CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-148

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Disciplinary Team Leader Review
NDA 22-148
Cymbalta (duloxetine) for Fibromyalgia

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

MEMORANDUM

DATE: May 2, 2008

TO: File, NDA 22-148
File, NDA 22-427

FROM: Celia Jaffe Winchell, M.D.
Medical Team Leader

RE: Cross-Disciplinary Team Leader Review of Type 6 NDA

1 Introduction to Review

Cymbalta (duloxetine) is selective serotonin and norepinephrine reuptake inhibitor (SSNRI) approved initially (August 3, 2004) as an anti-depressant and subsequently for indications of the pain associated with diabetic peripheral neuropathy (DPN) on September 3, 2004, and generalized anxiety disorder (GAD) and maintenance treatment of major depression in 2007.[1] The present submission seeks a supplemental indication "for the management of fibromyalgia [redacted]
This is filed as a Type 6 NDA rather than an efficacy supplement because the approved application is held by the Division of Psychiatry Products. The referenced application is NDA 21-427.

The clinical studies of the effectiveness and safety of this product in fibromyalgia have been reviewed by Ricardo Dent, M.D. The application has also been reviewed by Joan Buenconsejo, Ph.D. (statistics), Emmanuel O. Fadiran, R.Ph., Ph.D., (clinical pharmacology and bipharmaceutics), and Raanan A. Bloom, Ph.D. (chemistry). In this memo, I will briefly review the effectiveness and safety data summarized in the primary clinical and statistical reviews, as well as any relevant information found in the primary reviews from the other disciplines, and make appropriate recommendations for action on the applications.

2 Background/Regulatory History/Previous Actions/Foreign Regulatory Actions/Status

Fibromyalgia (FM) is a chronic condition characterized by diffuse musculoskeletal pain, disordered sleep and fatigue. It affects primarily women, particularly between the ages of 30 to 50, but it is also seen in men as well as children and adolescents. It affects approximately 1-2% of the adult US population. It varies in severity but may be debilitating in a substantial proportion of patients. It is frequently associated with a variety of nonspecific complaints such as cognitive difficulties, depression, anxiety, and headaches.

The first product approved for the treatment of FM was Lyrica (pregabalin), a compound previously approved for the treatment of epilepsy, DPN, and the pain associated with post-herpetic neuralgia (PHN). The efficacy supplement for FM was approved on June 21. 2007.

Lilly requested priority review status for this application, citing advantages over Lyrica. However, absent comparative studies, this was not viewed as a basis for granting priority review, and this application was reviewed under a standard review clock.

[redacted]

3 CMC/Microbiology/Device

The only CMC issue in this application was an Environmental Impact assessment, which has been determined to be acceptable.

4 Nonclinical Pharmacology/Toxicology

No new non-clinical pharmacology/toxicology information was included in this application.

5 Clinical Pharmacology/Biopharmaceutics

Very little new clinical pharmacology information was included in this application. Most importantly, duloxetine pharmacokinetics are similar in healthy subjects and in patients with MDD, SUI, DPNP, or FM. The clinical pharmacology reviewer, Dr. Fadiran summarizes his findings as follows:

> Sparse plasma samples were obtained in Study HMEF and pooled with data from previous studies to enable identification of covariates because demographic distribution of the patients in HMEF consisted of mainly nonsmoking Caucasian females.
>
> Duloxetine PK were adequately described using a one-compartment model, parameterized in terms of absorption rate constant (Ka), oral clearance (CL/F), and apparent volume of distribution (V/F) (Table 1). The results from this population PK analysis are consistent with prior results with ethnic origin being the only additional significant covariate.

He also noted that:

> Women and nonsmokers have lower duloxetine oral clearance (CL/F) relative to men and smokers, respectively. Typically, women had 64% higher average duloxetine concentrations at steady state (Cav,ss) than males receiving the same dose of duloxetine. Similarly, nonsmokers had nearly 43% higher Cav,ss than smokers receiving the same dose of duloxetine. The effect of sex and smoking status is likely related to the higher CYP1A2 activity or concentration in men and smokers. The combined effects of sex, smoking, age, dose, and ethnic origin explained only about 8% and 27% of the interpatient variability in CL/F and volume of distribution (V/F), respectively. There remains a high degree of interpatient variability (60 to 100%) unexplained in duloxetine pharmacokinetics. Specific dose recommendations for duloxetine based upon sex, smoking status, age, dose, or ethnic origin are not warranted because the effect of these covariates are small relative to the magnitude of interpatient variability.

Dr. Fadiran's analyzed the data for evidence of an exposure-response relationship. A PK-PD relationship was explored between the baseline-to-endpoint change scores for the BPI average pain score and endpoint of PGI-Improvement during the 6-month acute therapy phase in Study HMEF. There did not appear to be an effect of duloxetine Cav,ss on 30% or 50% reduction in BPI pain score, but probability of a patient reporting an improvement on PGI-Improvement score increased with increasing duloxetine Cav,ss. It should be noted that Study HMEF did not include a wide range of dosing (all patients began on 60 QD and in the later phases could be titrated between 60 mg and 120 mg QD as needed/tolerated). The overall results of this study did not demonstrate an effect of duloxetine on pain scores. Therefore, the ambiguous results may reflect the fact that the study was conducted at a dose range where the dose-response curve is flat; analysis of a study using lower doses might show a stronger relationship between exposure and response.

5.1 *General clinical pharmacology/biopharmaceutics considerations*

The absorption, distribution, metabolism, and excretion of duloxetine as a molecular entity are described in the current label for Cymbalta® Delayed Release Capsules (updated in November 2007). Duloxetine is well-absorbed after oral administration with a Cmax at 6 hours, a half-life of about 12 hours (range 8-17), with steady-state achieved after three days of dosing. Duloxetine is eliminated mainly through hepatic metabolism involving two P450 isozymes, CYP1A2 and CYP2D6.

5.2 *Drug-drug interactions*

The labeling notes that both CYP1A2 and CYP2D6 are responsible for duloxetine metabolism and mentions interactions with:

- Inhibitors of CYP1A2
- Inhibitors of CYP2D6
- Drugs that Interfere with Hemostasis (e.g., NSAIDs, Aspirin, and Warfarin)
  Due to serotonergic effect on platelets, altered anticoagulant effects, including increased bleeding, have been reported when SSRIs or SNRIs are coadministered with warfarin.
- Drugs that Affect Gastric Acidity
  In extremely acidic conditions, Cymbalta, unprotected by the enteric coating, may undergo hydrolysis to form naphthol.
- Drugs Metabolized by CYP1A2
  Duloxetine is an inhibitor of the CYP1A2 isoform in in vitro studies.
- Drugs Metabolized by CYP2D6
  Duloxetine is a moderate inhibitor of CYP2D6.
- Monoamine Oxidase Inhibitors
  Concomitant use in patients taking monoamine oxidase inhibitors (MAOIs) is contraindicated due to the risk of serious, sometimes fatal, drug interactions with serotonergic drugs.

- Serotonergic Drugs
  Based on the mechanism of action of SNRIs and SSRIs and the potential for serotonin syndrome.
- Triptans
  Based on postmarketing reports of serotonin syndrome with use of an SSRI and a triptan.
- Alcohol
  Based on observation of liver injury in patients with heavy alcohol use
- CNS Drugs
  Due to CNS action of duloxetine.
- Drugs Highly Bound to Plasma Protein
  Duloxetine is highly bound to plasma protein, and may cause increased free concentrations another drug that is highly protein-bound.

5.3 *Pathway of Elimination*

Duloxetine is metabolized hepatically and only trace (<1% of the dose) amounts of unchanged duloxetine are present in the urine. Most (about 70%) of the duloxetine dose appears in the urine as metabolites of duloxetine; about 20% is excreted in the feces.

Patients with clinically evident hepatic insufficiency have decreased duloxetine metabolism and elimination. The labeling states that Cymbalta should not be used in patients with hepatic insufficiency. Population PK analyses suggest that mild to moderate degrees of renal dysfunction (estimated CrCl 30-80 mL/min) have no significant effect on duloxetine apparent clearance, but the label indicates that Cymbalta should not be used in patients with end-stage renal disease.

5.4 *Demographic interactions/special populations*

Although sex, smoking status, age, ethnic origin, and dose had a statistically significant effect on duloxetine PK, there remains a high degree of interpatient variability (60 to 100%) unexplained in duloxetine pharmacokinetics. Specific dose recommendations for duloxetine based upon sex, smoking status, age, dose, or ethnic origin are not warranted because the effect of these covariates are small relative to the magnitude of interpatient variability.

6 Clinical Microbiology

Not applicable

7 Clinical/Statistical

This application includes data from four placebo-controlled studies and one dose-controlled study with open-label run-in, described in the table below:

Study ID	Design/ Control type	Number of subjects by arm entered/ completed	Duration	Gender	Primary Endpoint(s)
HMBO	Parallel, double-blind, placebo-controlled	Randomized: 104 duloxetine, 103 placebo. Completed: 58 duloxetine, 66 placebo.	3 months	Male and female patients	Reduction in FIQ Pain Item and FIQ Total Score
HMCA	Parallel, double-blind, fixed dose, placebo-controlled study	Randomized: 234 duloxetine, 120 placebo. Completed: 148 duloxetine, 68 placebo.	3 months	Female patients	Reduction in average pain item of the BPI scale
HMCJ	Parallel, double-blind, fixed dose, placebo-controlled study	Randomized: 376 duloxetine, 144 placebo Completed 3-month therapy phase: 242 duloxetine, 84 placebo Completed 6-month therapy phase: 206 duloxetine, 72 placebo	3 month therapy phase, 3 month continuation phase	Male and female patients	Reduction in average pain item of the BPI scale and improvement in the PGI-I scale
HMEF	Parallel, double-blind, placebo-controlled study	Randomized: 162 duloxetine, 168 placebo Completed: 101 duloxetine, 103 placebo	6 months	Male and female patients	Reduction in average pain item of the BPI scale and improvement in the PGI-I scale
HMEH	open-label period, followed by a double-blind period.	Randomized: 307 duloxetine Completed: 195 duloxetine (duloxetine 60mg: 71 Duloxetine 120mg: 124)	2 months open label followed by 1 year double-blind	Male and female patients	Safety and tolerability Persistence of efficacy was also assessed

Abbreviations: BID = twice daily; BPI = Brief Pain Inventory; FIQ = Fibromyalgia Impact Questionnaire; HMBO = Study F1J-MC-HMBO; HMCA = Study F1J-MC-HMCA; HMCJ = Study F1J-MC-HMCJ; HMEF = Study F1J-MC-HMEF; HMEH = Study F1J-MC-HMEH; ID = identification; MDD = major depressive disorder; PGI-I = Patient's Global Impressions of Improvement.

Source: Clinical study reports for Study HMBO, Study HMCA, Study HMCJ, Study HMEF, and Study HMEH.

Study HMEF, based on Lilly's analysis, did not provide evidence of efficacy for duloxetine 60 mg QD. Study HMBO did not involve the dose recommended for marketing, 60 mg QD. The efficacy claims in this application rest primarily on the results of Studies HMCA and HMCJ, [redacted]

As noted above, during the development program, the Division communicated with Lilly on several occasions concerning the data necessary to support this supplemental application. At the time of initial interaction, Studies HMCA (in women only) and HMBO were complete. Lilly was informed that the results of study HMBO (which, by Lilly's report, showed efficacy on its primary endpoint only in a subset analysis excluding male patients) would not be considered appropriate to support an efficacy supplement because of the "failure of the endpoints in the overall population." Moreover, Lilly was informed that it would be necessary to study both men and women, but "the number of men studied would not need to be powered for a statistically significant subgroup analysis, but to provide enough information to give some confidence as to whether men demonstrated any benefit or worsening of their symptoms." Studies HMCJ, HMEF, and HMEH included male patients.

Global ratings of improvement and scales assessing function (including the Fibromyalgia Impact FIQ) were included in the studies in keeping with the advice provided at the time of protocol development.

7.1 *Efficacy*

7.1.1 Dose identification/selection and limitations

Dose selection for the Phase 3 trials appears to have been based primarily on the experience with Cymbalta in the treatment of other conditions (such as depression and neuropathic pain).

The labeled dose for the other approved indications in the Cymbalta label is 60 mg once daily, without regard to meals. The label notes that some patients may benefit from beginning at 30 mg/day and that non-responders may benefit from titration to 120 mg/day. Although Lilly proposed that [redacted] the Division advised that it would be necessary to explore lower doses as well to identify a minimum effective dose. One study, HMCJ, included a 20 mg arm for the first three months of treatment, after which those in the 20 mg arm were titrated to 60 mg. Lilly anticipated this dose would be shown to be ineffective, and that its inclusion would be interpreted as supporting the conclusion that the dosing for FM should be [redacted] However, as discussed below, in the single study in which it was evaluated, the 20 mg dose appeared in some analyses to be as effective as higher doses of Cymbalta.

The data also suggest little incremental benefit for the 120 mg/day dose over the 60 mg/day dose. Neither HMCA, which included 120 mg/day in divided doses (60 mg BID) nor HMCJ, which included a single daily dose of 120 mg/day, demonstrated any benefit

of the higher dose. In addition, the design of Study HMEH also permitted an assessment of whether patients classified as non-responders after 8 weeks of treatment with 60 mg/day could achieve response if up-titrated to 120 mg/day; the results suggest that up-titration did not benefit the non-responders. In fact, dropouts due to lack of efficacy were more common in the higher-dose arm during the double-blind dose-controlled phase of the study.

7.1.2 Phase 3 Clinical Studies Essential To Regulatory Decision

Detailed descriptions of the pivotal studies in this application may be found in Dr. Dent's review.

