

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
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CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	October 13, 2010
From	Ellen Fields, M.D., M.P.H., Clinical Team Leader
Subject	Cross-Discipline Team Leader Review
NDA/BLA #	22-516
Supplement#	Supplement no.
Applicant	Eli Lilly and Co.
Date of Submission	May 15, 2009
PDUFA Goal Date	March 15, 2010
Action Date	October 19, 2010
Proprietary Name / Established (USAN) names	Cymbalta/ duloxetine hydrochloride
Dosage forms / Strength	Oral capsule/ 60mg
Proposed Indication(s)	Management of Chronic Pain
Recommended Action:	Approval

Material Reviewed/Consulted	
OND Action Package, including:	
Primary Medical Officer Review	Anjelina Pokrovnichka, M.D.
Statistical Reviews	Youngman Kim, Ph.D., Dionne Price, Ph.D.
DDMAC	Mathilde Fienkeng, Pharm.D.
DSI	Susan Leibenhaut, M.D.

Cross Discipline Team Leader Review

1. Introduction

Duloxetine hydrochloride is a selective serotonin (5-HT) and norepinephrine (NE) reuptake inhibitor (SSNRI) which also has minor inhibition of dopamine reuptake. It is approved in the United States for the treatment of major depressive disorder (MDD, 2004), diabetic peripheral neuropathy (DPN), generalized anxiety disorder (GAD), maintenance treatment of major depression, and fibromyalgia (FM). This supplement was submitted by the Applicant to obtain a general indication for Cymbalta for the treatment of chronic pain. The Applicant has submitted trials conducted in patients with chronic pain due to osteoarthritis (OA) and chronic low back pain (CLBP). The general chronic pain indication would be based on findings from those studies, in addition to previous findings of efficacy in patients with DPN and fibromyalgia. Cymbalta is the first non-opioid, non-NSAID to be evaluated for this indication. Its mechanism of action as an analgesic differs from opioids and NSAIDs, in that serotonin and norepinephrine are thought to mediate analgesia in the brain and spinal cord. Duloxetine is believed to act via the potentiation of descending inhibitory pain pathways.

2. Background

The development program for duloxetine hydrochloride for the treatment of chronic pain/fibromyalgia was conducted under IND 63,615 and was first submitted to the Division of Anesthesia, Analgesia, and Rheumatology Products (DAARP) in March 2001.

The proposed indication for duloxetine at the time of the Pre-IND meeting held on September 7, 2005 was CLBP. The Division recommended that a broader pain indication be sought, that studies in two appropriate pain populations be conducted, and that one positive study in each population would be sufficient. During a teleconference held on March 7, 2006, the Applicant was told specifically that one successful study in CLBP and one in OA would be sufficient to obtain a chronic pain indication.

On May 15, 2008, a NDA application for the management of chronic pain (NDA 22-333) was submitted to the Division. This NDA application was subsequently withdrawn on November 26, 2008, after the Applicant was notified that the Division did not agree with the efficacy results in their submission.

To support a chronic pain indication, the Applicant has conducted clinical trials in four chronic pain conditions, DPN, fibromyalgia, OA, and CLBP. In addition to the already approved pain indications of DPN (NDA 21-733) and fibromyalgia (NDA 22-148), the Applicant has submitted the following five new clinical trials, three in CLBP, and two in OA: HMEP (OA trial), HMEN (CLBP trial), HMFG (OA trial), HMEO (CLBP trial), and HMGC (CLBP trial).

Overseas, duloxetine is also approved for treatment of stress urinary incontinence (SUI) and international names include Yentreve, Xeristar, and Ariclaim.

3. CMC/Device

none

4. Nonclinical Pharmacology/Toxicology

none

5. Clinical Pharmacology/Biopharmaceutics

none

6. Clinical Microbiology

none

7. Clinical/Statistical- Efficacy

Dr. Anjelina Pokrovnichka performed a full review of the clinical trials submitted in support of the efficacy of Cymbalta for the treatment of chronic pain. What follows is a summary of her review, along with a summary of the statistical review performed by Youngman Kim, Ph.D.

Applicant has submitted the following five clinical trials, three in CLBP, and two in OA: HMEP (OA), HMFG (OA), HMEN (CLBP), HMEO (CLBP), and HMGC (CLBP). The first four study reports were submitted at the time of filing and HMGC was submitted with the 120-day safety update. Although this study was submitted with the 120-day update, it was reviewed in full by Dr. Pokrovnichka.

All of primary chronic pain trials in OA and CLBP had similar key characteristics. Study subjects were required to have had chronic pain for at least three months prior to entry and a baseline pain score of four or greater on an 11-point Likert scale. Patients with major depressive disorder (MDD) were excluded from all trials. To focus on patients with non-neuropathic back pain, CLBP trials excluded patients with neurological deficits or clinical evidence of either central findings (spinal stenosis) or peripheral neuropathy (radiculopathy). Patients were allowed to remain on their regular dose of non-steroidal anti-inflammatory drugs (NSAIDs) provided that they were using them at the time of enrollment. Randomization was stratified by NSAID use.

All trials were considered to be adequate and well-controlled based on the trial design. The following summarizes the design of each trial as described in Dr. Kim's 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).

Statistical Analyses

The primary efficacy endpoint chosen by the applicant for all OA and CLBP trials was the change from baseline to Week 13 (Week 12 for HMGC) in pain severity. The primary analysis for the flexible-dose trials (HMFG, HMEP, and HMEN) was based on the combined 60-120mg QD duloxetine arm versus placebo. In all five trials, a mixed-model repeated measures analysis (MMRM) was pre-specified for the primary efficacy measure. To assess the impact of missing data on the ANCOVA analysis, the additional analyses were conducted using last observation carried forward (LOCF), baseline observation carried forward (BOCF), and modified BOCF (mBOCF) imputation strategies. In the mBOCF approach, a BOCF strategy was used to impute missing data from dropouts due to lack of efficacy (LOE) or adverse event (AE) and an LOCF strategy was used to impute missing data from dropouts due to other reasons.

