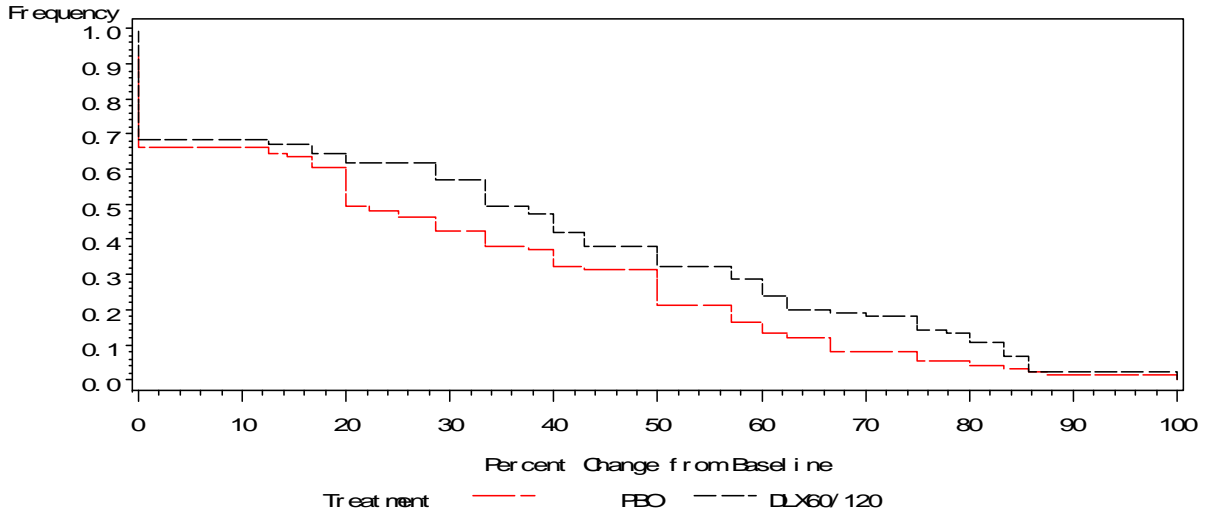
Note: mITT population excluded patients with no post-baseline observations.

Reviewer's Primary Efficacy Analysis: HMFG (ITT)

LS Mean Change (SE) from Baseline to Week 13 in BPI 24-hour average pain	Placebo (N=128)	DLX60-120mg (N=128)	P-value
ANCOVA/BOCF*	-1.6 (0.19)	-2.2 (0.20)	0.013
ANCOVA/mBOCF*	-1.6 (0.18)	-2.3 (0.19)	0.005

*P-value calculated from ANCOVA model with terms for treatment, site, NSAID use, and baseline score as covariate.

Reviewer's Continuous Responder Analysis on Primary Efficacy Variable: HMFG (ITT)



Note: P-value of **0.016** is generated by van der Waerden test.

HMGC:

Applicant's Primary Efficacy Analysis: HMGC (mITT)

LS Mean Change (SE) from Baseline to Week 12 in BPI 24-hour average pain	Placebo (N=203)	DLX60mg (N=198)	P-value
MMRM*	-1.9 (0.15)	-2.5 (0.16)	0.001
ANCOVA/BOCF**	-1.4 (0.15)	-1.9 (0.15)	0.004
ANCOVA/mBOCF**	-1.6 (0.15)	-2.1 (0.15)	0.004

*P-value calculated from MMRM model with terms for treatment, week, treatment*week, site, baseline, week*baseline.