7.1.2.1 Acute Efficacy

As noted above, there were four placebo-controlled efficacy studies. Studies HMCA and HMCJ, based on both the applicant's and Dr. Buenconsejo's analyses, provide evidence of efficacy for duloxetine in the treatment of fibromyalgia.[2] Briefly, both studies were double-blind, placebo-controlled, parallel-group studies in adult patients with fibromyalgia (study HMCA enrolled only female patients). Patients were treated with study drug for 3 months (HMCA) or 6 months (HMCJ) and were assessed at intervals of approximately 2-4 weeks. Pain intensity using the Brief Pain Inventory (BPI) was assessed at each visit and a functional assessment in both studies, and the Fibromyalgia Impact Questionnaire (FIQ) was repeated approximately biweekly in HMCA and approximately monthly in HMCJ. The doses studied in HMCA included placebo, duloxetine (DLX) 60 mg QD, and DLX 60 mg BID. The doses studied in HMCJ included placebo, DLX 20 mg QD (blindly switched to 60 mg QD after the first three months), 60 mg QD, and 120 mg QD.

The primary outcome analyzed in these studies was the change from baseline to endpoint in the average pain score on the Brief Pain Inventory (BPI). This instrument is described by Lilly as follows:

> The Brief Pain Inventory (BPI) (severity and interference scores) is a self-reported scale that measures the severity of pain and the interference of pain on function. The severity scores range from 0 (no pain) to 10 (pain as bad as you can imagine). There are four questions assessing the severity for worst pain, least pain, and average pain in the past 24 hours, and the pain right now. The interference scores range from 0 (does not interfere) to 10 (completely interferes). There are seven questions assessing the interference of pain in the past 24 hours for general activity, mood, walking ability, normal work, relations with other people, sleep, and enjoyment of life.

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[2] Study HMBO was described by Lilly as a Phase 2 exploratory trial, and did not pre-specify the BPI average pain score as a primary analysis and did not study the recommended dose, 60 mg QD. Study HMEF did not demonstrate a statistically significant advantage of duloxetine over placebo, even by the sponsor's own analysis. These studies therefore will not be discussed further.

The BPI has been accepted as an appropriate assessment tool in previous marketing applications.

The analytic approach taken by Lilly focused on group mean changes from baseline, using a last-observation-carried-forward (LOCF) imputation strategy for patients discontinuing the study prematurely. For reasons that have been extensively discussed elsewhere (see, for example, Dr. Buenconsejo's review), the Division has focused on analyses of the proportion of patients exhibiting a clinically meaningful response to the drug. Several definitions of response are employed in the analyses, including 30% reduction in pain from baseline, 50% reduction, and a curve displaying all possible definitions of response. Dr. Buenconsejo's strategy for handling missing data was to impute the baseline score (i.e., non-response) to patients who did not complete the study (BOCF), or to use a "hybrid" strategy, assigning the baseline observation only to patients who dropped out due to adverse events (as those who cannot tolerate the drug are considered non-responders); in this strategy, the last observation is carried forward for other dropouts (LOCF/BOCF).

A summary table of effects of duloxetine on average pain scores based on Dr. Buenconsejo's reanalysis of the data from the pivotal studies, HMCA and HMCJ, is shown below. The conclusions in HMCJ depend, to some degree, on the imputation strategy selected. However, as shown below, consistent results in other analyses point to an effect of duloxetine:

Brief Pain Inventory Average Pain Score Mean Change from Baseline to Endpoint at Endpoint: All Randomized Patients in the 3-Month Therapy Phase Placebo-Controlled Studies: F1J-MC-HMCA, and F1J-MC-HMCJ

		BPI Average Pain Score (BOCF)			BPI Average Pain Score (LOCF/BOCF)	
Study	Treatment Group	Baseline	LSMean Change	p-value	LSMean Change	p-value
HMCA	Placebo	6.52	-0.9		-1.0	
	Duloxetine 60 mg QD	6.37	-2.1	<0.001†	-2.2	<0.001†
	Duloxetine 60 mg BID	6.37	-1.8	0.001	-2.1	<0.001
HMCJ	Placebo	6.58	-1.1		-1.2	
	Duloxetine 20 mg QD	6.77	-1.6	0.135†	-1.9	0.039†
	Duloxetine 60 mg QD	6.49	-1.6	0.065	-1.8	0.036
	Duloxetine 120 mg QD	6.39	-1.7	0.036	-1.8	0.038

†unadjusted p-value.

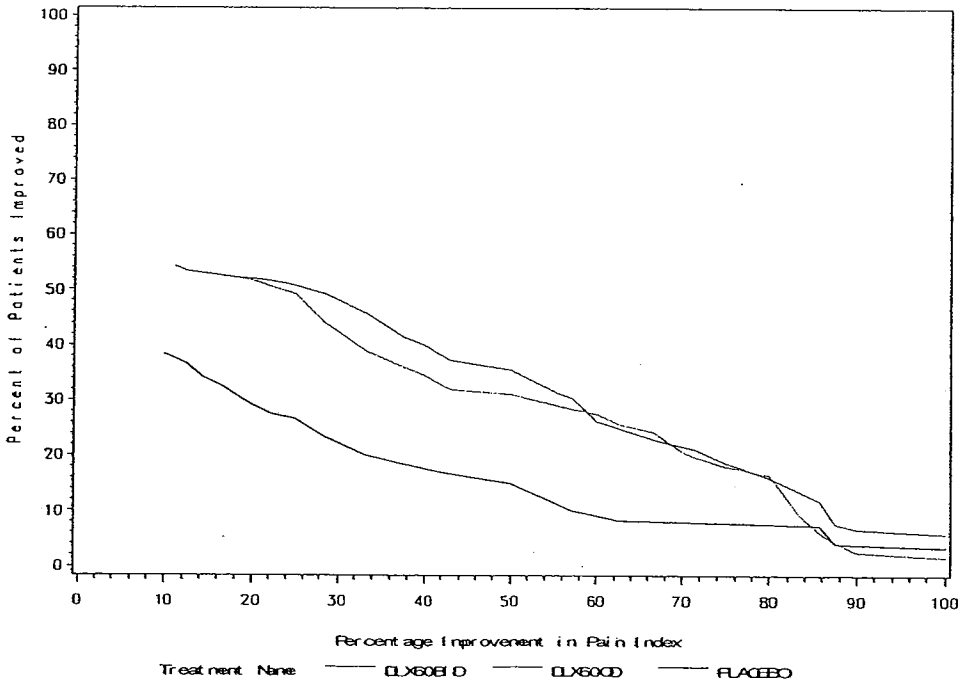
The table below illustrates Dr. Buenconsejo's calculation of responder rates in the two pivotal efficacy studies, HMCA and HMCJ. In addition to showing the superiority of duloxetine 60 mg or 120 mg over placebo, this tabulation illustrates the numerical, although not statistically significant, similarity between the response rates on the 20 mg QD dose and the higher doses used in HMCJ. Furthermore, it displays the lack of apparent benefit of 120 mg over 60 mg.

Responder Analysis of Brief Pain Inventory Average Pain Score at Endpoint: All Randomized Patients in the 3-Month Therapy Phase Placebo-Controlled Studies: F1J-MC-HMCA and F1J-MC-HMCJ

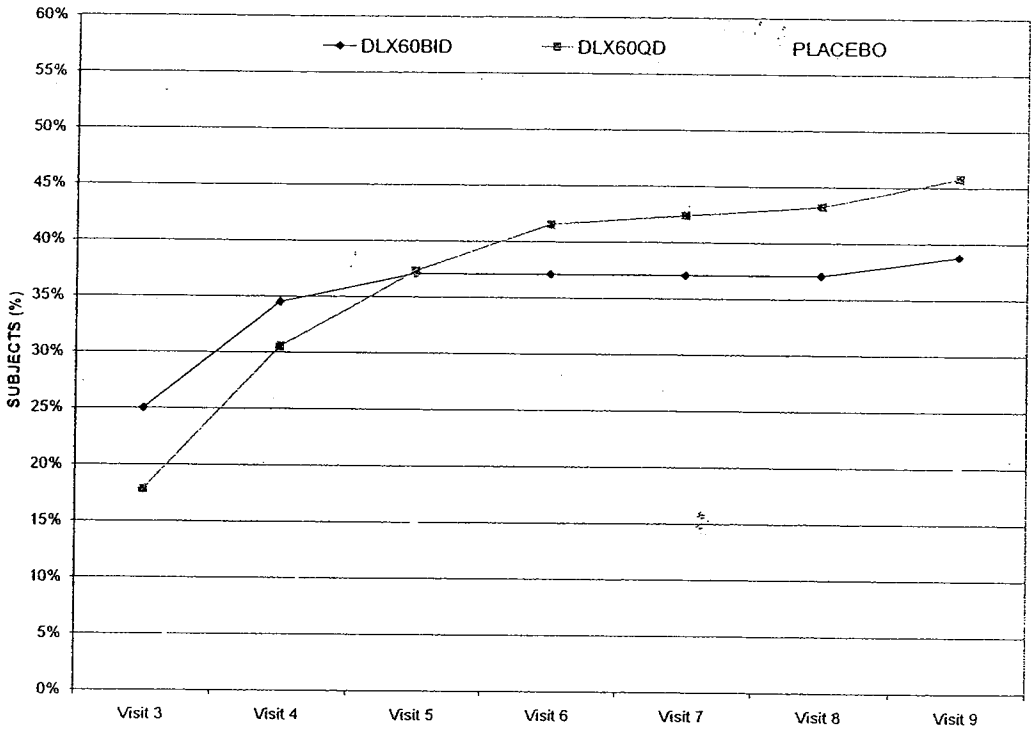
		≥ 30% Improvement in Pain			≥ 50% Improvement in Pain	
Study	Treatment Group	N	n(%)	p-value	n(%)	p-value
HMCA	Placebo	120	24 (20%)		18 (15%)	
	Duloxetine 60 mg QD	118	54 (46%)	<0.001	42 (36%)	<0.001
	Duloxetine 60 mg BID	116	45 (39%)	0.002	36 (31%)	0.003
HMCJ	Placebo	144	37 (26%)		26 (18%)	
	Duloxetine 20 mg QD	79	28 (35%)	0.126	22 (28%)	0.089
	Duloxetine 60 mg QD	150	56 (37%)	0.032	42 (28%)	0.043
	Duloxetine 120 mg QD	147	57 (39%)	0.017	44 (30%)	0.018

Dr. Buenconsejo also constructed curves showing the proportion of patients considered responders across the full range of possible response definitions. These are shown below. In each figure, the placebo group is clearly different from the duloxetine groups, but little difference across duloxetine doses is apparent.

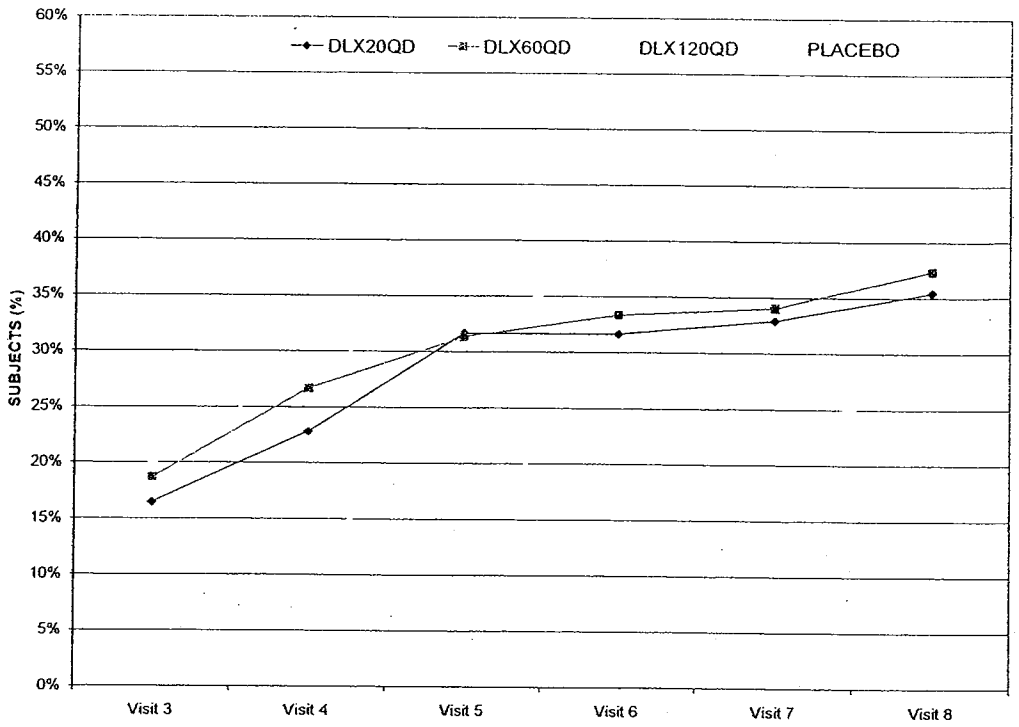
Figure 1: Overall Response Profile for Study HMCA



Proportion of Responders by Week (30% Improvement) – Study HMCA



Proportion of Responders by Week (30% Improvement) – Study HMCJ



Other endpoints assessed in the efficacy studies included function (Fibromyalgia Impact Questionnaire; FIQ) and global impression of improvement (PGI). Dr. Buenconsejo notes that:

> ... it is difficult to draw any conclusions from the analyses of these endpoints because multiplicity adjustments were not applied to these endpoints.

Nonetheless, the trends are notable and a treatment effect on these endpoints is apparent. The tables below summarize the results of the analyses of FIQ and patient global assessments. Note that WOCF indicates "worst observation carried forward" as there was no baseline score for the patient global impression of change.