The Applicant's primary analysis was conducted on the modified intent-to-treat (mITT) population defined as all patients who were randomized and had baseline scores and at least 1 post-baseline observation.

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.

For the analysis of the secondary outcome variables (Patient Global Impression of Improvement (PGI-I) and the Western Ontario and McMaster Universities (WOMAC) physical function subscale), an ANCOVA model with terms for treatment, NSAID use, site, and baseline score as covariate was used. In order to adjust for multiple testing on these secondary endpoints, a serial gate-keeper multiple testing methods was used, i.e., PGI-I and WOMAC physical function subscale were tested sequentially only if the primary endpoint was statistically significant.

Study HMEO failed to show efficacy of duloxetine for the treatment of CLBP and the results will not be discussed below.

Results

Study HMEP (OA) was a 13-week, double-blind, placebo-controlled, 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.

Of the 231 subjects randomized, 25% discontinued prior to the end of the study, 20% from the placebo group, and 31% from the combined 60-120mg duloxetine group. As expected, a larger proportion of patients in the duloxetine group (14%) dropped out due to AEs compared to the placebo group (6%), however the same proportion (2%) dropped out due to lack of efficacy in each treatment group. Dropouts due to either "subject decision" or "other" comprised 11% of the placebo group and 15% of the duloxetine group. No important imbalances were noted with respect to demographic variables of age, race, sex, and weight, or baseline pain scores.

The primary efficacy variable was the change from baseline to Week 13 in the weekly mean of the 24-hour average pain. A statistically significant treatment effect was achieved by patients

receiving DLX 60-120mg as compared to those receiving placebo using the Applicant’s MMRM analysis, but not ANCOVA/BOCF.

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.

Dr. Kim was not able to reproduce exactly the Applicant’s primary analysis, however when he conducted the same ANCOVA analysis with BOCF on the mITT population, his analysis resulted in a similar conclusion (p=0.338).

The Applicant’s primary analysis excluded four subjects who had no post-baseline observations. The following analysis of the ITT population conducted by Dr. Kim included those patients. The BOCF analysis and continuous responder analysis of the ITT population did not demonstrate a statistically significant difference between treatment groups, however the mBOCF analysis did. This was partly due to the fact that more than half of the dropouts from duloxetine were not attributed to clinical reasons such as LOE or AE and, therefore, the mBOCF used LOCF for those dropouts, which led to imputations of good scores to the majority of duloxetine dropouts. The Applicant had been asked to identify the underlying reason for early discontinuations attributed to subject decision or other as these frequently are a reflection of a treatment-related effect, either adverse event or lack of efficacy, and only one dropout in the subject decision group was adjudicated as an adverse event. Dr. Kim stated in his review that although the mBOCF analysis on the ITT population demonstrated a statistically significant difference between duloxetine and placebo, in light of the large proportion of subjects who dropped out for non clinical reasons (imputed as LOCF), and the failure of the conservative BOCF analysis and continuous responder analysis to show statistical significance, Dr. Kim considered this to be a failed study. The following table from Dr. Kim’s review illustrates these results.

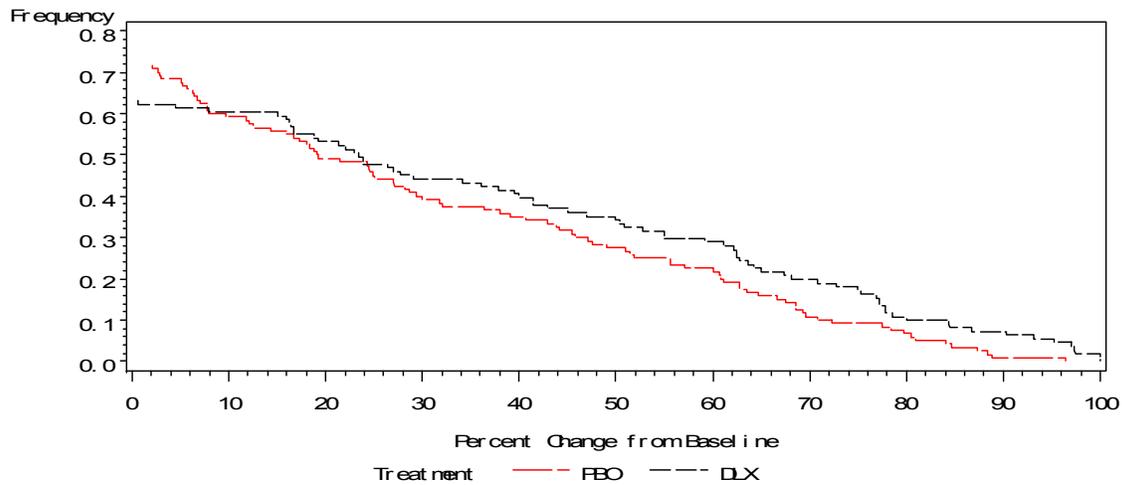
Reviewer’s Primary Efficacy Analysis: HMEP (ITT)

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.

The continuous responder curve from Dr. Kim’s review follows:

Cumulative Improvement in Pain from Baseline



The secondary efficacy analyses on PGI-I and WOMAC physical function appeared to demonstrate a statistically significant difference. However, since the primary analysis failed to demonstrate statistical significance this analysis does not fulfill the gatekeeper objectives.

In summary, only the ANCOVA/mBOCF analysis for the ITT population showed statistical significance for the primary efficacy endpoint. For reasons already stated, the MMRM analysis, and use of the mITT population (must have post-baseline assessment) for analysis, are not acceptable. As stated above, in view of the totality of evidence, this study was considered a failed study by Dr. Kim. However, Dr. Price, in her supervisory statistical memo, stated that although the primary endpoint failed to show efficacy using the most conservative imputation method (BOCF), in view of the statistically significant result when the mBOCF imputation was employed, and the separation of the placebo and treatment curves in the cumulative responder analysis, this study could provide supportive evidence of efficacy for duloxetine in the treatment of chronic pain due to OA.

Study HMEN (CLBP) was a 13-week, double-blind, placebo-controlled, 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 response criterion defined as at least 30% reduction in pain scores had their dose increased to 120mg.