**P-value calculated from ANCOVA model with terms for treatment, site, and baseline score as covariate.

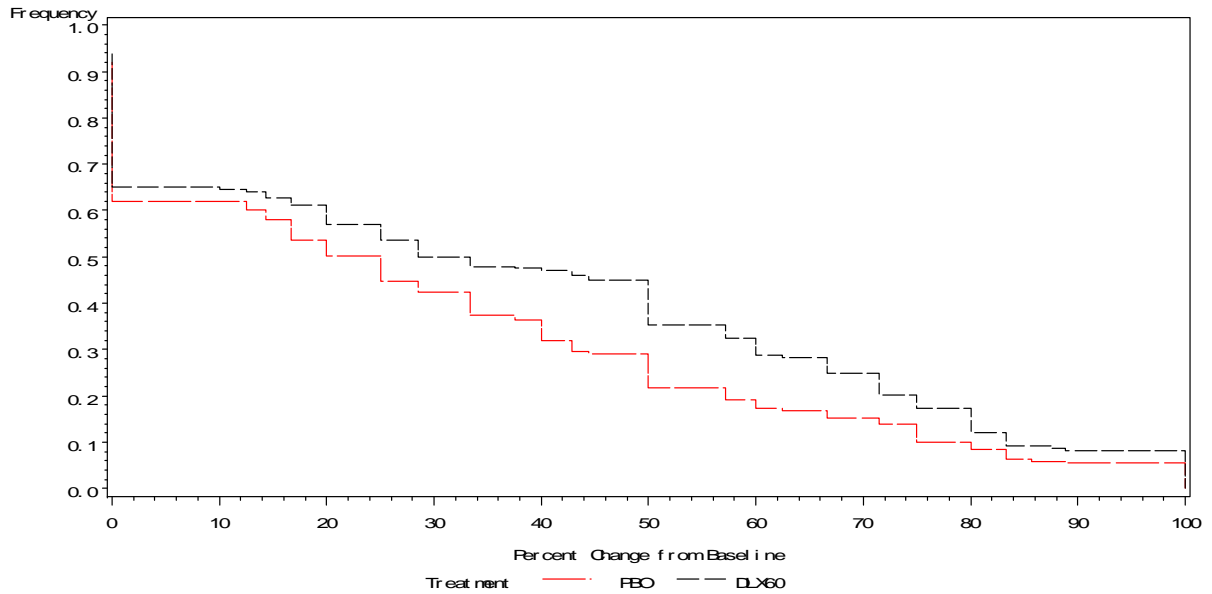
Note: mITT population excluded patients with no post-baseline observations.

Reviewer’s Primary Efficacy Analysis: HMGC (ITT)

LS Mean Change (SE) from Baseline to Week 12 in BPI 24-hour average pain	Placebo (N=203)	DLX60mg (N=198)	P-value
ANCOVA/BOCF*	-1.5 (0.15)	-2.0 (0.15)	0.004
ANCOVA/mBOCF*	-1.8 (0.18)	-2.6 (0.18)	<0.001

*P-value calculated from ANCOVA model with terms for treatment, site, and baseline score as covariate.

Reviewer’s Continuous Responder Analysis on Primary Efficacy Variable: HMGC (ITT)



Note: P-value of **0.024** is generated by van der Waerden test.

The review team performed additional exploratory analyses on the individual doses. In Study HMEP, Dr. Kim's analyses did not demonstrate a statistically significant treatment effect for the 60 mg dose. The following table reproduced from page 14 of Dr. Fields' review is Dr. Kim's summary of the collective evidence supporting the efficacy of Cymbalta for the primary outcomes in the OA and CLBP trials:

Summary of Primary Efficacy Analyses

Prespecified primary analysis of 60mg-120mg	HMEN (CLBP)		HMEP (OA)	HMFG (OA)		HMGC (CLBP)
MMRM	P<0.05		P<0.05	P<0.05		
ANCOVA/BOCF	P<0.05		NS	P<0.05		
ANCOVA/mBOCF	P<0.05		P<0.05	P<0.05		
CRA/vdW*	P<0.05		NS	P<0.05		
Focusing on DLX60mg**		Focusing on DLX60mg up to week 7			Focusing on DLX60mg up to week 7	Prespecified primary analysis of 60mg
MMRM	P<0.05		NS			P<0.05
ANCOVA/BOCF	P<0.05	P<0.05	NS	P<0.05	P<0.05	P<0.05
ANCOVA/mBOCF	P<0.05		NS	P<0.05		P<0.05
CRA/vdW*						P<0.05

*vdW stands for van der Waerden test comparing two cumulative responder curves.