Fibromyalgia Impact Questionnaire Total Score Change from Baseline to Endpoint*: All Randomized Patients in the 3-Month Therapy Phase, HMCA and HMCJ

		FIQ Total Score (BOCF)			FIQ Total Score (LOCF/BOCF)	
Study	Treatment Group	Baseline	LSMean Change	p-value†	LSMean Change	p-value†
HMCA	Placebo	53.1	-6.7		-7.6	
	Duloxetine 60 mg QD	51.4	-13.6	0.001	-14.2	0.002
	Duloxetine 60 mg BID	52.5	-12.9	0.003	-14.3	0.002
HMCJ	Placebo	53.0	-8.0		-9.1	
	Duloxetine 20 mg QD	54.0	-11.1	0.130	-13.3	0.053
	Duloxetine 60 mg QD	51.7	-12.1	0.017	-12.9	0.032
	Duloxetine 120 mg QD	51.7	-11.7	0.030	-12.7	0.048

*negative implies improvement
†unadjusted p-value

PGI-Improvement at Endpoint: All Randomized Patients in the 3-Month Therapy Phase HMCA and HMCJ

			PGI Improvement Score (LOCF)		PGI Improvement Score (WOCF)	
Study	Treatment Group	N	LSMean Change	p-value	LSMean Change	p-value
HMCA**	Placebo	111	3.8		3.9	
	Duloxetine 60 mg QD	114	3.2	0.005†	3.2	0.002†
	Duloxetine 60 mg BID	111	3.1	0.003	3.2	0.002
HMCJ**	Placebo	139	3.4		3.6	
	Duloxetine 20 mg QD	77	2.9	0.012†	3.1	0.010†
	Duloxetine 60 mg QD	143	3.0	0.026	3.1	0.009
	Duloxetine 120 mg QD	142	2.9	0.004	3.0	0.002

*Generalized linear model (GLM) Model: PGIImp=Treatment+Pool Investigator +Treatment*Pool Investigator
**GLM Model: PGIImp=Treatment+Pool Investigator
†unadjusted p-value.

7.1.2.2 Maintenance of Efficacy

Two studies which involved six months of treatment, Study HMCJ and Study HMEF, did not demonstrate an effect of duloxetine at the six-month time point. [redacted]

Lilly's own analysis, using LOCF, does support an effect of duloxetine at the 6-month time point.

Brief Pain Inventory Average Pain Score Mean Change from Baseline to Endpoint (Six Months) and PGI Improvement at Endpoint: All Randomized Patients in the 6-Month Therapy Phase Study HMCJ

	BPI Average Pain Score (LOCF)			PGI-Improvement (LOCF)		
Treatment Group	Baseline	LSMean Change	p-value	Baseline	LSMean Endpoint	p-value
Placebo	6.57	-1.4		4.06	3.4	
Duloxetine 20 mg QD	6.74	-2.3	0.018	4.20	2.8	0.006
Duloxetine 60 mg QD	6.46	-1.9	0.041	3.78	3.1	0.108
Duloxetine 120 mg QD	6.41	-2.1	0.003	3.82	2.9	0.012

Source: Clinical Study Report HMCJ, page 128 and 130

However, reanalysis by Dr. Buenconsejo using different imputation strategies does not support this conclusion. Her results are shown below:

Brief Pain Inventory Average Pain Score Mean Change from Baseline to Endpoint (Six Months): All Randomized Patients in the 6-Month Therapy Study HMCJ

	BPI Average Pain Score (BOCF)			BPI Average Pain Score (LOCF/BOCF)		BPI Average Pain Score (LOCF/BOCF)*	
Treatment Group	Baseline	LSMean Change	p-value	LSMean Change	p-value	LSMean Change	p-value
Placebo	6.58	-1.1		-1.2		-1.2	
Duloxetine 20 mg QD/60 mg QD	6.77	-1.9	0.018	-2.2	0.003	-2.2	0.004
Duloxetine 60 mg QD	6.49	-1.4	0.391	-1.7	0.048	-1.7	0.057
Duloxetine 120 mg QD	6.39	-1.4	0.251	-1.7	0.093	-1.6	0.121

* Eight patients who dropped out at Visit 11 retained their Visit 11 score.

Responder Analysis of Brief Pain Inventory Average Pain Score at Endpoint: All Randomized Patients in the 6-Month Therapy Phase Placebo-Controlled Study: F1J-MC-HMCJ

		≥ 30% Improvement in Pain			≥ 50% Improvement in Pain	
Study	Treatment Group	N	n(%)	p-value	n(%)	p-value
HMCJ	Placebo	144	37 (26%)		21 (15%)	
	Duloxetine 20/60 mg QD	79	30 (38%)	0.056	24 (30%)	0.005
	Duloxetine 60 mg QD	150	42 (28%)	0.656	33 (22%)	0.101
	Duloxetine 120 mg QD	147	47 (32%)	0.237	34 (23%)	0.063

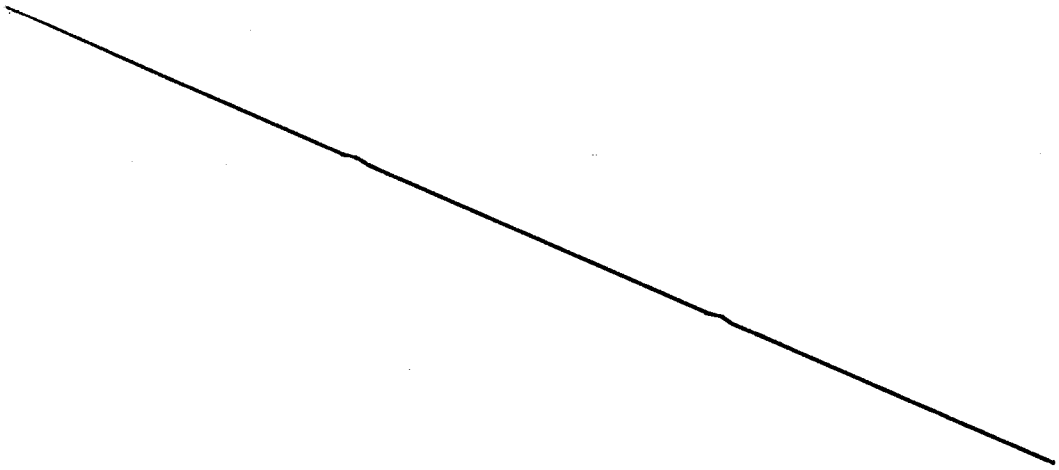
In order to understand why the drug appears to work for the first three months but no longer demonstrates statistically significant effects at six months, Dr. Buenconsejo and I explored the possible reasons for this outcome. If large numbers of dropouts for various reasons occurred over the second three months, the BOCF imputation strategy which assigns a "nonresponder" status to each dropout could obscure a result in patients who remained on-study. To determine whether the apparent lack of efficacy at the 6-month time point was simply a result of our data imputation strategy combined with patients dropping out over time, we examined the fate of patients who were considered responders at the three-month point. At the 6-month time-point, 61% of the original 56 responders to 60 mg/day of duloxetine still met the 30% improvement from baseline criteria. As shown in the table below, a similar proportion of the patients in the 120 mg/day remained in the responder category, but sustained response was more common among patients switched from 20 mg to 60 mg, and among placebo-treated patients.

Responder Status (30% improvement) Endpoint based on responder status at three months: All Randomized Patients in the 6-Month Therapy Phase, HMCJ

	Responders at 3 months			NonResponders at 3 months	
Treatment Group	N	Remained Responders at 6 months	Became non-responders at 6 months	N	Became responders at 6 months
Placebo	37	27 (73%)	10 (27%)	107	10 (9%)
Duloxetine 20/60 mg QD	28	22 (79%)	6 (21%)	51	8 (16%)
Duloxetine 60 mg QD	56	34 (61%)	22 (39%)	94	8 (9%)
Duloxetine 120 mg QD	57	35 (61%)	22 (39%)	90	12 (13%)

The remaining patients fell into two categories—patients who discontinued, and patients who continued on drug but whose pain scores increased to the point that they no longer met the responder definition. Both are coded as non-responders in a BOCF analysis. To understand more fully what actually happened, we identified those patients who were coded as becoming nonresponders based on *observed* information: either an endpoint pain score that was no longer 30% below baseline, or a discontinuation due to lack of efficacy. We found that the drug "stopped working" for 22% of placebo responders between months 3 and 6, vs. 29% of duloxetine 60 mg QD responders and 26% of duloxetine 120 mg QD responders. It is also notable that some patients who were not

considered responders at the 3 month timepoint experienced sufficient improvement in pain to be considered responders at 6 months, but this was as common among placebo-treated patients as among those treated with 60 mg/day of duloxetine. To some extent, this represents fluctuation in severity of pain, and it is difficult to draw conclusions about these findings other than to report them in the label.



This study involved 8 weeks of open-label treatment with duloxetine 60 mg QD, followed by randomization to double-blind treatment with either 60 mg QD or 120 mg QD. All completers of the open-label phase, whether responders or non-responders, were randomized. Lilly conducted a protocol-specified analysis of mean pain scores involving an arbitrarily-selected degree of change that would be considered ignorable—essentially, a non-inferiority margin. Dr. Buenconsejo notes that ...

> The Applicant evaluated the persistence of the efficacy of duloxetine 60 mg on patients who were responders at Week 8 and remained on duloxetine 60 mg in the double-blind study phase. This was done by evaluating the change from baseline to endpoint on BPI average pain and comparing the upper bound of the 90% two-sided confidence interval to 0.5. The Applicant did not specify the basis of the 0.5 margin. ...The upper bound of the 90% two-sided confidence interval in duloxetine 60 mg QD treatment group within the response status 'yes' was 2.15 which is more than the margin specified by the Applicant (i.e. 0.5). The Applicant's conclusion is that
>
> > For persistence of efficacy analysis, mean change in BPI average pain from baseline to endpoint did not reach significance in the initial responders on duloxetine 60 mg QD. However, initial responders began and ended the double-blind study phase with mean BPI average pain scores in the mild range that were well below the mean baseline pain scores at Visit 2. In addition, decreases (improvements) in mean average pain score were observed for non-responders within both treatment groups.
>
> In my opinion, regardless of the basis of this margin, what this implies is that duloxetine treatment effect on pain reduction on the fibromyalgia patients was not maintained in the one-year double-blind study phase. Furthermore, applying mean change from baseline to measure persistence of effect does not appear to be informative.

Importantly, even if the analysis chosen by Lilly were appropriate, a statistically significant effect of duloxetine was not demonstrated in this analysis.

Along the lines described above regarding study HMCJ, Dr. Buenconsejo examined the data from this study to determine how many patients who were considered responders at the time of randomization to treatment were still considered responders at the end of the study (week 52). Those patients can be said to have experienced "persistence of efficacy." Because both responders and non-responders to open-label 60 mg/day were randomized to the double-blind phase, this study also provides an opportunity to assess whether up-titration to 120 mg would be beneficial for non-responders to 60 mg/day.

After 8 weeks of treatment (one week of 30 mg/day and 7 weeks of 60 mg/day), 36% of enrolled patients were considered responders using the 50% improvement definition. Of these treatment responders who continued on the label-recommended dose of 60 mg QD, 38% met the same responder criteria at week 52 (using BOCF imputation for missing data). Examining the data on completers, Dr. Buenconsejo found that the drug could be said to have "stopped working" for 35% of the original responders to 60 mg QD between Week 8 and Week 52. Again, it is difficult to draw statistical conclusions about this finding ——— To facilitate comparison with the data from HMCJ, Dr. Buenconsejo repeated the analysis using a 30% improvement definition of responder and found that 57% of those considered responders at Week 8 remained in the responder category at week 52. Using the data on completers, it could be said that duloxetine 60 mg QD "stopped working" for 27% of the original responders. This figure is nearly identical to the findings in Study HMCJ, in whom 61% of initial responders were still responders at the 6 month time point. ———

———

———

This analysis also showed that titration to 120 mg did not increase the chances of responders to 60 mg staying in the responder category at Week 52.

7.1.3 Other efficacy issues

Several specific efficacy issues require focused discussion. These include the effect of duloxetine in male patients, an examination of differences in response between patients with major depression and those without, and examination ———

———

7.1.3.1.1 Effect in Male Patients

Although FM patients are overwhelmingly female, the condition does occur in men. The Division ———

——— and encouraged them to study male patients. The total male enrollment in the development program was only 5%, and insufficient to draw any conclusions about

the efficacy of duloxetine in men. In some analyses, little treatment effect is seen. However, it is also not possible to conclude that duloxetine is ineffective.

A difference in clearance between male and female patients has been observed in clinical pharmacology studies; however no dosing modifications based on gender are recommended the effect is small relative to the magnitude of interpatient variability. Taken together with ambiguous results from the exposure-response analysis, it is not clear whether differences in clearance, and therefore exposure, might explain the results; however this seems to be a plausible explanation. It may be that higher doses would be appropriate for male patients. However, given the risks of higher doses, further study would be needed, documenting a benefit, before this could be recommended.

The tables below, taken from Dr. Buenconsejo's review, shows the effect of duloxetine on pain scores and patient ratings of improvement in male and female patients.