Approximately 23% of the patients discontinued before the end of study. More patients from the duloxetine group (27%) discontinued compared to placebo group (19%). As expected, the majority of duloxetine dropouts (14%) were due to adverse events. Unexpectedly, the majority of placebo dropouts were not due to lack of efficacy, but due to subject decision. Six percent of placebo patients discontinued due to adverse events and 1% of placebo patients discontinued due to lack of efficacy.

There were no noticeable imbalances among treatment groups with respect to demographic variables of age, race, sex, and weight, or baseline pain scores.

The primary efficacy endpoint was the pain severity as measured by the BPI 24-hour average pain scores from baseline to Week 13. The Applicant’s analysis methods were identical to those of study HMEP.

The table below from Dr. Kim’s review illustrates the Applicant’s primary efficacy analysis; a greater treatment effect was achieved by patient receiving duloxetine 60-120mg as compared to placebo.

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.

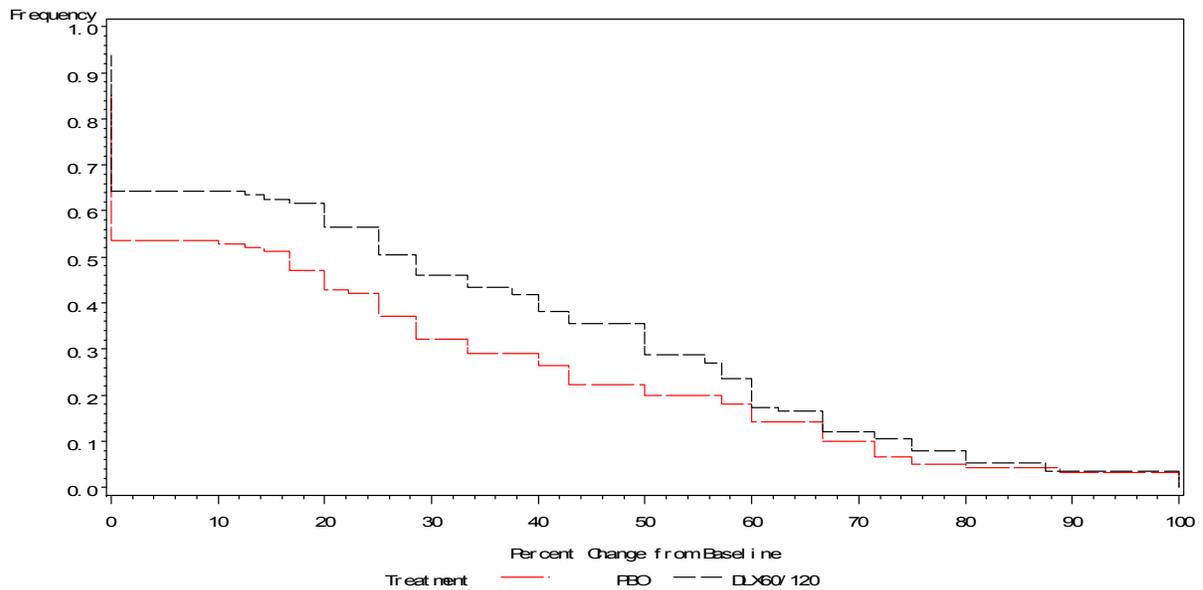
The applicant’s primary analysis excluded 12 patients who had no post-baseline observations. Dr. Kim conducted the same analysis on the ITT set including those patients. His BOCF and mBOCF analyses and continuous responder analysis also demonstrated a statistically significant difference, as shown below in the table and graph from his review.

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.

The secondary efficacy analyses on PGI-I and RMDQ-24 total score also demonstrated a statistically significant difference.

In summary, the conservative analyses on the primary endpoint performed by Dr. Kim provide evidence of efficacy for duloxetine for the treatment of CLBP, which is supported by the analyses of the secondary endpoints.

Study HMFG was a 13-week, double-blind, placebo-controlled, multi-center trial investigating the safety and efficacy of duloxetine in patients with OA knee pain. In HMFG, 256 eligible patients were randomized in a 1:1 ratio to DLX 60mg QD (n=128) or placebo (n=128). At Week 7, patients who did not meet response criteria, defined as at least 30% reduction in weekly mean of the BPI average score compared to baseline, had their dose increased to 120mg QD.

Approximately 20% of the patients discontinued before the end of study. More patients from the duloxetine group discontinued (27%) compared to placebo group (13%). As expected, majority of duloxetine dropouts were due to adverse events (19%). Unexpectedly, the proportion of placebo patients dropping out due to adverse events (5%) was similar to the dropout rate for lack of efficacy (4%) in this group.

There were no noticeable imbalances among treatment groups with respect to demographic variables of age, race, sex, and weight, or baseline pain scores.

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. The statistical methods used in HMFG were identical to those in HMEP.

A greater treatment effect was achieved by patients receiving duloxetine 60-120mg as compared with those receiving placebo, according to the Applicant’s analysis as shown in the following table from Dr. Kim’s review:

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.