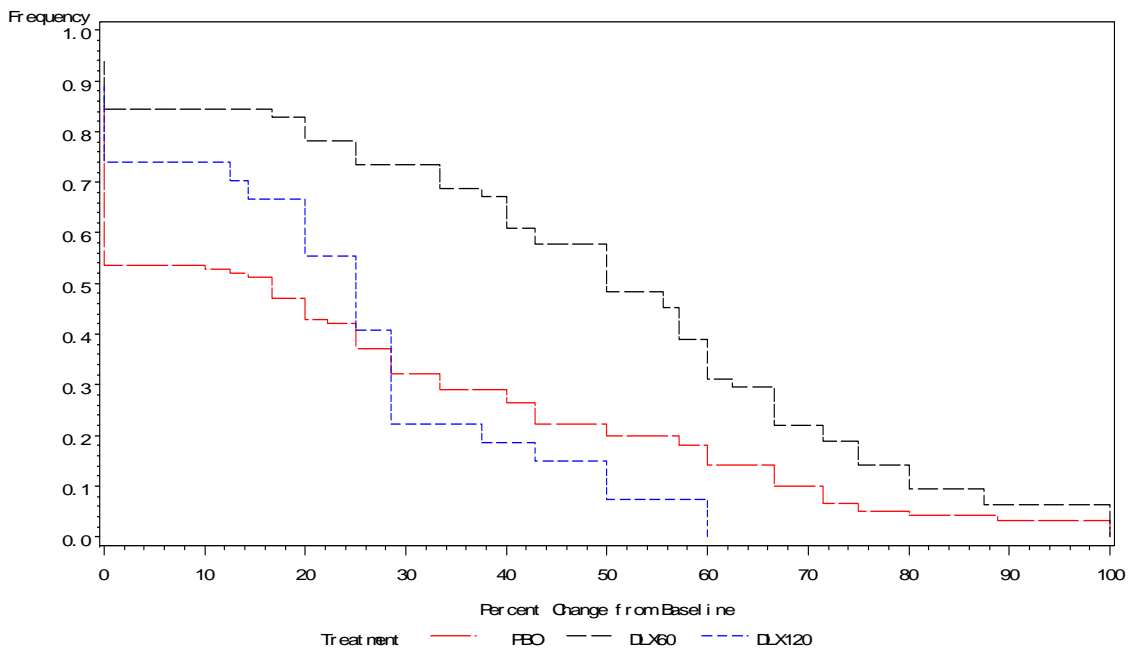
** Post-hoc analyses on duloxetine 60mg dose in HMEN, HMFG, and HMGC were conducted on ITT population and analysis in HMEP was conducted on the sub-population with patients re-randomized to duloxetine 60mg and placebo patients. Patients who did not show at least 30% pain reduction at Week 7 regardless of randomized treatment group were treated as failures.

At the advisory committee meeting, Dr. Kim presented his exploratory analyses comparing the efficacy of the 60 mg and the 120 mg doses in continuous responder curves. Dr. Kim made the following comments and presented the slides reproduced below the comments:

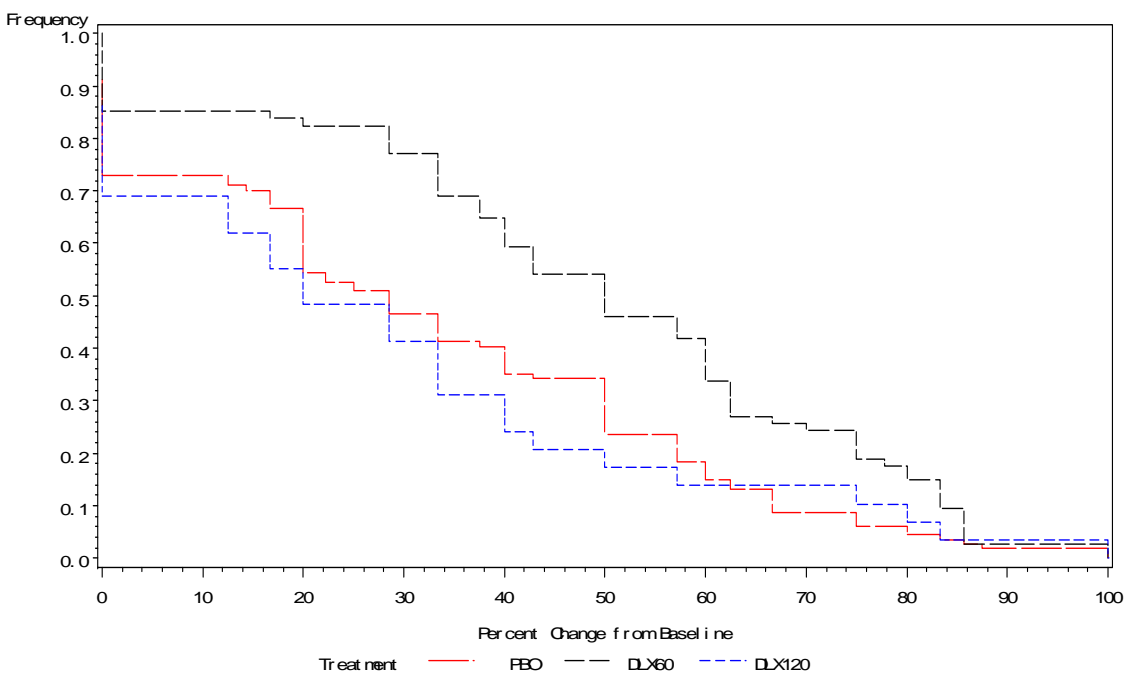
After splitting DLX into two subgroups...DLX60mg/60mg (denoted by black) is separated from placebo as in the original curves. However, DLX60mg/120mg (denoted by blue) is not separated from placebo and overlaps with placebo.

This suggests that the efficacy of the flexible dose of DLX is mainly driven by the DLX60mg dose and that DLX120mg is not contributing to the efficacy of DLX.

Exploratory continuous responder curves – HMEN



Exploratory continuous responder curves – HMFG



The sponsor also performed secondary analyses of improvement in function and improvement on a global impression of change scale. Based on Dr. Kim's analyses, these endpoints did not consistently demonstrate a statistically significant treatment effect for Cymbalta and, thus, they will not be included in the product label. However, the results of these analyses were supportive of the overall improvement in pain.

Dr. Fields' summary of the evidence in support of efficacy from page 16 of her review has been reproduced below:

Efficacy Summary and Conclusions

1. In terms of the primary efficacy endpoint analyses based on the Division's preferred conservative methods of imputation of missing data:
 - a. Trial HMEN demonstrated efficacy of duloxetine 60-120mg in the treatment of non-neuropathic chronic low back pain.
 - b. Trial HMGC demonstrated efficacy of duloxetine 60mg in the treatment of non-neuropathic chronic low back pain.
 - c. Trial HMFG demonstrated efficacy of duloxetine 60-120mg in the treatment of chronic pain associated with osteoarthritis.
 - d. Trial HMEP failed to demonstrate efficacy of duloxetine 60-120mg in the treatment of chronic pain associated with osteoarthritis based on the most conservative analysis for the ITT population (BOCF imputation for missing data). However because the mBOCF analysis for the ITT population was significant, and the separation of the placebo and treatment group curves in the continuous responder analysis, this trial can lend supportive evidence to findings of efficacy for trial HMFG in patients with chronic pain due to OA.