Endpoint Mean Brief Pain Inventory Average Pain Score: All Randomized Patients in the 3-Month Therapy Phase Placebo-Controlled Studies by Gender: F1J-MC-HMCJ

	Women			Men		
Treatment Group	N	Baseline	Endpoint Mean	N	Baseline	Endpoint Mean
BOCF						
Placebo	137	6.6	5.5	7	6.1	5.6
Duloxetine 20 mg QD	76	6.8	5.1	3	6.3	6.3
Duloxetine 60 mg QD	136	6.5	5.0	14	6.2	4.9
Duloxetine 120 mg QD	143	6.4	4.8	4	7.0	4.5
LOCF/BOCF						
Placebo	137	6.6	5.4	7	6.1	5.7
Duloxetine 20 mg QD	76	6.8	4.8	3	6.3	6.3
Duloxetine 60 mg QD	136	6.5	4.9	14	6.2	4.3
Duloxetine 120 mg QD	143	6.4	4.7	4	7.0	4.5

PGI-Improvement at Endpoint by Gender: All Randomized Patients in the 3-Month Therapy Phase Placebo-Controlled Studies: F1J-MC-HMCJ

		Women		Men	
Study	Treatment Group	N	Endpoint Mean	N	Endpoint Mean
LOCF					
HMCJ	Placebo	138	3.0	4	2.5
	Duloxetine 20 mg QD	75	2.9	2	4.0
	Duloxetine 60 mg QD	130	3.1	13	3.2
	Duloxetine 120 mg QD	132	3.5	7	3.7
WOCF					
HMCJ	Placebo	138	3.1	4	2.5
	Duloxetine 20 mg QD	75	3.1	2	4.5
	Duloxetine 60 mg QD	129	3.2	13	3.3
	Duloxetine 120 mg QD	132	3.7	6	3.8

7.1.3.1.2 Lack of Benefit of Up-Titration in Non-Responders

The general Dosing and Administration section of the proposed labeling (Highlights section) reads: '

However, data from Study HMEH illustrate a lack of benefit of the 120 mg dose even in patients who do not respond to treatment with 60 mg QD. As shown in the table below, constructed from Dr. Buenconsejo's review, patients who were *non-responders to initial treatment* were no more likely to become responders at 52 weeks if titrated up to 120 mg than if they continued on 60 mg.

52-Week Response Status in *Non-Responders* at Week 8, Study HMEH

Study	Treatment Group	N 50% improvement	Responders at Week 52 50% improvement	N 30% improvement	Responders at Week 52, 30% improvement
LOCF	DLX 120 mg QD	128	37 (29%)	98	36 (37%)
	DLX 60 mg QD	67	19 (28%)	48	16 (33%)
BOCF	DLX 120 mg QD	**128**	**26 (20%)**	**98**	**25 (26%)**
	DLX 60 mg QD	**67**	**17 (25%)**	**48**	**13 (27%)**
LOCF/BOCF	DLX 120 mg QD	128	32 (25%)	98	32 (33%)
	DLX 60 mg QD	67	19 (28%)	48	15 (31%)

7.1.3.1.3 Effect of Presence or Absence of MDD

During the development program, Lilly had been informed that the Division had concerns about differentiating duloxetine's anti-depressant effects from its analgesic effects. One communication noted, "Since duloxetine is approved for major depressive disorder (MDD), inclusion of patients with MDD may confound interpretation of results of patients with fibromyalgia who do not have depression. Therefore, consideration should be given to stratifying patients as to the presence or absence of MDD." Consequently, Lilly attempted to address this concern by a "path analysis" which purports to distinguish the effect of duloxetine on depression, as measured by HAM-D score, from its effect on pain.

It should be noted that in the ensuing time, duloxetine's analgesic efficacy has been demonstrated via approval for the treatment of DPN. Furthermore, the Division has determined that a drug which demonstrates an effect on pain scores, even if mediated through an effect on depressive symptoms, would be appropriately viewed as effective

for the treatment of pain. Therefore, Lilly's path analysis did not receive in-depth scrutiny.

However, it is important to establish that the drug's effects in fibromyalgia, even if mediated through some effect on mood, are seen both in patients with a diagnosis of major depression and patients without.

During the screening period of the placebo-controlled trials, patients were administered the Mini International Neuropsychiatric Interview (MINI) to determine whether they met criteria for a diagnosis of major depressive disorder. Approximately 25% of the enrolled patients met diagnostic criteria for MDD. The subset of patients with MDD had a higher mean pain score at baseline than patients without. However, at endpoint, the groups were very similar with respect to mean pain score, as shown in the table below, constructed by Dr. Buenconsejo.

Endpoint Mean Brief Pain Inventory Average Pain Score: All Randomized Patients in the 3-Month Therapy Phase Placebo-Controlled Studies by Major Depressive Disorder Status: F1J-MC-HMCA and F1J-MC-HMCJ

		No MDD			With MDD		
Study	Treatment Group	N	Baseline	Endpoint Mean	N	Baseline	Endpoint Mean
BOCF							
HMCA	Placebo	88	6.3	5.2	32	7.2	6.4
	Duloxetine 60 mg QD	89	6.3	4.3	29	6.7	4.3
	Duloxetine 60 mg BID	84	6.2	4.5	32	6.8	4.6
HMCJ	Placebo	109	6.4	5.3	35	7.0	6.0
	Duloxetine 20 mg QD	57	6.6	5.1	22	7.2	5.4
	Duloxetine 60 mg QD	115	6.4	4.9	35	6.7	5.1
	Duloxetine 120 mg QD	113	6.3	4.7	34	6.6	5.1
LOCF/BOCF							
HMCA	Placebo	88	6.3	5.1	32	7.2	6.2
	Duloxetine 60 mg QD	89	6.3	4.3	29	6.7	4.1
	Duloxetine 60 mg BID	84	6.2	4.4	32	6.8	4.0
HMCJ	Placebo	109	6.4	5.2	35	7.0	6.0
	Duloxetine 20 mg QD	57	6.6	4.8	22	7.2	5.0
	Duloxetine 60 mg QD	115	6.4	4.8	35	6.7	4.9
	Duloxetine 120 mg QD	113	6.3	4.7	34	6.6	4.9

Thus, the magnitude of change is greater for patients with MDD. Accordingly, more patients with MDD meet responder criteria which are based on magnitude of change from baseline. In addition, patients with MDD were less likely to respond to placebo treatment. Therefore, the comparison between treatment and placebo groups shows a greater effect of duloxetine in patients with MDD than in patients without. However, an effect of treatment is evident in both groups, as shown in the table below, constructed from analyses performed by Dr. Buenconsejo. It does not appear that the overall effect is driven only by a response in the subset of patients with MDD.

	Placebo	DLX 60 QD	DLX 60 BID* /120 QD
HMCA: 30% improvement			
WITH MDD	3/32 (9%)	15/29 (52%)	16/32 (50%)
WITHOUT MDD	21/88 (24%)	39/89 (44%)	29/84 (35%)
HMCA: 50% improvement			
WITH MDD	3/32 (9%)	12/29 (41%)	14/32 (44%)
WITHOUT MDD	15/88 (17%)	30/89 (34%)	22/84 (26%)
HMCJ: 30% improvement			
WITH MDD	7/35 (20%)	15/35 (43%)	14/34 (41%)
WITHOUT MDD	30/109 (28%)	41/115 (36%)	43/113 (38%)
HMCJ: 50% improvement			
WITH MDD	4/35 (11%)	9/35 (26%)	10/34 (29%)
WITHOUT MDD	22/109 (20%)	33/115 (29%)	34/113 (30%)

*60 BID in HMCA, 120 QD in HMCJ
Not shown in table: DLX 20 QD in HMCJ: 41% vs 33%, 30% improvement, 36% vs 25%, 50% improvement.

[redacted]

As noted above, Dr. Buenconsejo took exception to the lack of appropriate statistical correction for the multiple secondary endpoints. [redacted]

In fact, Dr. Buenconsejo expressed some reservation even about allowing claims regarding the FIQ and PGI based on statistical concerns; however, because the FIQ and PGI form part of the three-fold approach to assessment of fibromyalgia drugs originally

recommended by the Agency, and these particularly relevant measures that showed consistent findings, these claims seem more important to consider for inclusion in labeling. Moreover, the labeling for Lyrica included claims for effects on these PROs based on similar (i.e., not entirely statistically convincing) results. Therefore, I recommend including the claims regarding function (FIQ) and patient global well-being (PGI) [redacted]

7.1.4 Discussion of Primary Reviewers' Comments and Conclusions

Other than as noted above regarding the inclusion of the FIQ and PGI claims in labeling, I concur with the conclusions of the primary clinical and statistical reviewers.

7.1.5 Pediatric use/PREA waivers/deferrals

Lilly requested deferral of pediatric studies in adolescents until after the approval of the adult fibromyalgia indication on the grounds that adult studies are completed and ready for approval.

Lilly requested a Partial Waiver for pediatric age groups including neonates, infants and children due to the low prevalence of FM condition in these pediatric populations. A waiver for children under the age of – would be appropriate due to the impracticality of studying younger children. A safety and efficacy study in children –-17 should be required under PREA.

7.1.6 Discussion of Notable Efficacy Issues

Key efficacy issues in this application were:

- Efficacy of duloxetine at the label-recommended dose of 60 mg, once daily.

I believe the studies presented provide substantial evidence of efficacy of this dose of duloxetine for the treatment of fibromyalgia.

- Efficacy of duloxetine in fibromyalgia patients both with and without comcomitant major depression.

Although the treatment effect is more clearly demonstrated in patients with major depression than in patients without, I believe the overall data support the effectiveness of the drug in the overall population, and that the results are not driven exclusively by the subset of patients with major depression. However, I do not feel the efficacy was independently established and confirmed in the two sub-populations, and that the proposed label language conveys this impression. I believe it would be more appropriate to note, in the clinical studies section, simply that approximately 25% of the participants had comorbid MDD.

- Long-term efficacy of duloxetine

The longer term studies did not provide statistically significant evidence of efficacy of duloxetine beyond 3 months of treatment. About 60% of duloxetine-treated patients (vs about 70% of placebo-treated patients) who respond to treatment initially continue to report improvement in pain at 6-12 months. On the other hand, 27% of patients who respond to treatment and remain on treatment long-term experience a documented reemergence of pain and no longer meet criteria for 30% improvement.

- Efficacy of duloxetine in male fibromyalgia patients.

The data in this application are insufficient to determine the efficacy of duloxetine in male patients. Limited information on exposure/response and the established gender differences in duloxetine clearance suggest that male patients might benefit from higher doses; however, this requires evaluation in future studies.

7.2 *Safety*

The integrated safety database for duloxetine (all trials and all indications except fibromyalgia) consists of 25,933 patients, 8569 of whom were enrolled in placebo-controlled studies. The other indications include: diabetic peripheral neuropathic pain (DPNP), generalized anxiety disorder (GAD), lower urinary tract disorder (LUTD), and major depressive disorder (MDD). Safety of duloxetine in patients with fibromyalgia (FM) was evaluated in a total of 1236 patients in 5 completed clinical studies administering doses of 20, 60, and 120 mg, including long-term treatment of up to 60 weeks with duloxetine. There were 876 fibromyalgia patients treated with duloxetine in placebo-controlled trials, 350 in a long-term trial, and an additional 10 patients in a compassionate use study.

The size of the analysis populations are shown in the table below:

Total Number of Patients by Analyses Group

Fibromyalgia Placebo-Controlled Studies		Fibromyalgia Long-Term Safety Study	Fibromyalgia Open-Label Compassionate Use Study	Placebo-Controlled Studies for all Other Indications		Total Exposures for all Other Indications
PBO	DLX	DLX	DLX	PBO	DLX	DLX
N=535	N=876	N=350	N=10	N=6235	N=8569	N=25,933

All indications includes: diabetic peripheral neuropathic pain (DPNP), generalized anxiety disorder (GAD), lower urinary tract disorder (LUTD), major depressive disorder (MDD), and fibromyalgia (FM).
PBO = placebo, DLX = duloxetine

7.2.1 General safety considerations

The labeling for Cymbalta carries several Warnings and Precautions. These include:

- Antidepressant class label boxed warning concerning suicidality in children and adolescents.
- Transaminase elevation (recent review reveals more serious hepatotoxicity cases, some fatal; label to be updated)
- Orthostatic hypotension and syncope
- Mydriasis/risk in patients with narrow-angle glaucoma
- Effect on glycemic control in diabetic patients
- Class effect risk of serotonin syndrome
- Activation of mania/hypomania
- Elevation of blood pressure
- Seizures (0.03% vs 0.01% in placebo)
- Hyponatremia

Recent review by the Division of Psychiatry Products also identifies bleeding (due to serotonergic effect on platelet function) as a risk.

The major focus in this review was to determine whether any new safety findings, specific to the FM population, were identified in the safety data. Overall, the safety

profile in FM patients resembled the established safety profile for the drug. FM patients, overall, in both placebo- and drug-treated groups, reported more AEs than patients in the other populations studied, but it did not appear that there was a greater risk of AEs attributable to duloxetine.

Because of duloxetine's known toxicities, the review team was particularly interested in the apparent effectiveness of the 20 mg dose, and considered withholding approval from the 60 mg dose and asking Lilly to repeat studies in the lower dose. Examination of the safety data by dose was complicated by the fact that the 20 mg dose was used only in study HMCJ, and only for the first three months of treatment. Therefore, the exposure time at the 20 mg dose is much shorter than for the higher doses, particularly the 120 mg dose which was used in long-term extensions. Therefore, at FDA's request, Lilly provided a tabulation of adverse events by dose from the first three months of HMCJ and HMEF, combined with the data from the three-month studies. Examination of this tabulation (at the HLGT level to facilitate identification of trends by combining like events) revealed few events that were obviously less common in the 20 mg group compared to the groups treated with higher doses. Similarly, although evaluation of the SAEs by dose seems to implicate the 120 mg dose as being less safe than lower doses, the 20 mg dose does not emerge as clearly safer than the 60 mg dose. Therefore, while it remains advisable to continue to explore the lowest effective dose in future studies, the safety findings did not support withholding approval of the 60 mg dose.

7.2.2 Safety findings from submitted clinical trials

7.2.2.1 Deaths

There were no deaths in the fibromyalgia clinical trials.

7.2.2.2 Serious Adverse Events and Other Significant Events

Serious adverse events were reported more commonly in fibromyalgia patients than in patients studied for other indications in the safety database. However, examination of data from placebo-controlled trials suggested that the contribution of duloxetine seemed to be similar in the fibromyalgia population compared to the rest of the safety database. A total of 2.4% of duloxetine-treated patients and 2.1% of placebo-treated patients enrolled in fibromyalgia placebo-controlled trials reported SAEs; this compares to 1.3% of duloxetine-treated patients and 1.1% of placebo-treated patients in placebo-controlled trials of all other indications (1.3%).