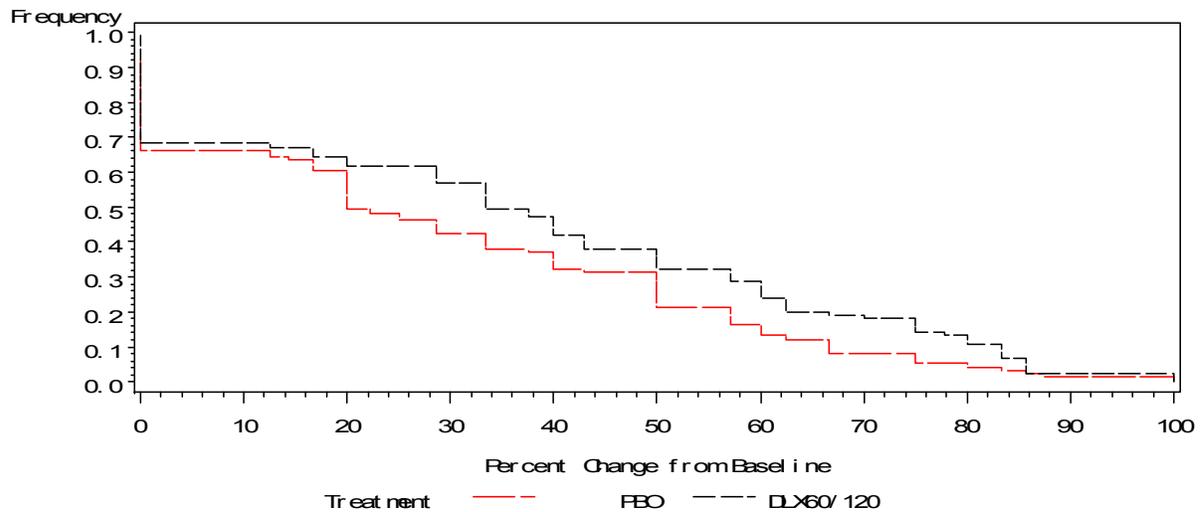
The Applicant’s primary analysis excluded eight patients who had no post-baseline observations. Dr. Kim conducted the same analysis on the ITT population including those patients. His BOCF and mBOCF analyses and continuous responder analysis on the ITT analysis set also demonstrated a statistically significant difference, as shown below in the table and figure from Dr. Kim’s review:

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.

The secondary efficacy analysis on PGI-I failed to demonstrate a statistically significant difference. Since the analysis on PGI-I failed, the sequential test procedure stopped and the next analysis on WOMAC physical function should not be considered.

In summary, the conservative analyses on the primary endpoint provided evidence of a treatment effect of duloxetine. Analysis of the secondary endpoints did not however provide supportive findings for the primary analysis.

Study HMGC was a 12-week, double-blind, placebo-controlled, multi-center trial investigating the safety and efficacy of duloxetine in patients with CLBP. In HMGC, 401 eligible patients were randomized in a 1:1 ratio to DLX 60mg QD (n=198) or placebo (n=203) stratified by non-steroidal anti-inflammatory drug (NSAID) use.

Approximately 24% of the patients discontinued before the end of study. More patients from the duloxetine group discontinued (26%) compared to placebo group (23%). As expected, the

majority of duloxetine dropouts (15%) were due to adverse events compared to 5% in the placebo group. The majority of placebo dropouts were not due to lack of efficacy (4%), but due to subject decision (7%).

There were no noticeable imbalances among treatment groups with respect to demographic variables of age, race, sex, and weight, or baseline pain scores.

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 statistical methods used by the Applicant were identical to those used in the other studies.

A greater treatment effect was achieved by patients receiving duloxetine 60mg as compared with those receiving placebo, according to the Applicant’s analysis as shown in the following table from Dr. Kim’s review:

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.

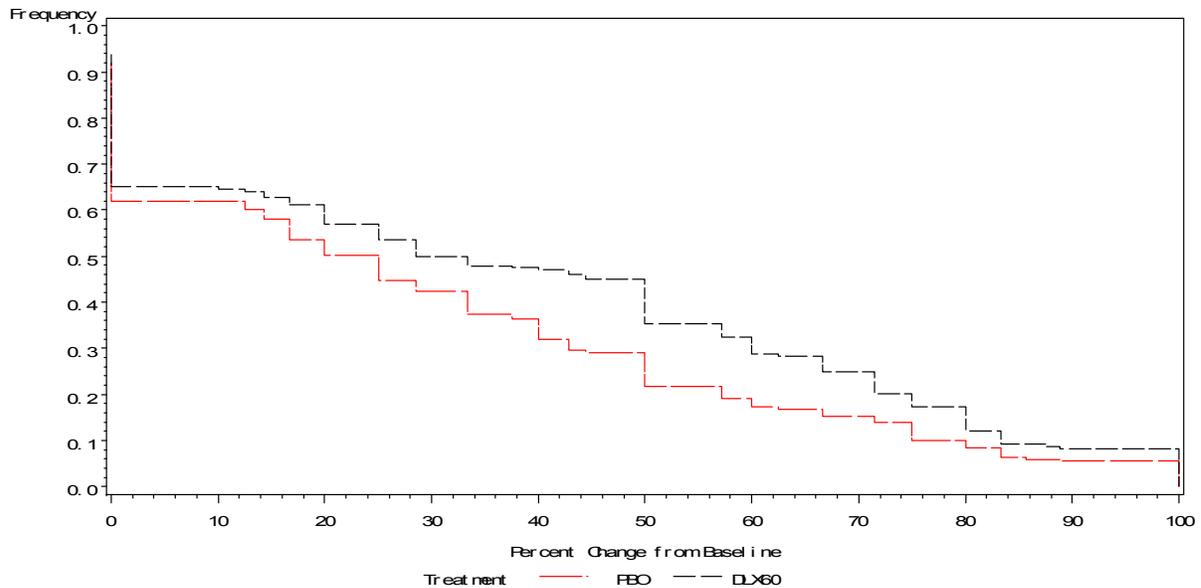
The Applicant’s primary analysis excluded seven patients who had no post-baseline observations. Dr. Kim conducted the same analysis on the ITT set including those patients. His BOCF and mBOCF analyses and continuous responder analysis on the ITT set also demonstrated a statistically significant difference as shown below in the table and figure from Dr. Kim’s review:

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 secondary efficacy analysis on PGI-I demonstrated a statistically significant difference while the secondary efficacy analysis on RMDQ-24 failed to demonstrate a statistically significant difference.

In summary, the BOCF analysis and continuous responder analysis conducted on the ITT population demonstrated a statistically significant difference between the duloxetine 60mg and placebo treatment groups. The secondary efficacy analysis on PGI-I demonstrated a statistically significant difference, while the analysis on RMDQ-24 failed.

Subgroup Analyses

Dr. Kim performed subgroup analyses across age groups, race, and sex. There were no statistically significant interactions noted for the primary efficacy variables for any study.