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2. Continuous responder analyses demonstrated statistically significant separation between placebo and treatment in Trials HMEN, HMGC, and HMFG.
3. Additional *post hoc* analyses demonstrated:
 - a. Trials HMFG (OA) and HMEN (CLBP) demonstrated efficacy of duloxetine 60mg at Week 7 (of 13 week trial).
 - b. There is no evidence, according to an exploratory analysis, that duloxetine 120mg confers benefit over duloxetine 60mg for patients who did not respond to 60mg during the first 7 weeks of treatment.

The cumulative evidence of efficacy from the above trials shows that duloxetine has analgesic efficacy at the combined 60mg-120mg dose and at the 60mg dose for OA and CLBP. Two trials in CLBP and one trial in OA were clearly positive based on the conservative statistical analyses preferred by the Division. One OA trial (HMEP) lends supportive evidence of efficacy based on the mBOCF analysis and the cumulative responder analysis. An exploratory analysis showed there is no evidence that the 120mg dose confers any benefit in terms of efficacy to patients who did not respond to 60mg.

I agree with the review team that the applicant has provided adequate evidence of the efficacy of Cymbalta 60 mg in the treatment of CLBP and the pain of OA.

8. Safety

The following table reproduced from page 17 of Dr. Fields' review summarizes the overall subject exposure to Cymbalta:

Exposure to duloxetine

Number of Patients Exposed by Analysis Group				
OA and CLBP Trials (HMEN, HMEP, HMFG, HMEO, and HMGC)		Placebo-controlled Trials for all indications (excluding OA and CLBP)		Total exposure to DLX for all other Indications
PBO	DLX	PBO	DLX	DLX
N=689	N=839	N=7010	N=9685	N=29,237

There was one death in the OA/CLBP safety database. An 82 year old woman who had been treated with Cymbalta for 39 days for OA at doses of 30 mg and 120 mg died ten days after discontinuing the medication. Her death was attributed to cardiopulmonary arrest and Dr. Pokrovnichka's review of the narrative for this case resulted in her conclusion that the death did not appear to be related to treatment with Cymbalta.

Overall, the adverse event profile of Cymbalta in the OA and CLBP patient populations was not clinically distinct from the safety profile demonstrated in the previously approved patient populations. The frequency of serious adverse events was greater in the Cymbalta-treated subjects compared to the placebo-treated subjects, but the events occurred with very low frequencies in any particular specific system/organ class and did not appear to be dose related.

Again, there were more discontinuations due to adverse events in the Cymbalta-treated subjects. The most common reasons for discontinuation were events related to nausea and sleep disturbances such as somnolence and insomnia. Overall, more Cymbalta-treated subjects experienced treatment-emergent adverse events compared to the placebo-treated subjects. The most common adverse events were: nausea, insomnia, dizziness, dry mouth, somnolence, constipation, and fatigue. Most of these appeared to be dose dependent.

The incidence and types of hepatic-related adverse events were consistent with what is already described in the Cymbalta label. The most common hepatic adverse events were elevated enzymes. Marked elevations were infrequent. There were no enzyme elevations associated with bilirubin elevations and no cases that met Hy's Law criteria for drug induced liver inflammation. The majority of the hepatic adverse events occurred in subjects with pre-existing liver disease and the enzymes generally returned to normal levels, even on continued treatment with Cymbalta.

As noted above, Dr. Stone, a primary reviewer in the DPP, undertook a series of extensive analyses and reviews of the hepatotoxicity of Cymbalta. He concluded that the incidence of clinically relevant liver injury with Cymbalta was significantly higher than that seen with other antidepressants. He recommended that the labeled warnings for Cymbalta hepatotoxicity be increased to include a boxed warning. There has been extensive internal Agency discussion of Dr. Stone's reviews and conclusions. The DAAP clinical review team, the reviewers from OSE, and clinical senior management reviewers all felt that the overall profile of the hepatotoxicity of Cymbalta had already been adequately addressed in the product labeling and that a boxed warning was not warranted, as the degree of hepatotoxicity was not clinically more concerning than that of other drugs in this pharmacologic class which do not have boxed warnings.