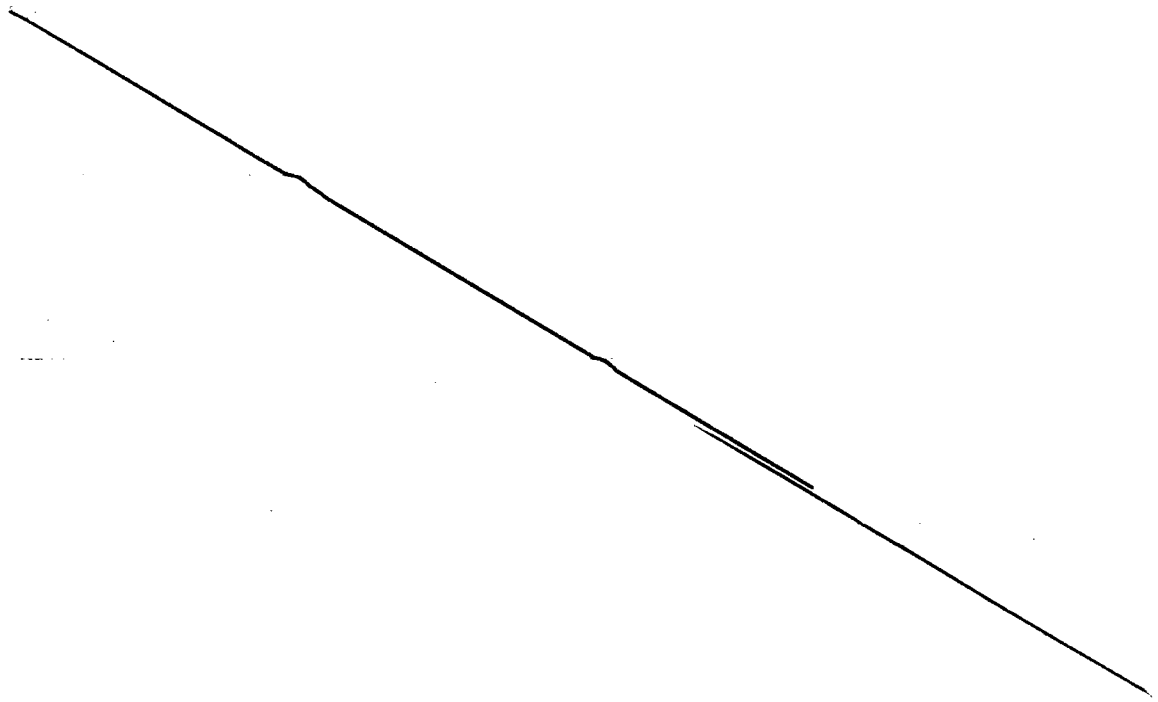
There were 41 SAEs in the original submission and 22 additional SAEs in the safety update report. Dr. Dent reviewed the specific cases of serious adverse events and identified possibly drug-related cases. These included cases of expected AEs such as suicidal ideation, hyperglycemia, and some cases that could be linked to a duloxetine effect on bleeding, such as uterine hemorrhage and subdural hematoma (occurring in setting of motor vehicle accident, but role of duloxetine in hematoma cannot be excluded). No events identifying new safety concerns unique to the FM population were reported.

7.2.2.2.1 Suicidal Ideation

There were no completed suicides in the FM studies. Five cases involving suicidal ideation and/or behavior were observed in duloxetine-treated patients in the FM database, or 0.47%. This is similar to the observed rate in the overall safety database. Only one case in a duloxetine-treated patient occurred in a placebo-controlled study; there was also one case in a placebo-treated patient. Lilly presented data from the overall safety database showing the incidence of suicide-related events in various populations from their placebo-controlled trials. These data show that the FM population falls between the psychiatric (MDD and GAD) and non-psychiatric (urinary indications, DPNP) populations in terms of the occurrence of suicide-related events, as would be expected.

7.2.2.2.2 Hepatotoxicity

A risk of hepatic transaminase elevation was suspected at the time of initial NDA review and more clearly identified through postmarketing safety reports after the initial approval of Cymbalta. The labeling currently reads:



In the fibromyalgia placebo-controlled studies, one SAE of hepatic enzyme abnormality was reported in a duloxetine-treated patient (none in placebo-treated patients), and 5 duloxetine-treated (vs no placebo-treated) patients discontinued due to hepatic-related AEs. The hepatic AEs that were observed occurred within the first three months of treatment, suggesting long-term treatment does not increase risk.

Duloxetine-treated patients had higher incidence of ALT values > 3 x ULN and 5 x ULN than did placebo-treated patients. Also, there were 4 cases of ALT values > 10 x ULN in duloxetine-treated patients and no similar cases in placebo-treated patients. No cases of Hy's Rule were observed in the fibromyalgia population. The mean changes from

baseline to maximum were higher for duloxetine-treated than for placebo-treated patients for ALT, AST, Alkaline Phosphatase, and GGT, but not for Total Bilirubin.

The four patients with ALT >10 x ULN are described by Lilly as follow. In each case, the transaminase abnormalities reversed upon discontinuation of duloxetine:

Study F1J-MC-HMBO Patient: 105-1523

A 46-year-old female, with secondary conditions of bronchitis, irritable bowel syndrome, mitral valve prolapse, multiple allergies, and sinusitis, was started on duloxetine 60 mg BID on 26 Oct 01. At baseline, liver enzymes were within normal range. Fifty-six days after starting duloxetine, the ALT increased to 543 U/L (>6X ULN based on the Lilly reference ranges used during the study, but >10X ULN based upon ——— reference ranges), AST increased to 311 U/L (>5X ULN), and ALKPH slightly increased, but still within normal range. The patient also experienced pruritus 5 days before, and disturbance in attention on the same day of the blood test results. The patient used acetaminophen/paracetamol and acyclovir sporadically before the blood test results. Four days later, the duloxetine was discontinued. Serologies were all negative and included hepatitis B surface antigen (HBSAG), total antibody to hepatitis B core antigen (A-HB-C), anti-hepatitis immunoglobulin M (HA-IGM), and hepatitis C antibody (ANTIHC). Following duloxetine discontinuation, liver enzymes continued to decline and completely normalized 17 days later. The total bilirubin remained within normal range throughout the trial.

Study F1J-MC-HMCA Patient: 112-2217

A 49-year-old female, with secondary conditions of irritable bowel syndrome, migraine, and multiple allergies, was started on duloxetine 60 mg once daily (QD) on 03 July 2003. At baseline, liver enzymes were within normal range. The patient had no known history of hepatic dysfunction or elevated liver enzymes. Fifty-seven days after starting duloxetine, the ALT increased to 561 U/L (>7X ULN based on the Lilly reference ranges used during the study (80) or >10X ULN based upon ——— reference ranges), AST increased to 250 U/L (>4X ULN). The patient had been treated for several years with loperamide, cyanocobalamin, tocopherol, zolmitriptan, cetirizine, triamcinolone, magnesium /calcium. The patient also reported that on average she took Excedrin (combination product including acetaminophen/paracetamol) 2 tablets, 3 times per week. Four days later, the duloxetine was discontinued. Following duloxetine discontinuation, liver enzymes continued to decline and completely normalized 33 days later. Alkaline phosphatase (ALKPH) and total bilirubin (TBILI) remained within normal range throughout the trial and the patient was asymptomatic.

Study F1J-MC-HMEF Patient 308-3602

A 59-year-old female, with secondary conditions of non-insulin-dependent diabetes mellitus and hypertonia, was started on duloxetine 60 mg QD on 23 May 2006. At baseline, liver enzymes were within normal range. Fifty-nine days after starting duloxetine, the ALT increased to 471 U/L (>13X ULN), AST increased to 170 U/L (5X ULN), C-reactive protein and lymphocytes were above the normal limit. The patient had been treated for several years with metoprolol and metformin. The day after, duloxetine was discontinued. Following duloxetine discontinuation, liver enzymes continued to decline and completely normalized 25 days later. Alkaline phosphatase (ALKPH) and total bilirubin remained within normal range throughout the trial and the patient was asymptomatic. The patient took acetaminophen/paracetamol for headache a few days after the liver enzymes increased; however, there was no mention of previous use of acetaminophen/paracetamol.

Study F1J-MC-HMEF Patient 608-6612

A 46-year-old female, with secondary conditions of drug hypersensitivity, hypercholesterolaemia, arterial hypertension, and gastrooesophageal reflux disease, was started on duloxetine 60 mg QD on 15 Nov 2005. At baseline, liver enzymes were within normal range. Fifty-eight days after starting duloxetine, the ALT increased to 629 U/L (>18X ULN), AST increased to 264 U/L (>7X ULN), C-reactive protein was above the normal limit. The patient had been treated for several years with atorvastatin and pantoprazole, and more recently she started taking valsartan, acetylsalicylic acid, chondroitin, glucosamine. On the same day, duloxetine was discontinued. Following duloxetine discontinuation, liver enzymes continued to decline and almost completely normalized 13 days later. Alkaline phosphatase (ALKPH) and total bilirubin remained within normal range throughout the trial and the patient was asymptomatic. Hepatic serologies were not performed. Abdominal ultrasound evidenced diffuse fatty infiltration and status post-cholecystectomy, but otherwise was considered unremarkable.

Dr. Dent noted that: "When comparing the fibromyalgia duloxetine-treated population to the overall duloxetine-treated population, a small difference was noted in the frequency of patients with ALT > 3 x ULN (1.37% vs. 1.11%). A similar phenomenon was observed in placebo-treated patients (0.44% vs. 0.23%), which suggests the possibility of an indication-specific occurrence. Similarly, an increased incidence of ALT > 5 x ULN was observed in a higher percentage of duloxetine-treated fibromyalgia patients than duloxetine-treated patients for other indications (0.96% vs. 0.59%). Likewise, ALT > 10 x ULN was higher in duloxetine-treated fibromyalgia patients than for duloxetine-treated patients for other indications (0.55% vs. 0.20%)."

A tabulation by dose of treatment-emergent abnormalities in ALT across the entire development program (Lilly tabulated only ALT) is shown below:

Treatment-Emergent Abnormally High ALT Values at Anytime by Dose
All Randomized Patients with Normal Baseline Values (≤1x ULN)
All Placebo-Controlled Trials for All Indications

Analyte	Reference Limits	Therapy	N	n	Percent
ALT	>3X ULN	Placebo	5578	13	(0.23%)
		DLX < 40	1033	3	(0.29%)
		DLX 40	350	6	(1.71%)
		DLX 60	1627	13	(0.80%)
		DLX 80	3080	38	(1.23%)
		DLX 90	90	1	(1.11%)
		DLX 120	1452	24	(1.65%)
		ALL DLX	7632	85	(1.11%)
	>5X ULN	Placebo	5578	3	(0.05%)
		DLX < 40	1033	2	(0.19%)
		DLX 40	350	2	(0.57%)
		DLX 60	1627	5	(0.31%)
		DLX 80	3080	23	(0.75%)
		DLX 90	90	0	(0.00%)
		DLX 120	1452	13	(0.90%)
		ALL DLX	7632	45	(0.59%)
	>10X ULN	Placebo	5578	0	(0.00%)
		DLX < 40	1033	0	(0.00%)
		DLX 40	350	0	(0.00%)
		DLX 60	1627	4	(0.25%)
		DLX 80	3080	5	(0.16%)
		DLX 90	90	0	(0.00%)
		DLX 120	1452	6	(0.41%)
		ALL DLX	7632	15	(0.20%)

N = Number of patients with normal lab result at all baseline visits.
n = Number of patients with abnormally high values.
Applicant's Table, Page 4371, 5.3.5.3 Multistudy Analyses

The category DLX<40 includes the 20 mg/day dose used in the FM trials. This category seems clearly less likely to be associated with significant ALT elevations. Other than the 90 mg dose (where the N is very small) and the 40 mg dose (which Lilly explains was used only in stress urinary incontinence studies where all patients were female and therefore more prone to ALT abnormality), a dose-reponse relationship is apparent from these data. This underscores the benefit of using the lowest effective dose.

In addition, Dr. Marc Stone of the Division of Psychiatry Products has recently conducted an analysis of post-marketing cases of hepatotoxicity. Dr. Stone provides the following historical perspective on the experience with duloxetine:

> At 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 of 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 law 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.
>
> Many of the cases of duloxetine-associated hepatotoxicity could not rule out the contribution of other causes. Lilly suggested that the apparent high reporting rates for duloxetine could be the result of confounding because of the drug's use in a sicker population where the background rate of significant hepatic disease could be higher. Lilly also argued that prior changes to the labeling concerning hepatotoxicity could have stimulated reporting of less-serious cases.

To address these possible alternative explanations, Dr. Stone and colleagues conducted a blinded review of case series that compared duloxetine to two other anti-depressants: paroxetine, a drug that is not believed to have serious hepatotoxicity problems that nevertheless had a high reporting rate for hepatotoxicity in its initial years of marketing, and nefazodone, a drug with serious hepatic issues that merited a black box warning. He concluded that "The results of this exercise confirm the impression of the previous reviews of an elevated risk for hepatotoxicity with duloxetine. The magnitude of risk is difficult to establish but it is unlikely to be worse than nefazodone and is most likely somewhat less." Dr. Stone provides recommendations for labeling revisions which provide greater prominence to the information about post-marketing cases, noting that some have been fatal. These changes will be incorporated in our proposals to Lilly, although no such cases were observed in the FM database.