Post Hoc Efficacy Analysis of duloxetine 60mg in Studies HMEP, HMEN, and HMFG

Studies HMEP, HMEN, and HMFG were designed to perform efficacy analyses for the combined 60mg and 120mg doses. Because of concerns regarding dose-related hepatotoxicity of duloxetine, and the fact that doses above 60mg are not approved for the other pain indications (DPN and fibromyalgia), the Division requested the Applicant and Dr. Kim perform *post hoc* efficacy analyses for the 60mg duloxetine alone. What follows is a description of these analyses as stated in Dr. Kim’s review (DLX=duloxetine).

To investigate the effectiveness of DLX 60mg dose in studies HMEP, HMEN, and HMFG, post-hoc analyses were conducted. First, the pain changes at Week 13 were compared between the DLX 60mg group and the placebo group from studies HMEP, HMEN and HMFG. When comparing DLX 60mg with placebo in HMEP, only

patients re-randomized to DLX 60mg and patients initially randomized to placebo were compared. The analysis did not demonstrate a significant difference. When comparing DLX 60mg with placebo in HMEN and HMFG, the non-responders at Week 7 were treated as failures regardless of randomized treatment group. The results of the analyses demonstrated a significant difference between DLX 60mg and placebo at Week 13. Second, I compared DLX 60mg with placebo in terms of BPI average pain change from baseline to Week 7 in studies HMEN and HMFG. A statistically significant difference between DLX 60mg and placebo was demonstrated.

In conclusion, OA study HMEP failed to demonstrate a difference in pain when comparing DLX 60mg with placebo. The OA study HMFG yielded significant differences between DLX 60mg and placebo both in 7-week and 13-week analyses. Two CLBP studies, HMEN and HMGC, demonstrated statistically significant differences when comparing the DLX 60mg dose to placebo. The evidence of efficacy of the DLX 60mg dose was apparent in both 7-week and 13-week analyses in the two CLBP studies.

The following table from Dr. Kim’s review summarizes the collective evidence from the Applicant’s primary and sensitivity analyses, as well as Dr. Kim’s additional analyses, of both the combined 60 to 120mg duloxetine treatment, and of 60mg duloxetine alone.

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

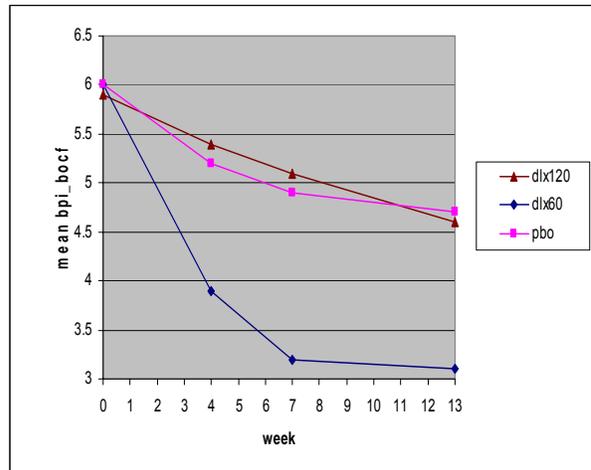
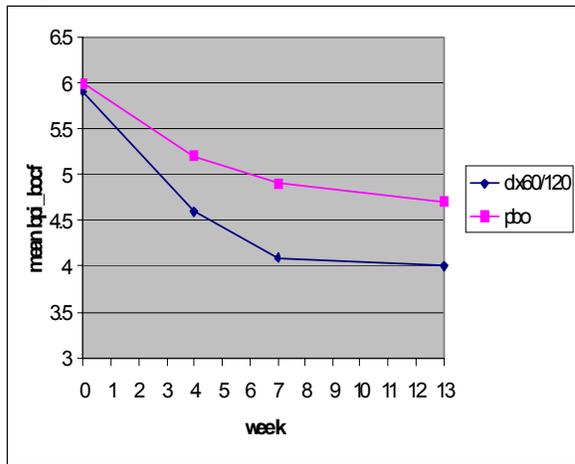
*vdW stands for van der Waerden test comparing two cumulative responder curves.

** 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.

Post Hoc Efficacy Analysis of Duloxetine 120mg

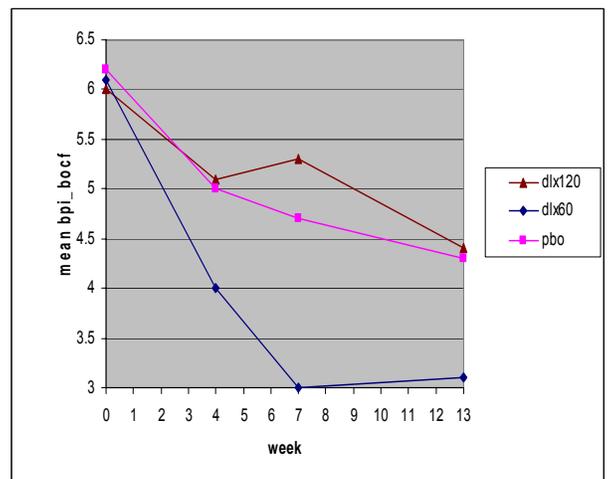
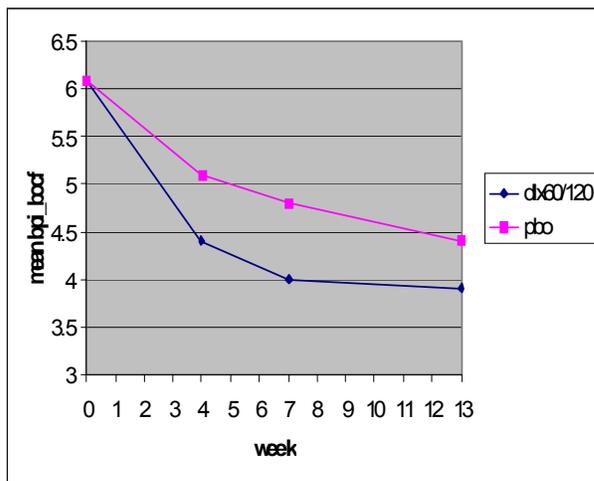
The clinical review team requested that Dr. Kim perform an additional *post hoc* analysis to assess whether the 120mg dose contributed to findings of efficacy for the combined 60mg-120mg dose. In two trials, HMEN and HMFG, subjects who did not respond to duloxetine 60mg at Week 7 were increased to duloxetine 120mg for another 6 weeks. As stated in Dr. Pokrovnichka’s review, Dr. Kim performed an exploratory mean plot analyses using BOCF of the BPI score comparing the three treatments, placebo, duloxetine 60mg and duloxetine 120mg (60mg for seven weeks followed by 120mg for six weeks). This showed that the duloxetine 120mg group presented similarly to the placebo group. Those subjects who showed no response to duloxetine 60mg during the first seven weeks of treatment did not respond to duloxetine at Week 13 despite a dose increase to 120mg at Week 7. Figures from Dr. Kim representing this exploratory analysis are shown below.