On May 18, 2010, Dr. Thomas Laughren, Director of DPP, filed a memo analyzing Dr. Stone's reviews and conclusions. Dr. Laughren's memo carefully addresses each of Dr. Stone's reasons for recommending the additional warning language, and disputes each with reasoned arguments supported by the available data. The following, from the conclusion section of Dr. Laughren's memo, has been reproduced from page 4 of that document:

This has been an evolving process over the last 6 years, and I think we have established that duloxetine is capable of causing substantial transaminase elevation, associated in some cases with clinical symptoms. I also agree with the view that this is a drug that bears continued close surveillance regarding hepatotoxicity. I agree, however, with Dr. Crensil that a sufficient case has not been made to justify adding a box warning regarding hepatotoxicity for duloxetine. Duloxetine already has, as I have noted, very strong labeling regarding hepatic injury, and I think that labeling remains adequate, given the current level of evidence for hepatic injury. Although there is an impressive amount of evidence pointing to hepatic injury for duloxetine, the most important missing piece to support a box warning and second line status is the absence of clean cases of death or transplant due to hepatic failure. Given this doubt, I am reluctant to ask for a box warning for this drug. The only rationale for a box warning would be that we had reached a conclusion that this drug should not be used as a first line treatment for its approved indications. I do not believe we have reached that point.

At the advisory committee meeting held in August of this year, Dr. Victor Crentsil, Deputy Director for Safety in DPP, presented an overview of that division's assessment of the hepatotoxicity of Cymbalta and clearly expressed the conclusion that the overall database of hepatic adverse events and laboratory data from all patients and subjects exposed to the drug over many years did not support an increased level of warning in the product label. The committee members concurred with this conclusion. I also concur with the DPP conclusion which is consistent with that of my own clinical review team and the other clinical CDER staff who have reviewed this matter, with the exception of Dr. Stone.

9. Advisory Committee Meeting

A joint meeting of the Anesthetics and Life Support Drugs Advisory Committee and the Drug Safety and Risk Management advisory committee was convened on August 19, 2010, at which this application was reviewed. The committee was asked to address the overall risk-benefit profile of a broadened indication for pain. They were specifically not asked to address what the actual indication should be because, as I noted above, we had already decided on the appropriate category for this application by that time. The following questions were posed to the committee members (with the actual vote tallies following each question):

1. Does the data from the clinical trials provide adequate evidence of efficacy for the management of chronic low back pain?

Yes-8 No-5 Abstain-1

2. Does the data from the clinical trials provide adequate evidence of efficacy for the treatment of chronic pain due to osteoarthritis?

Yes-4 No-9 Abstain-1

3. Is there evidence that the 120mg dose provides additional efficacy over that provided by the 60mg dose?

Yes-2 No-12 Abstain-0

4. Does the safety profile of duloxetine and the overall risk-benefit profile for this product warrant expansion of the indication? Please consider the potential for hepatotoxicity due to duloxetine in addressing this question.

Yes-9 No-4 Abstain-1

5. Should this supplement for expansion of the pain indications for duloxetine to a broader population be approved?

Yes-8 No-6 Abstain-0

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Cymbalta

For the management of chronic musculoskeletal pain

November 4, 2010

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Dr. Fields has summarized the discussion that occurred at that meeting and I have reproduced it below from pages 21 and 22 of her review:

Summary of discussion

The majority of the AC members voted yes and felt that the data from the clinical trials in chronic low back pain supports the use of duloxetine for the management of CLBP. Some members remained concerned however regarding the homogeneity of the study population and the heterogeneity of CLBP presenting to physicians in clinical practice.