7.2.2.2.3 Withdrawal/Discontinuation-Emergent Symptoms

The package insert for Cymbalta describes symptoms occurring upon discontinuation of duloxetine. The Highlights section included the statement that [redacted] In the FM database, discontinuation-emergent adverse events were reported in 34% of duloxetine-treated patients vs 12% of placebo-treated patients, despite the use of a tapering phase in the clinical trials. Therefore, Lilly has proposed that the label be changed to indicate that discontinuation, whether abrupt or gradual, may be associated with these symptoms. Furthermore, the FM patients reported additional symptoms not mentioned in the labeled list. The terms in italics in the table below (from Dr. Dent's review) are not currently mentioned in the highlights section of labeling. More comprehensive description of the symptoms possible during duloxetine discontinuation may be needed.

Adverse Events Reported In Fibromyalgia Studies By Patients Who Entered Drug-Tapering Phase In Studies HMEF, HMCA, and HMCJ (Reported by ≥ 3 Patients)				
MedDRA Preferred Term	PLACEBO (N=92) n (%)		DULOXETINE (N=203) n (%)	
Patients with ≥ 1 Discontinuation-Emergent Adverse Event	11 (12.0)		68 (33.5)	
Dizziness	1	(1.1)	18	(8.9)
Nausea	1	(1.1)	12	(5.9)
Insomnia	1	(1.1)	8	(3.9)
Diarrhoea	0	(0)	7	(3.4)
Myalgia	1	(1.1)	6	(3.0)
Fatigue	2	(2.2)	4	(2.0)
Headache	0	(0)	6	(3.0)
Abnormal dreams	0	(0)	4	(2.0)
Depression	0	(0)	4	(2.0)
Anxiety	0	(0)	3	(1.5)
Applicant's Table, Page 131, Summary of Clinical Safety				

7.2.2.2.4 Other labeled Warnings/Precautions

No cases of hyponatremia, seizure, activation of mania, severe cutaneous reactions (not a labeled warning/precaution but an event of interest[3]) were observed in the FM safety database. Consistent with labeling, some cases of ———— syncope, ———— and hypotension were resported. Four cases of mydriasis, a labeled precaution, were noted in duloxetine-treated patients. Urinary hesitation was reported by 12 (1%) of duloxetine-treated patients and urinary retention by 5 (0.4%). As mentioned above, two cases involving bleeding may have been duloxetine-related.

7.2.2.3 Discontinuations due to AEs

In the fibromyalgia placebo-controlled studies, a total of 171(20%) patients taking duloxetine dropped out due to adverse events and 63(12%) patients taking placebo dropped out due to adverse events. In placebo-controlled studies for all other indications (MDD, GAD, LUTD, DPNP) at total of 1154(13%) patients taking duloxetine dropped out due to adverse events and 247(4%) patients taking placebo dropped out due to adverse events. Patients in the studies of other indications were over three times more likely to discontinue prematurely if they were treated with duloxetine than if they were treated with placebo. In the FM studies, duloxetine-treated patients were not even twice ask likely to drop out as placebo-treated patients, suggesting that the higher dropout rate is more a population-specific phenomenon than a matter of increased sensitivity to the effects of duloxetine.

The table below was compiled from Lilly's study reports, and summarizes the likelihood of premature study drug discontinuation due to adverse events by dose, across studies. This tabulation illustrates that the low dose (20 QD) was least likely be associated with dropout due to AE. The high dose (120 mg/day, whether given as one dose or divided

[3] DPP requested that Lilly ———— about serious skin reactions (e.g. Stevens-Johnson Syndrome) in 2007. Lilly disagreed with DPP's conclusions and ultimately Lilly and DPP agreed upon inclusion of the information in the Post-Marketing Safety section ————

doses) was slightly, but not dramatically, more likely to be associated with dropout due to AE.

Table 7.6
Likelihood of Premature Study Drug Discontinuation Due to Adverse Events by Dose

	Placebo	DLX 20 QD	DLX 60 QD	DLX 60 BID	DLX 120 QD
HMBO	11/103 (11%)			18/104 (17%)	
HMCA	14/120 (12%)		25/118 (21%)	27/116 (23%)	
HMCJ (first three months)[a]	17/144 (12%)	8/79 (10%)	22/150 (15%)		32/147 (22%)
HMEF (first 8 visits)[b]	14/168 (8%)		23/162 (14%)		
HMEH (open-label phase)			26/350 (7%)		
HMEH (double-blind phase)			14/104 (14%)		34/203 (17%)

[a]After three months, patients on 20 mg were changed to 60 mg QD
[b]After the first 8 visits, non-responders could be titrated upwards to 120 mg QD

In the FM database, the most common events leading to discontinuation which were more common in duloxetine-treated than placebo-treated patients were nausea, somnolence, fatigue, insomnia, headache, diarrhea, dizziness, hyperhidrosis and constipation. These are similar to the causes of discontinuation in the broader safety population.

Lilly's presentation of reasons for discontinuation by dose was tabulated by *highest tolerated dose*, showing the dose at which the patient discontinued taking the medication (rather than the treatment group to which the patient was assigned) because most studies included dose-titration to the final assigned dose. However, the denominators do not accurately reflect the total number of patients exposed to the dose because patients who were subsequently switched to another dose are not included in the N for a given column. Efforts to obtain more suitably-denominatored data from Lilly were not entirely successful; nevertheless, some conclusions can be drawn from the tabulations provided.

The tabulation by highest tolerated dose (shown in Dr. Dent's review) shows that 22 patients discontinued due to adverse events while taking 30 mg/day, which was only used as a titration dose. An estimated ~800 patients were exposed to 30 mg at some time during the studies and therefore the discontinuation rate would be approximately 3% over the 1-2 weeks of exposure to this dose. Gastrointestinal symptoms predominate as reasons for discontinuation during this early period of treatment.

7.2.2.4 Common AEs

Lilly reports that, Eli Lilly states that the following TEAEs had an incidence of $\geq$ 5% in duloxetine-treated patients in the fibromyalgia placebo-controlled studies and were more common in the duloxetine group than the placebo group: nausea, headache, dry mouth, insomnia, fatigue, constipation, diarrhea, dizziness, somnolence, hyperhydrosis, and decreased appetite. The Highlights section of the label currently mentions nausea, dry mouth, constipation, somnolence, hyperhidrosis, and decreased appetite but not the terms in italics below, because a rubric of "5% and at least twice the placebo rate" was used for the Highlights section. A more complete presentation, including all terms below, is in the Adverse Reactions section.

Treatment-Emergent Adverse Events by Decreasing Frequency Reported in ≥ 5 % Fibromyalgia Patients By MedDRA Preferred Term		
	Fibromyalgia Placebo-Controlled	
Event	PBO N=535 n(%)	DLX N=876 n(%)
ANY EVENT	425(79)	777(89)
Nausea	61(11)	257(29)
Headache	64(12)	175(20)
Dry mouth	29(5)	159(18)
Insomnia	49(9)	127(15)
Fatigue	38(7)	118(14)
Constipation	19(4)	127(15)
Diarrhoea	42(8)	102(12)
Dizziness	36(7)	96(11)
Somnolence	15(3)	84(10)
Hyperhidrosis	6(1)	60(7)
Decreased appetite	3(1)	57(7)
PBO = placebo, DLX = duloxetine Modified from Applicant's Table, Page 39, Clinical Safety Summary		

Lilly performed their analyses using MedDRA Preferred Terms (PT). At this level, a cut off of 5% is a very crude method of identifying adverse events. Moreover, the analyses combined all doses of duloxetine, including the (admittedly few) patients treated with doses below the 60 mg/day recommended for marketing and the large number of patients treated with twice the recommended dose. To better understand the adverse event profile of the recommended dose, and to more closely explore whether the 20 mg dose represented an important safety benefit over the recommended 60 mg dose, we asked Lilly for additional tabulations by dose. Since the 20 mg dose was used only for the first three months of Study HMCJ, Lilly combined data from the first three months of each of the placebo-controlled trials, which permitted a comparison across doses. In order to ensure that important drug-related events were not obscured by the use of multiple Preferred Terms for similar concepts, we looked at the tabulation by Higher Level Group Term (HLGT). Dr. Dent identified the most common and/or important HLGTs and constructed the table below. The highlighted rows indicate terms for which the 20 mg dose appears advantageous, or terms of particular interest. Note that there are relatively few HLGTs which are notably less common in the 20 mg group than in the 60 mg group. These include GI motility/defecation (subsumes both PT diarrhea and PT constipation), salivary gland conditions (primarily PT dry mouth), headaches, movement disorder (PT tremor), sleep disorder (PT insomnia), and anxiety disorders/symptoms.

An additional finding made obvious by this tabulation is the difference between 120 mg dosed as a single morning dose and 120 mg dosed as 60 mg BID. Sleep disorders are notably more common among the patients dosed BID (29%) compared with those dosed in the morning (20%). This suggests that duloxetine taken later in the day may impair sleep. Conversely, HLGT movement disorders (primarily PT tremor) were reported in 12% of patients treated with a single 120 mg dose daily, vs. 4% treated with the divided dose and 5% treated with a single 60 mg dose. This suggests that the size of the single dose is also important for some AEs. Rates were similar for 60 mg BID and 120 mg QD for a number of other terms.

Treatment-Emergent Adverse Events by Assigned Dose By System Organ Class and by High Level Group Term All Randomized Patients in Fibromyalgia Placebo-Controlled Studies at 3 Months (HMBO, HMCA, HMCJ & HMEF)					
EVENT **(Patients with ≥ 1 TEAE)**	**Placebo** **(N=535)n(%)**	**DLX 20 QD** **(N=79)n(%)**	**DLX 60 QD** **(N=430)n(%)**	**DLX 60 BID** **(N=220)n(%)**	**DLX 120 QD** **(N=147)n(%)**
All Body Systems Combined	394(73.64%)	65(82.28%)	367(85.35%)	191(86.82%)	130(88.44%)
Cardiac Disorders	12(2.24%)	2(2.53%)	11(2.56%)	5(2.27%)	6(4.08%)
Cardiac arrhythmias	4(0.75%)	0(0.00%)	3(0.70%)	0(0.00%)	1(0.68%)
Eye Disorders	16(2.99%)	5(6.33%)	18(4.19%)	10(4.55%)	11(7.48%)
Vision disorders	3(0.56%)	2(2.53%)	8(1.86%)	3(1.36%)	4(2.72%)
Eye disorders NEC	5(0.93%)	1(1.27%)	4(0.93%)	2(0.91%)	2(1.36%)
Gastrointestinal Disorders	147(27.48%)	34(43.04%)	227(52.79%)	115(52.27%)	78(53.06%)
Gastrointestinal signs and symptoms	87(16.26%)	24(30.38%)	148(34.42%)	70(31.82%)	51(34.69%)
Gastrointestinal motility and defecation conditions	61(11.40%)	12(15.19%)	96(22.33%)	34(15.45%)	36(24.49%)
Salivary gland conditions	26(4.86%)	7(8.86%)	72(16.74%)	43(19.55%)	27(18.37%)
General Disorders & Administration Site Conditions	101(18.88%)	17(21.52%)	98(22.79%)	72(32.73%)	33(22.45%)
General system disorders NEC	90(16.82%)	15(18.99%)	82(19.07%)	63(28.64%)	27(18.37%)
Immune System Disorders	12(2.24%)	1(1.27%)	6(1.40%)	8(3.64%)	4(2.72%)
Allergic conditions	12(2.24%)	1(1.27%)	6(1.40%)	8(3.64%)	4(2.72%)
Infections & Infestations	142(26.54%)	21(26.58%)	96(22.33%)	41(18.64%)	38(25.85%)
Infections – pathogen class unspecified	110(20.56%)	15(18.99%)	75(17.44%)	34(15.45%)	34(23.13%)
Viral infectious disorders	25(4.67%)	6(7.59%)	21(4.88%)	9(4.09%)	5(3.40%)
Bacterial infectious disorders	8(1.50%)	2(2.53%)	7(1.63%)	0(0.00%)	2(1.36%)
Investigations	15(2.80%)	1(1.27%)	24(5.58%)	13(5.91%)	16(10.88%)
Hepatobiliary investigations	3(0.56%)	0(0.00%)	6(1.40%)	1(0.45%)	2(1.36%)
Metabolism & Nutriton Disorders	28(5.23%)	9(11.39%)	50(11.63%)	30(13.64%)	22(14.97%)
Appetite and general nutritional disorders	20(3.74%)	7(8.86%)	44(10.23%)	27(12.27%)	19(12.93%)
Glucose metabolism disorders (incl diabetes mellitus)	1(0.19%)	1(1.27%)	2(0.47%)	0(0.00%)	2(1.36%)
Musculosketal & Connective Tissue Disorders	122(22.80%)	17(21.52%)	88(20.47%)	39(17.73%)	20(13.61%)
Musculoskeletal and connective tissue disorders NEC	62(11.59%)	9(11.39%)	36(8.37%)	23(10.45%)	6(4.08%)
Muscle disorders	29(5.42%)	6(7.59%)	32(7.44%)	17(7.73%)	13(8.84%)
Joint disorders	31(5.79%)	4(5.06%)	26(6.05%)	6(2.73%)	3(2.04%)
Nervous System Disorders	123(22.99%)	26(32.91%)	173(40.23%)	96(43.64%)	69(46.94%)
Neurological disorders NEC	62(11.59%)	15(18.99%)	89(20.70%)	57(25.91%)	45(30.61%)
Headaches	64(11.96%)	12(15.19%)	88(20.47%)	50(22.73%)	29(19.73%)
Movement disorders (incl Parkinsonism)	5(0.93%)	2(2.53%)	21(4.88%)	8(3.64%)	17(11.56%)
Mental impairment disorders	9(1.68%)	2(2.53%)	8(1.86%)	4(1.82%)	4(2.72%)
Sleep disturbances (incl subtypes)	4(0.75%)	1(1.27%)	6(1.40%)	3(1.36%)	0(0.00%)
Psychiatric Disorders	119(22.24%)	12(15.19%)	100(23.26%)	86(39.09%)	47(31.97%)
Sleep disorders and disturbances	55(10.28%)	6(7.59%)	58(13.49%)	64(29.09%)	29(19.73%)
Anxiety disorders and symptoms	29(5.42%)	2(2.53%)	23(5.35%)	20(9.09%)	9(6.12%)
Depressed mood disorders and disturbances	32(5.98%)	1(1.27%)	11(2.56%)	8(3.64%)	5(3.40%)
Sexual dysfunctions, disturbances & gender identity disorders	3(0.56%)	4(5.06%)	12(2.79%)	7(3.18%)	12(8.16%)
Changes in physical activity	3(0.56%)	3(3.80%)	10(2.33%)	3(1.36%)	7(4.76%)
Mood disorders and disturbances NEC	11(2.06%)	1(1.27%)	7(1.63%)	2(0.91%)	2(1.36%)
Suicidal and self-injurious behaviors NEC	2(0.37%)	0(0.00%)	0(0.00%)	0(0.00%)	1(0.68%)
Renal & Urinary Disorders	16(2.99%)	4(5.06%)	21(4.88%)	5(2.27%)	11(7.48%)
Urinary tract signs and symptoms	13(2.43%)	3(3.80%)	20(4.65%)	5(2.27%)	9(6.12%)
Respiratory, Thoracic & Mediastinal Disorders	40(7.48%)	11(13.92%)	37(8.60%)	21(9.55%)	18(12.24%)
Respiratory disorders NEC	29(5.42%)	8(10.13%)	28(6.51%)	11(5.00%)	16(10.88%)
Upper respiratory tract disorders (excl infections)	11(2.06%)	5(6.33%)	10(2.33%)	9(4.09%)	4(2.72%)
Skin and Subcutaneous Tissue Disorders	47(8.79%)	13(16.46%)	62(14.42%)	24(10.91%)	27(18.37%)
Skin appendage conditions	18(3.36%)	6(7.59%)	39(9.07%)	14(6.36%)	18(12.24%)