Exploratory Mean Plot for BPI (BOCF)-HMEN



(source: Dr. Youngman Kim)

Mean Plot for BPI (BOCF) -HMFG



(source: Dr. Youngman Kim)

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.
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.

4. Safety

A comprehensive review of the safety of duloxetine was completed by Dr. Pokrovnichka. The following summarizes her review.

The exposure to duloxetine was adequate to assess the safety for the intended population of patients with OA and CLBP as shown in the table below from Dr. Pokrovnichka's review. Exposure to duloxetine is described for the OA and CLBP trials, all placebo-controlled trials excluding OA and CLBP, and the total number exposed for all trials in all indications. Over 29,000 subjects have been exposed to duloxetine in clinical trials.

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

The safety review focused on findings from the OA and CLBP trials, since safety for the already approved pain indications (DPN and fibromyalgia) has already been reviewed. However, during the review, Dr. Pokrovnichka assessed whether there were any important differences between the safety profile for the OA and CLBP trials, and the other approved pain indications.

Review of safety data from OA and CLBP trials resulted in no new or unexpected safety signals. One death occurred during these placebo-controlled, double-blind trials. The patient was an 82 year old woman who was treated with duloxetine for 39 days for OA at doses of 30mg to 120mg. She died 10 days after discontinuing treatment due to cardiopulmonary arrest. Dr. Pokrovnichka reviewed the narrative and determined that this death did not appear related to duloxetine treatment.

The overall incidence of serious adverse events (SAEs) was greater in the duloxetine-treated patients (2.3%) than those treated with placebo (1.2%). SAEs were also analyzed for the first seven weeks and the last six weeks of the treatment, and the frequency of SAEs during each period was similar (1.3% vs. 1.2%). There was no dose dependent relationship for SAEs, nor any specific system/organ class involvement. No significant difference between treatment groups was observed for individual SAEs.

Significantly more duloxetine-treated patients discontinued due to adverse events (17%) compared with placebo-treated patients (6%). The most common reasons for early discontinuation were gastrointestinal (nausea) and sleep disturbance (somnolence/insomnia) related symptoms.

Significantly more duloxetine-treated patients (62.0%) than placebo-treated patients (50.0%) experienced at least one treatment-emergent adverse event (TEAE). Patients treated with duloxetine in the OA and CLBP trials experienced the following common adverse events more frequently than placebo treated patients: nausea, insomnia, dizziness, dry mouth, somnolence, constipation, and fatigue. Most of these events were dose dependant. Patients treated with duloxetine 120mg experienced the highest frequency of TEAEs during the first 7 weeks of treatment (71%-120mg, 53%- 60mg, 59% -20mg, and 37% placebo). During the second 6 weeks of treatment, 21% of the placebo group and 25-26% of all dose groups of duloxetine reported TEAEs. In general, the common TEAEs reported by duloxetine treated patients were

mild-to-moderate in severity, although more duloxetine-treated patients (12%) reported their AEs as severe compared to placebo-treated patients (5%). Overall, TEAEs occurred early in treatment (within the first week), and the majority of the events resolved between 15 and 30 days after onset.

The analyses of hepatic-related adverse events and liver enzyme elevation in the OA and CLBP trials were consistent with what is already described in the Cymbalta label. The most commonly reported hepatic-related TEAE was hepatic enzyme increase. Elevation in AST/ALT was not associated with bilirubin elevation, and no patients met the Hy's Rule criteria. Increase in transaminases was more frequently reported with duloxetine 120mg dose compared to duloxetine 60mg dose. However, no difference in the magnitude of the transaminase elevations was observed between the 60mg and the 120mg duloxetine dose groups. Analysis of the cases with elevated liver enzymes over time showed that the majority returned to baseline after drug discontinuation, and for some cases with less than three times the upper limit of normal increase, even with continuous treatment with duloxetine. The majority of the reported hepatic-related TEAEs occurred in patients with pre-existing liver enzyme abnormalities. Markedly abnormal increases in ALT and AST were infrequent in the primary chronic pain trials. Because of the small numbers it was difficult to evaluate for dose response. When such elevations occurred, ALT and AST levels either normalized or were trending back towards normal values at subsequent visits. In summary, analyses of hepatic laboratory analytes and hepatic-related AEs from OA and CLBP trials did not identify safety information that is different from what has been seen in other placebo-controlled trials of duloxetine.

Analysis of other laboratory analytes were consistent with the current Cymbalta label, with the exception of high bicarbonate levels observed during the first seven weeks of treatment more frequently by duloxetine 120mg treated patients (2.8%) than duloxetine 60mg (0.9%) or placebo (0%) treated patients, and greater, albeit small, decreases in calcium, chloride, sodium, and total protein for patients administered duloxetine 60mg compared with patients administered placebo. Dropouts due to chemistry abnormalities consisted of one subject each from the 60mg and 120mg duloxetine groups (hepatic enzyme increase) and one subject from the 120mg duloxetine group due to high creatinine.

Vital sign analyses showed that patients treated with duloxetine had mild increases in systolic and diastolic blood pressure, and pulse, and decreases in weight. These findings are consistent language in the Cymbalta label.

The Division requested that the Applicant perform Standard MedDRA Queries (SMQ) for depression and self-injury in the primary chronic pain patient population. No significant differences were observed between treatment groups for these SMQs. No patients reported a TEAE related to suicide/self-injury. There was no difference in the occurrence of signs and symptoms of depression between duloxetine and placebo treated patients, which was less than 1% for all groups.