In contrast, the majority of AC members voted that the results of the clinical trials in OA patients did not support the efficacy of duloxetine in this condition. There was concern among some members that one successful and one failed study in OA patients represented equivocal results and they recommended additional studies in this population.

The Committee members voted that there did not appear to be evidence to support that the 120mg dose of duloxetine provided additional benefit over the 60mg dose, although some members stated that it may be useful to some patients, and recommended additional studies in larger groups of patients to obtain evidence of added benefit for this dose beyond that provided by the 60mg dose.

There was extensive discussion regarding the safety profile of duloxetine and its potential for hepatotoxicity. Both the Applicant and the Agency, specifically the Division of Psychiatry Products and the Office of Safety and Epidemiology, presented the data that had been reviewed by Dr. Mark Stone and others in their divisions. The AC members felt that the safety profile of duloxetine was well characterized based on its use in large numbers of patients, and that the overall safety profile and concerns regarding hepatotoxicity should not preclude an expanded indication for duloxetine for the treatment of pain.

The committee's consensus was marginally in favor of recommending the Agency approve the expansion of the pain indication. However, those members who voted no expressed concerns over the numbers and types of studies that were done. They requested that additional studies be conducted to further define the efficacy and safety of duloxetine for the treatment of chronic pain conditions.

The clinical and statistical review teams disagree with the committee members regarding whether efficacy has been established for Cymbalta as a treatment for the pain of OA. While only one of the studies in OA demonstrated a statistically significant treatment effect for Cymbalta, both the division and the academic experts who attended the workshop discussed in Section 2 above have concluded that, once efficacy has been established via two adequate and well-controlled trials in one musculoskeletal condition, it is acceptable to extrapolate that finding to other similar musculoskeletal conditions with the support of a single trial in the second condition. (Of note, they also agreed that this extrapolation did not extend to conditions such as rheumatoid arthritis and ankylosing spondylitis.) Some committee members expressed concern that there were an equal number of trials in OA that demonstrated positive and negative results. However, we commonly find that multiple clinical trials in certain conditions, particularly those with patient-reported outcomes such as pain or depression, may have negative results, while positive results are more difficult to achieve. This may be the consequence of study design, regression to the mean, placebo effects, or any number of other factors that make it difficult to demonstrate a treatment effect in these conditions. While additional research is warranted to better understand this phenomenon and

to design more effective and efficient trials, this is the standard with which we must work at this time. Therefore, I support the conclusion of the review team that the sponsor has demonstrated efficacy in both CLBP and in the pain of OA, allowing for the broader indication of the management of musculoskeletal pain.

10. Pediatrics

The following summary of the Agency decision regarding pediatric study requirements for this application has been reproduced from page 22 of Dr. Fields' review:

The Applicant has requested a full waiver for pediatric studies because the conduct of such studies in the pediatric population would not be feasible due to extremely small numbers of patients with chronic musculoskeletal pain that is non-rheumatologic in origin. The studies in adults were conducted in patients with osteoarthritis and chronic low back pain. Osteoarthritis is not considered to be a condition that occurs in pediatric patients, and CLBP occurs in a very small number of pediatric patients.

The Waiver request was submitted to the Pediatric Research Committee (PeRC), and they are in agreement with the request. Therefore a waiver of pediatric studies for this indication is granted.

11. Other Relevant Regulatory Issues

There are no other unresolved relevant regulatory issues.

12. Labeling

The division and the applicant have reached consensus on the labeling language. However, it is important to provide some discussion of the framework upon which we have built our decision to employ the new and broadened indication, "for the management of chronic musculoskeletal pain." This decision was based on our attempt to find an appropriate and reasonable balance between assuring the safe use of analgesic drug products while providing increased access to these products for patients with a variety of painful conditions.