Epidermal and dermal conditions	25(4.67%)	6(7.59%)	22(5.12%)	8(3.64%)	9(6.12%)
Vascular Disorders	19(3.55%)	2(2.53%)	24(5.58%)	12(5.45%)	8(5.44%)
Vascular disorders NEC	12(2.24%)	2(2.53%)	17(3.95%)	9(4.09%)	6(4.08%)
N = Number of randomized patients, n = Number of patients with TEAE, for HMCJ & HMEF visit 8 is last visit of comparator period Applicant's Table, Regulatory Response 4-March-2008 – Adverse Events by Dose, Pages 94- 104.					

7.2.2.5 Laboratory tests and Vital Signs

As described above, elevations in alkaline phosphatase, AST, and ALT were noted in duloxetine-treated groups.

As noted in the product label for duloxetine, creatine phosphokinase (CPK) values were also found to be elevated in the fibromyalgia studies. CPK values in the placebo arms increased from a baseline value of 84 to an endpoint value of 86 (SD = 56), whereas duloxetine arms increased from a baseline value of 90 to an endpoint value of 116 (SD = 596). Dr. Dent reviewed all CPK values and found that in the fibromyalgia placebo-controlled studies, there were a total of 77 placebo-treated (n=504, 15%) and 157 duloxetine-treated (n=819, 19%) patients who developed an elevated CPK. For the duloxetine arm, CPK elevations did not appear to be dose-dependent. Also, many patients with elevated CPK values entered the trial with elevated baseline CPK values and many of these patients were not re-tested.

For hematology analytes, no clinically relevant trends were detected. Slight elevations in both eosinophils and platelets were noted.

The Cymbalta labeling mentions duloxetine's effects on heart rate and blood pressure. In the FM database, a mean change in pulse of 1.22 beat per minute was seen for duloxetine-treated patients at end of therapy. Diastolic blood pressure was noted to have a mean rise of 0.91 mmHg and systolic blood pressure 1.04 mmHg.

Weight was noted to decrease an average of 0.43 kg at endpoint in the placebo-controlled trials.

Baseline and on-treatment ECGs were collected during studies HMBO, HMEF, and HMCJ. No notable clinical findings were reported.

7.2.3 Safety update

Discussed above where pertinent.

7.2.4 Special safety concerns

7.2.4.1.1 Titration strategies

Titration schedules varied across the clinical studies. Titration to the 120 mg/day dose was as rapid as 3 days or as long as two weeks; titration to the recommended dose (60 mg/day) involved a week of treatment at 30 mg/day in all but one study (HMCA; patient were started on this dose right away). The table below, compiled from the sponsor's

study reports, illustrates the effect of titration schedule on the rate of dropout due to adverse events in studies which used the label-recommended dose, 60 mg/day.

	Length of titration	Placebo	DLX 60 QD
HMCA	None	14/120 (12%)	25/118 (21%)
HMCJ (first three months)[a]	One week	17/144 (12%)	22/150 (15%)
HMEF (first 8 visits)[b]	One week	14/168 (8%)	23/162 (14%)
HMEH (open-label phase)	One week		26/350 (7%)

[a]After three months, patients on 20 mg were changed to 60 mg QD
[b]After the first 8 visits, non-responders could be titrated upwards to 120 mg QD

The value of the titration step in improving tolerability seems clear from the data. Although the label currently suggests a titration step it is probably appropriate to recommend it for all patients.

7.2.5 Discussion of primary reviewer's comments and conclusions

I concur with Dr. Dent's conclusions regarding this application.

7.2.6 Pre-Approval Safety Conference

Not a New Molecular Entity.

7.2.7 Discussion of notable safety issues

The emphasis in the safety review of this application was on determining whether the safety profile of duloxetine in the FM population differed from the already-established safety profile in other populations. In general, no new safety findings were identified, with the exception of the observation that discontinuation-emergent symptoms occurred even with gradual discontinuation of duloxetine. Although some adverse effects occurred more commonly in the FM population than in the general population, this was true of both drug-treated and placebo-treated patients; the FM population did not seem more sensitive to the effects of duloxetine than the general population.

Once the potential for efficacy of the 20 mg/day dose was identified in the efficacy review, an additional emphasis was placed on exploring whether there were unique safety advantages of the 20 mg dose that were so apparent that approval of the 60 mg dose would be inappropriate. However, although some clearly dose-dependent adverse events are apparent, including the very concerning risk of hepatotoxicity, no obvious disadvantage of the 60 mg dose was identified in the safety review.

8 Advisory Committee Meeting

Not applicable. No advisory committee input was sought as this is not a new molecular entity nor is this the first approval for this indication.

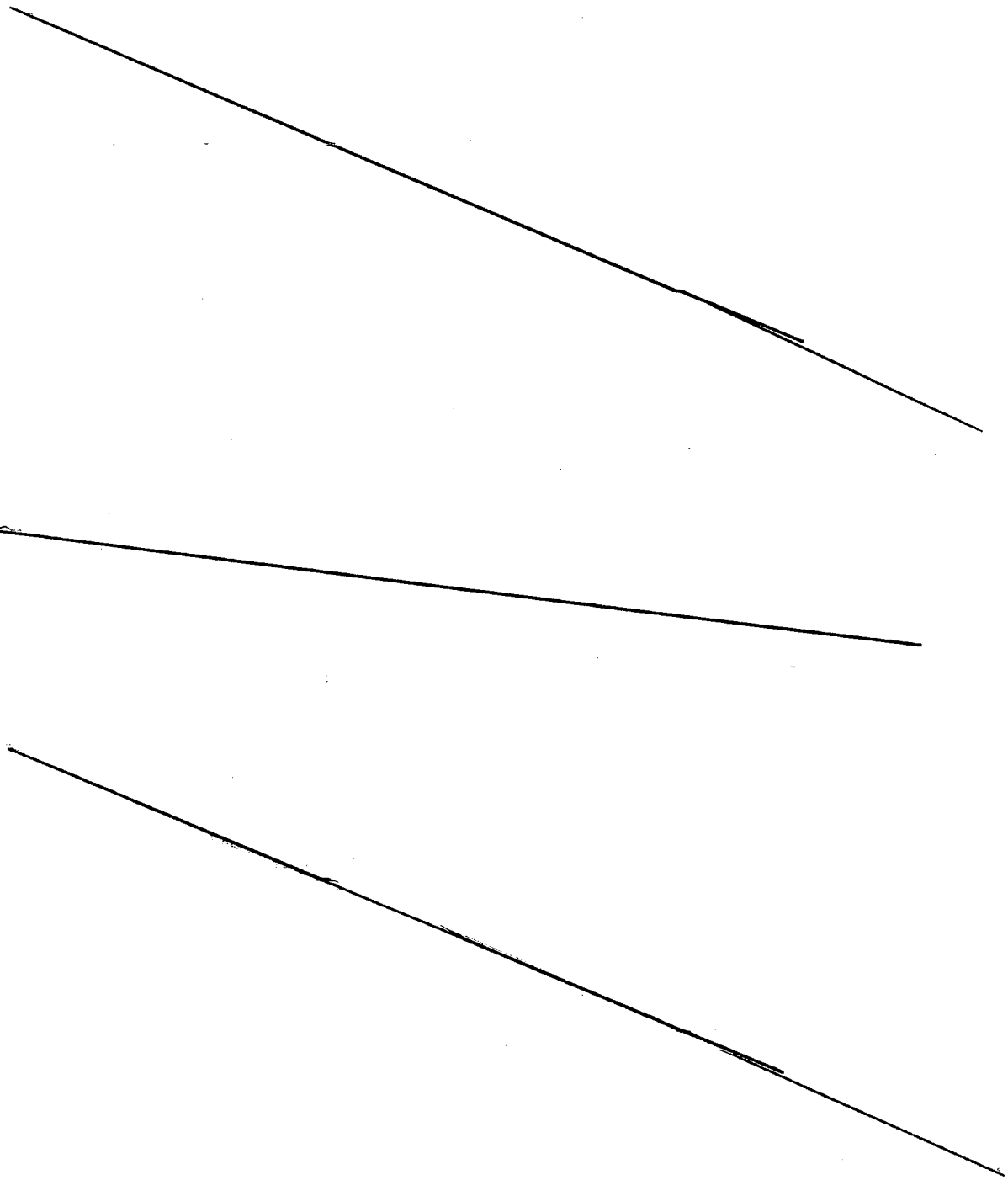
9 Financial Disclosure

No issues were identified in Dr. Dent's review of the financial disclosure information.

10 Labeling

10.1 *Proprietary name*

No proprietary name review required for this efficacy supplement.



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✓ Trade Secret / Confidential

_____ Draft Labeling

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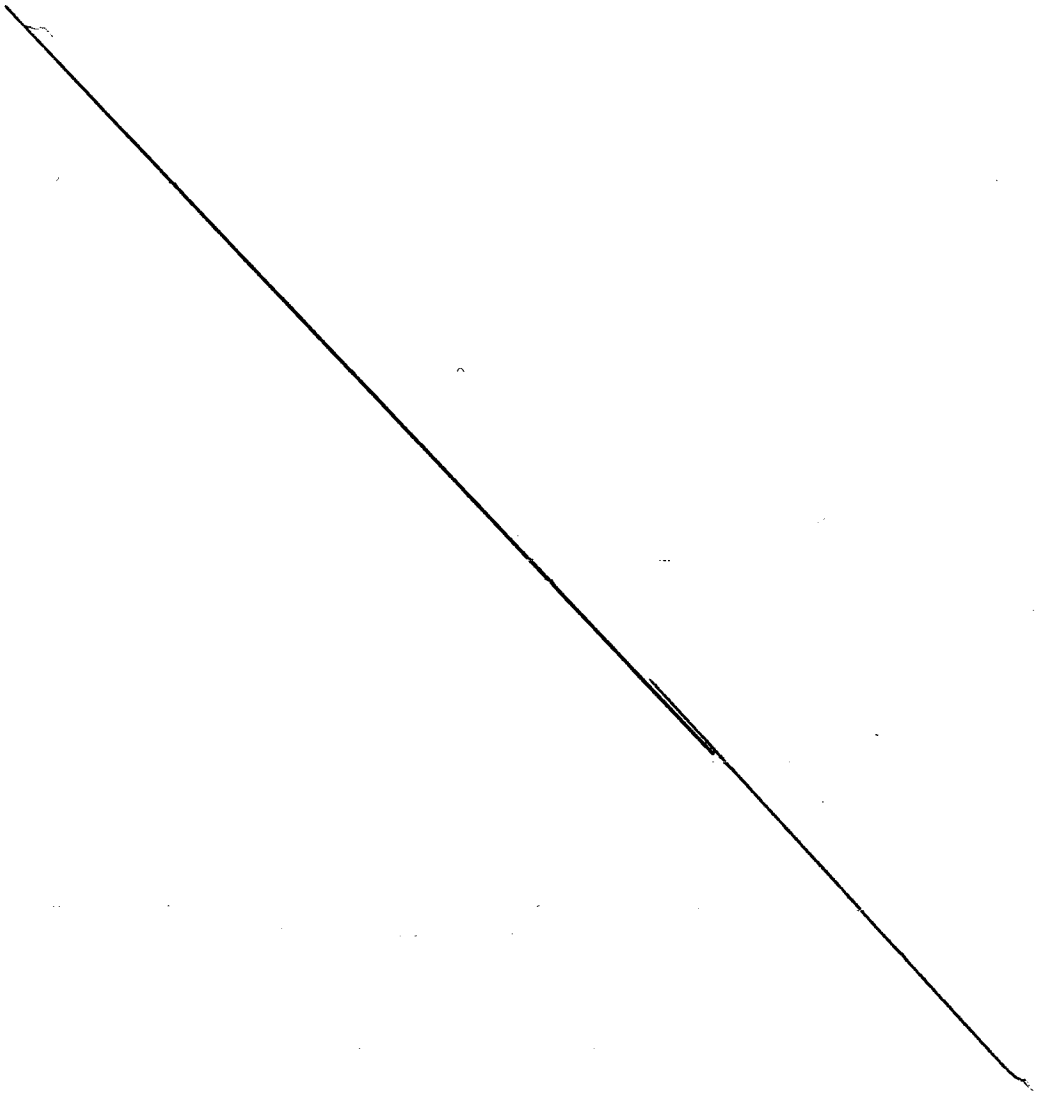


11.1 *Patient labeling/Medication Guide*

A Medication Guide is already included in the labeling, conveying the antidepressant class information about suicide risk. No additional findings warranting patient labeling for the fibromyalgia population were identified.