Because there have been post-marketing reports of rash, angioneurotic edema, Steven-Johnson Syndrome, and urticaria associated with duloxetine use (and included in the Cymbalta label),

the Applicant was requested to perform an SMQ analysis for severe cutaneous reactions. Four patients treated with duloxetine during the placebo-controlled trials reported related TEAEs; two cases of conjunctivitis, and one each of stomatitis and mouth ulceration. There was one report of stomatitis in the placebo group and one of conjunctivitis.

Analysis of the 120-day Safety Update that included safety data from study HMGC was consistent with the safety analysis described above.

Dr. Pokrovnichka completed a review of the postmarketing data for duloxetine provided by the Applicant. There were no new or unexpected findings.

Analysis of Hepatotoxicity by Division of Psychiatry Products (DPP)

Dr. Marc Stone of DPP has conducted an analysis of pre- and post-marketing cases of hepatotoxicity in patients treated with duloxetine. The following paragraphs (in edited form) from Dr. Stone's analysis provide an historical perspective on the experience with duloxetine:

At initial approval, the duloxetine labeling included the observation of an increased incidence of elevated transaminase levels relative to placebo observed in clinical trials, a concern that duloxetine and alcohol may interact to cause liver injury and advice against prescribing to patients with substantial alcohol use.

During the first year of marketing experience with duloxetine there were a number of reports of hepatic toxicity. These included cases of hepatitis with abdominal pain, hepatomegaly, and elevation of transaminase levels to more than twenty times the upper limit of normal with or without jaundice. Those cases that showed the most severe hepatocellular damage were confounded by coexisting hepatitis C or alcohol consumption. There were also cases of cholestatic jaundice with minimal elevation of transaminase levels that were not confounded and strongly suggested duloxetine as a likely cause. These and other cases of suspected hepatotoxicity from duloxetine were analyzed in a previous review (3 Aug 2005). Consequently, the labeling was modified to reflect this post-marketing experience and extend the precaution against prescribing duloxetine to patients with chronic liver disease. These changes were announced in a Dear Health Care Provider letter dated 5 October 2005.

A subsequent review (7 June 2006) considered additional reports of hepatotoxicity associated with duloxetine as well as a package submitted by Lilly. A third review (16 May 2007) described additional relevant cases that appeared since the prior review and compared the pattern of reporting of hepatic adverse events associated with duloxetine to that of other antidepressant drugs. The review noted that there continued to be frequent reports of serious and fatal hepatotoxicity associated with duloxetine with an increasing number of these cases that appeared to fit Hy's rule criteria. In comparison with other antidepressant drugs, it appeared that only duloxetine and nefazodone had reporting rates for deaths with hepatic failure that were significantly higher than

the presumed background rate of one per million patient-years and also appeared to have incidence rate ratios that were significantly higher than the others.

A fourth review (25 Aug 2008) reported the results of a blinded case review which compared reports of drug-induced liver injury occurring within the first three years of marketing of duloxetine, paroxetine and nefazodone. The results of this process indicated that the incidence of reports of liver failure that are plausibly due to duloxetine is higher than comparable rates for paroxetine. The incidence rate for nefazodone was judged to be about twice that of duloxetine. This review recommended additional labeling changes concerning hepatotoxicity that were incorporated in conjunction with approval for the fibromyalgia indication.

A fifth review (4 Mar 2009) concerned itself with a report prepared for Lilly by the i3 Drug Safety group that examined the incidence of hepatic and cardiovascular adverse events in a retrospective cohort study derived from a health insurance claims database. It concluded that the incidence of significant liver injury associated with duloxetine was significantly higher than that seen in patients treated with other antidepressants, untreated depressed patients and patients without depression.

Dr. Stone has also completed an analysis of AERS reports of drug induced liver injury (DILI) and deaths from hepatic failure associated with duloxetine, in addition to analyses of clinical trial data. He has concluded that the rate of liver injury associated with duloxetine is three to eight times that seen with other commonly used antidepressants, and approximately 10% of these reports provide evidence of potentially serious liver injury. Approximately 15% of the potentially serious cases meet the criteria for Hy's rule. The reporting rate for death from hepatic failure has averaged 0.5 cases per million prescriptions. He recommends that the warnings concerning hepatotoxicity for duloxetine be elevated to a Box Warning.

The Division of Psychiatry Products is in the process of analyzing Dr. Stone's report in order to determine how the hepatotoxicity warning will be evidenced in the product label. Currently warnings regarding liver injury are in the WARNING section of the label. DPP is considering elevating these warnings to a BOX WARNING, and possibly making Cymbalta a second-line treatment for their indications (MDD and GAD).

5. Advisory Committee Meeting

A meeting of the Arthritis and Life Support Drugs Advisory Committee (ALSDAC) was convened on August 19, 2010 to discuss this application. The Applicant and the Agency presented efficacy and safety data from the NDA application along with extensive postmarketing safety data for duloxetine, focusing particularly on hepatotoxicity. The Committee was not asked to provide recommendations regarding the exact indication to be granted to the Applicant for this NDA, since this decision is within regulatory purview of the Division. The following are the questions posed to the Committee and the voting results:

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

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.

1. Pediatrics

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 presented to the Pediatric Research Committee (PeRC) on October 13, 2010, and they are in agreement with the request. Therefore a waiver of pediatric studies is granted for this indication.

2. Other Relevant Regulatory Issues

Clinical inspections were conducted at five clinical investigator sites in response to a routine audit request to assess data integrity and human subject protection for clinical trials conducted for approval. The data from all sites appear acceptable in support of the proposed indication.

3. Labeling

Review of the labeling is ongoing at this time. Additions to the current Cymbalta label will include changes to the Indication, Clinical Trials, and Adverse Events sections of the label. Cymbalta has also has a class-wide Medication Guide that will not be amended at this time. Since there is currently no new safety information, the Division has been advised by the Safety Requirements Team (SRT) that this Medication Guide does not constitute a REMS.

4. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action

I recommend an Approval action for NDA 22-516 for Cymbalta 60mg for the management of chronic musculoskeletal pain. Chronic pain conditions in which efficacy has been demonstrated include the already approved indications of diabetic peripheral neuropathic pain and fibromyalgia, and the conditions that are the subject of this application, chronic pain due to osteoarthritis, and chronic low back pain. As a result of this action, the approved analgesic indications for Cymbalta will be:

- The management of neuropathic pain associated with diabetic peripheral neuropathy

- The management of fibromyalgia
- The management of chronic musculoskeletal pain as demonstrated in chronic low back pain and chronic pain due to osteoarthritis
- Risk Benefit Assessment

The efficacy of duloxetine for the treatment of chronic low back pain (CLBP) and chronic pain due to osteoarthritis (OA) has been demonstrated in three 12-week clinical trials, two in CLBP (HMEN and HMGC) and one in OA (HMFG), with supportive evidence from a second trial in OA patients (HMEP), as discussed in the efficacy section of this review. Both the combined 60mg-120mg duloxetine doses, and 60mg duloxetine alone demonstrated efficacy in both populations as determined by the prespecified analyses of the primary endpoints for these studies, and additional *post hoc* analyses. An exploratory *post hoc* analysis also showed that the 120mg dose of duloxetine did not appear to contribute to efficacy in patients who did not respond to 60mg.

My conclusions regarding efficacy differ slightly from those in Dr. Pokrovnichka's review. The statistical review of the second OA study (HMEP) by the primary statistical reviewer assessed it to be a failed study. The analyses were reviewed secondarily by Dr. Price who stated in her review that although efficacy was not demonstrated using the most conservative analysis (ANCOVA/BOCF), the analysis of the data using ANCOVA/mBOCF did show a statistical difference between treatment groups. The continuous responder analysis also showed a separation between duloxetine- and placebo-treated patients. I agree with Dr. Price that this study lends supportive evidence to the efficacy of duloxetine for the treatment of chronic pain associated with OA.

There has been extensive internal discussion regarding whether there is adequate evidence of efficacy in a sufficient number of pain populations to grant this drug product the broad chronic pain indication. Lilly was told during meetings with the Division in 2005 and 2006, that if they were able to demonstrate efficacy in patients in two appropriate pain populations i.e., CLBP and OA, in addition to their already approved indication of DPN, they would have adequate evidence of efficacy to obtain an indication for chronic pain.

In December, 2009, the Division conducted a workshop in order to promote discussion among academic experts regarding the scientific basis for requirements for the number and types of clinical trials necessary to grant a chronic pain indication. The consensus of this workshop was that in order to assess whether a drug product would be effective for the treatment of chronic pain, it should be studied in multiple pain populations, including patients with musculoskeletal, peripheral and central neuropathic, and visceral pain syndromes, with replication of efficacy in some populations. The Division continues to conduct internal discussions regarding these recommendations, and is in the process of writing a guidance for industry to convey the Agency's current thinking regarding the number and types of studies necessary to obtain the broad analgesic indications.

At this time, the evidence of efficacy for duloxetine does not meet the Division's current standards for the very broad indication for the treatment of chronic pain. However, the

Division has determined that along with the already approved indications for the treatment of neuropathic pain associated with diabetic peripheral neuropathy, and the treatment of fibromyalgia, the studies in CLBP and OA provide sufficient evidence of efficacy to obtain an indication for duloxetine for the treatment of chronic musculoskeletal pain. My decision to recommend approval of Cymbalta for chronic musculoskeletal pain differs from Dr. Pokrovnichka's recommendation for approval only for the treatment of chronic low back pain. As stated previously, Dr. Pokrovnichka disagreed that there was adequate evidence of efficacy in patients with chronic pain due to OA. Additionally, at the time Dr. Pokrovnichka wrote her review in February, 2010, the Division had not yet discussed the chronic musculoskeletal pain indication, so her review does not mention that possibility.

There were no new or unexpected safety issues reported in this submission. I agree with Dr. Pokrovnichka that the safety of duloxetine in the OA and CLBP populations is similar to that described for the approved indications of fibromyalgia and diabetic peripheral neuropathy. Common non-serious adverse events associated with duloxetine include nausea, headache, dizziness, insomnia, and fatigue. Less common, more serious labeled events include hepatotoxicity, increased bleeding when co-administered with aspirin, NSAIDs, Warfarin or other anticoagulants, and development of serotonin syndrome. The adverse event profile appears to be dose related. The current duloxetine label has the SSRI/SNRI class-wide BOX WARNING for suicidality in adolescents.

As noted in the safety section of this review, DPP has conducted multiple reviews in concert with the Office of Safety and Epidemiology to attempt to assess the nature and impact of duloxetine-associated hepatotoxicity. Dr. Marc Stone has conducted analyses resulting in his recommendation to elevate the hepatotoxicity warnings from the WARNING and PRECAUTIONS section of the label to a BOX WARNING. The issue has been discussed extensively with management in the Division of Psychiatry Products and the Office of New Drugs, and the decision has been made by DPP not to include the hepatotoxicity warnings in the Box Warning because the available evidence does not support this change. Lilly is planning to conduct an epidemiologic study to further investigate duloxetine-related hepatotoxicity.

Hepatotoxicity associated with Cymbalta was also presented to the Arthritis Advisory Committee (AAC) in August, 2010. As stated earlier in this review, the Committee voted affirmatively that the risks of hepatotoxicity are not sufficient to preclude approval of Cymbalta for a broader pain indication, such as chronic musculoskeletal pain.

In conclusion, the benefits of treatment of chronic musculoskeletal pain with Cymbalta 60mg appear to outweigh the risks, based on review of the current submission, postmarketing safety data for all of Cymbalta's indications, extensive review of the risks of hepatotoxicity associated with Cymbalta treatment, and recommendations from the AAC.

- Recommendation for Postmarketing Risk Management Activities

The label will include a MedGuide.

Cross Discipline Team Leader Review

- Recommendation for other Postmarketing Study Commitments
None
- Recommended Comments to Applicant
None

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

/s/

ELLEN W FIELDS
10/13/2010