The availability of recently approved analgesic drug products has been limited by an ongoing discussion in the clinical and scientific communities about whether the established efficacy of a product in one painful condition can be extrapolated to other similar painful conditions. This discussion has focused on the paucity of sound data regarding the pharmacological mechanisms of many analgesic drugs, as well as the paucity of sound data regarding the underlying pathophysiology which results in the pain associated many disorders. While it is certainly true that a great deal is still to be learned about these drugs and about the painful conditions they treat, the concerns raised about extrapolation have resulted in our often limiting the indications for analgesic drugs to narrowly defined patient populations. These narrow indications have been intended to prevent the products from being prescribed to patients for whom they may not work, and thereby prevent those patients from experiencing the many serious toxicities often associated with these drugs. However, by limiting the wide

spread use of these drugs by employing narrow indications, the well-informed prescriber may not have had the option of trying out an analgesic product approved for one painful condition in a patient with a similar painful condition. While the indication does not limit “off-label” prescribing, it does often result in the patient not being reimbursed by their insurer, or in the prescriber having to spend a great deal of time and effort to convince the insurer of the appropriateness of the drug for the specific patient and the patient’s particular painful condition. For instance, while some products are approved for the treatment of the pain of diabetic peripheral neuropathy, and may well work in other painful, distal, symmetrical peripheral neuropathic disorders, the absence of a specific indication for those other conditions, or a more broadly worded indication, will often preclude the use of those drugs in patients with the related disorders.

In attempting to strike a reasonable balance, we decided to provide as broad an indication as possible, without expanding that indication to general use for chronic pain. Therefore, based on the input we received during the scientific workshop described in Section 2, tempered by the practicalities associated with prescribing, we decided to employ a somewhat broadened indication that is supported by the applicant’s efficacy data, “for the management of chronic musculoskeletal pain.” This indication will be added to their already approved analgesic and psychiatric indications. However, we have concluded that the four painful conditions, CLBP, pain of OA, FM and DPN, which would constitute the approved analgesic indications, do not provide an adequate representation of the myriad conditions that cause chronic pain to allow the even broader indication, “for the treatment of chronic pain.” In time, it may be possible that, with additional evidence of efficacy in the treatment of pain due to other neuropathic and perhaps visceral disorders, we will be more comfortable with approving the general chronic pain indication, given the attendant risks associated with the expected wide spread prescribing that would follow. As noted above, though some reservations were expressed, particularly regarding the use of the product in “musculoskeletal” conditions such as rheumatoid arthritis, the advisory committee members concluded that our approach was reasonable and supported by the data. Clearly, it is essential that the labeling be as clear and explicit as possible in order to assure that health care practitioners understand the basis for this indication and that the applicant does not promote inappropriate prescribing, such as for the treatment of rheumatoid arthritis. Based on the carefully crafted wording in the product label, which clearly states the specific painful conditions in which the product was studied and found to be effective, we believe we have provided a sound basis for appropriate prescribing and promotion.

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action

Approval

- Risk Benefit Assessment

The applicant has provided adequate data to support the effective and safe use of Cymbalta for the management of chronic musculoskeletal pain, as studied in patients with CLBP and pain due to OA. Cymbalta has been approved for other painful disorders and for certain psychiatric disorders for a number of years, and many thousands of patients have been exposed to the product. While the product does carry risks, particularly associated with hepatotoxicity, dermatological toxicity, depression and suicidality, these risks are rare and clearly explicated in the product labeling and they do not outweigh the benefit of Cymbalta in providing analgesia to patients suffering from a variety of chronic painful conditions, such as FM, DPN and chronic musculoskeletal disorders exemplified by CLBP and the pain of OA. Careful prescribing of Cymbalta to appropriate patients, with appropriate monitoring for potential side effects, will be predicated upon health care practitioners' familiarity with the product labeling and the manufacturer's and distributor's adherence to that labeling in all promotional efforts.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

BOB A RAPPAPORT
11/04/2010