12 DSI Audits

Sites to be inspected by the Division of Scientific Investigation (DSI) for Studies HMCA and HMCJ were chosen based on enrollment, and also included the one investigator who reported significant financial interest in Lilly. No issues were identified by DSI that would affect the interpretation of the results.

However, after the primary medical review was finalized, Dr. Dent learned from Lilly that one investigator who enrolled 18 patients in Study HMEH, [redacted] The patients involved had also

been involved in Study HMEH. Lilly states that the violations (not properly completing case report forms and substituting phone calls for office visits) were note seen during HMEH at this site. Nevertheless, Dr. Buenconsejo identified ——— patients and determined that exclusion of the patients from our examination of the efficacy data would have no effect on the conclusions. (No statistical conclusions were drawn from this study.)

13 Conclusions and Recommendations

13.1 *Recommended regulatory action*

Approval of this supplemental indication is recommended.

The review team is in agreement that the studies included in this application provide substantial evidence of efficacy of duloxetine 60 mg, once daily, as a ———for fibromyalgia. Although evidence of efficacy for duloxetine 120 mg/day is also presented,[4] the data do not demonstrate any incremental benefit of this dose.

The drug has beneficial effects on pain and on indicators of function and patients' perceptions of well-being. Balanced against these benefits, the drug presents risks of several common, bothersome but non-serious adverse effects, including nausea, headache, dry mouth, insomnia, fatigue, constipation, diarrhea, dizziness, somnolence, hyperhidrosis and anorexia. In addition, it is associated with several more serious risks, most notably including hepatotoxicity. To ensure a favorable risk/benefit ratio, the labeling should clearly discourage use of higher doses of duloxetine, which have not been shown to provide incremental benefit, and Lilly should be asked to further explore the efficacy of lower doses of duloxetine.

13.2 *Safety concerns to be followed postmarketing*

The Division of Psychiatry Products will continue to follow the already-identified safety signals. This review did not reveal any previously-unidentified safety issues.

13.3 *Risk Evaluation and Mitigation Strategies*

In discussions with the Division of Psychiatry Products, the possibility of increasing the prominence of the hepatotoxicity warning in the label will be discussed. If it seems appropriate to add this information to the existing Medication Guide, this would constitute a REMS under the FDAAA legislation.

13.4 *Postmarketing Studies*

13.4.1 Identify Lowest Effective Dose

Given the adverse event profile of Cymbalta, which includes a number of potentially serious toxicities, and the evidence of efficacy for the 20 mg/day dose provided by the

[4] Although HMCA used 60 mg BID and HMCJ used 120 mg QD, I believe that, taken together, they provide support for a total daily dose of 120 mg/day.

results of study HMCJ, I believe it would be prudent to further explore whether lower doses of Cymbalta may be effective for the treatment of FM.

13.4.2 Identify Effective Dose for Male Patients

If feasible, Lilly should continue to evaluate duloxetine for the treatment of fibromyalgia in male patients. A higher dose may be necessary due to differences in clearance.

13.4.3 Determine Safety in Pregnant Patients

Because fibromyalgia affects women of child-bearing age, Lilly should evaluate the safety of duloxetine in pregnant patients with fibromyalgia, through such mechanisms as a pregnancy registry. This study would be considered a Post-Marketing Requirement under FDAAA.

13.4.4 Determine Safety and Efficacy in Pediatric Patients

Fibromyalgia occurs in pediatric patients. Therefore, as required under the Pediatric Research and Equity Act, studies in pediatric patients should be performed to evaluate the safety and efficacy of duloxetine in this population. This study would be considered a Post-Marketing Requirement.

APPENDIX

13.4.4.1 Study F1J-MC-HMCA ("HMCA"): Duloxetine Versus Placebo in the Treatment of Fibromyalgia [Female] Patients With or Without Major Depressive Disorder

This was a multi-center randomized, double-blind, placebo-controlled, parallel-group study to assess the efficacy of 12 weeks of treatment with duloxetine (60 mg QD and 60 mg BID) compared with placebo on the reduction of pain severity as measured by the average pain item on the Brief Pain Inventory (BPI) in patients with FM. The study was conducted at 21 US centers between 11/7/02-10/14-03.

Study participants were female outpatients ≥18 years of age who met the criteria for fibromyalgia as defined by the ACR: widespread aching pain in all four quadrants of the body and skeleton for >3 months duration and ≥11 of 18 tender points under digital palpitation examination an approximate force of 4 kg/cm2. A score of ≥4 on the average pain item of the BPI at Visit 2 was required for entry.

Eligible patients were randomized 1:1:1 to duloxetine 60 mg twice daily (BID), duloxetine 60 mg once daily (QD), or placebo, stratified into two groups: women with current MDD and women without current MDD. Medication was administered as 30 mg duloxetine capsules and matching placebo. Patients assigned to 60 mg BID began treatment with three days of 60 mg QD. Study visits occurred at 1, 2, 4, 6, 8, 10, and 12 weeks of treatment and at week 13 during the discontinuation phase. Efficacy assessments included BPI, Fibromyalgia Impact Questionnaire (FIQ) performed at each visit, and patient and clinician global assessments of improvement at weeks 4, 8, and 12.

The Hamilton Depression scale (HAM-D) was used to assess severity of depression for the purposes of exploring relationships between pain relief and the effect of duloxetine on depression.

A total of 746 patients were screened and 354 were randomized (120 patients in the placebo group, 118 patients in the duloxetine 60 QD group and 116 patients in the duloxetine 60 BID group). The patients were primarily (90%) Caucasian, with a median age of 51 years (49-52 across groups). 25-28% of each group met criteria for MDD, and each group had a wide range of HAM-D scores (from 1 to as high as 32). Baseline severity of pain and FM impact were similar (median FIQ score, 52-53; median BPI average pain, 6).

The table below, constructed from the sponsor's study report, illustrates patient disposition.

	Placebo N = 120	DLX 60 QD N = 118	DLX 60 BID N = 116
Completed acute phase	68 (57%)	77 (65%)	71 (61%)
Discontinued			
Adverse Event	14 (12%)	25 (21%)	27 (23%)
Patient decision	4 (3%)	1 (1%)	4 (4%)
Physician decision		1 (1%)	
Noncompliance	1 (1%)	3 (3%)	1 (1%)
Protocol Violation	1 (1%)		
Lack of Efficacy	18 (15%)	7 (6%)	4 (3%)

Medication exposure and compliance are summarized below by Dr. Buenconsejo:

> 61% of patients in the placebo group, 69% patients in the duloxetine 60 QD group, and 66% in duloxetine 60 BID group received at least 63 days (or 9 weeks) of study medication during acute therapy phase. The median durations of exposure were similar for all treatment groups: 86 days in placebo, 88 days in duloxetine 60 QD, and 88 days in duloxetine 60 BID group. However, patients in the duloxetine groups were more likely to have less than 7 days of exposure compared with patients in the placebo group. Patients in the placebo group were more likely to have 21 to 63 days of exposure compared with patients in the duloxetine groups. These differences are due to patients in the duloxetine treatment groups withdrawing because of adverse events during the first weeks of treatment more often than patients in the placebo treatment group. In general, patients were compliant with study drug administration during the study. In addition, at least 55% in the placebo group, 63% in the duloxetine 60 QD group, and 61% in the duloxetine 60 BID group remained compliant at Visit 9 (i.e. Week 12).

Protocol violations primarily involved visits outside the protocol-specified windows, which are of little significance as the endpoint analysis is of primary concern. A number of patients used prohibited concomitant medications (as many as 20% of the responders), even with these patients excluded, the response rates are consistently higher in drug-treated than in placebo-treated patients.

Results: Applicant's analysis

Lilly analyzed the change from baseline to endpoint in the BPI average pain score, using last-observation-carried-forward as an imputation strategy for missing data. The PGI-I was also analyzed using a similar approach. The table below is constructed from Lilly's Table 2.5.4.2 (clinical summary).

Treatment Group	BPI average pain score			PGI-I score	
	Baseline	LS Mean Change	p-value	LSMean at Endpoint	p-value
Placebo	6.47	-1.16		3.79	
DLX 60 QD	6.38	-2.39	<.001	3.17	.005
DLX 60 BID	6.36	-2.40	<.001	3.13	.003

Results: Reviewer's analysis

Dr. Buenconsejo explored the results using different imputation strategies, and also used various responder-analysis approaches.

She notes:

> The LOCF method was the primary approach used to impute missing data in all placebo-controlled studies. In general, the LOCF approach applies to data that is considered to be missing completely at random and unrelated to the treatment. However, patients who drop out of the studies due to treatment-related adverse events are not randomly missing but are non-responders. Assigning potentially good scores to patients who drop out for treatment-related adverse events can inflate the treatment effect. The Applicant did not perform any additional sensitivity analyses to handle missing data. Instead, they performed additional analysis using mixed model repeated measures approach to evaluate pain and global improvement over time without the intention, as far as I can tell, to correct for missing data.
>
> Therefore in my re-analyses, two imputation strategies were applied to missing data in the BPI average pain score, namely baseline observation carried forward (BOCF), and a hybrid LOCF/BOCF. In the hybrid LOCF/BOCF strategy, patients who dropped out of the study due to adverse events were assigned their baseline score, while the remaining patients who dropped out were assigned their last observed score. Furthermore, all randomized patients were included in the analyses. On the other hand, worst observation carried forward strategies were applied to missing data in the patient global improvement rating score.

The results of her analysis of change from baseline in mean pain scores using different imputation strategies is shown in the table below (constructed from Dr. Buenconsejo's review)

		BPI Average Pain Score (BOCF)			BPI Average Pain Score (LOCF/BOCF)	
Study	Treatment Group	Baseline	LSMean Change	p-value	LSMean Change	p-value
HMCA	Placebo	6.52	-0.9		-1.0	
	Duloxetine 60 mg QD	6.37	-2.1	<0.001†	-2.2	<0.001†
	Duloxetine 60 mg BID	6.37	-1.8	0.001	-2.1	<0.001

†unadjusted p-value.

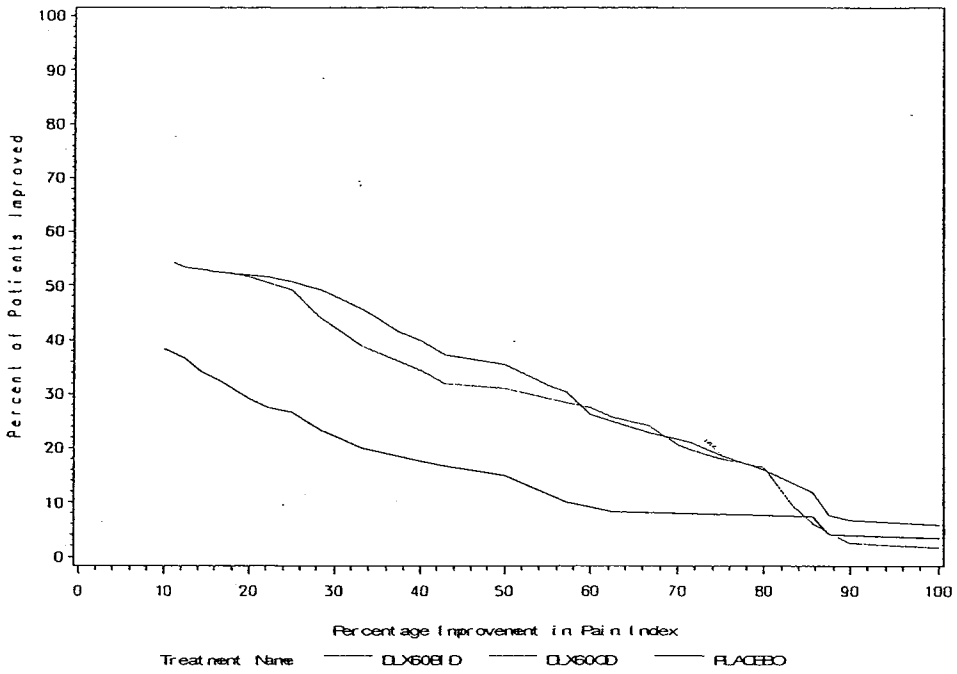
These analyses confirm Lilly's conclusion that both doses of duloxetine are superior to placebo in reduction of mean pain scores, but also further underscores the apparent lack of incremental benefit of the higher dose over the lower dose.

Dr. Buenconsejo also analyzed the proportion of subjects responding to treatment, defined either as experiencing a 30% or better reduction in pain compared to baseline, or a 50% or better reduction. She then constructed a cumulative response profile across a full range of responder definitions. The results of these analyses are shown below in a table constructed from her review, and a figure taken from her review.

		≥ 30% Improvement in Pain			≥ 50% Improvement in Pain	
Study	Treatment Group	N	n(%)	p-value	n(%)	p-value
HMCA	Placebo	120	24 (20%)		18 (15%)	
	Duloxetine 60 mg QD	118	54 (46%)	<0.001	42 (36%)	<0.001
	Duloxetine 60 mg BID	116	45 (39%)	0.002	36 (31%)	0.003

Appears This Way
On Original

Figure 3: Overall Response Profile for Study HMCA



These analyses further confirm the efficacy of duloxetine; however they also underscore the lack of relative benefit of the higher dose.

Other analyses performed by Dr. Buenconsejo illustrate that responders to treatment experience observable improvement in pain scores as early as a week after beginning treatment, and that further improvements are observed as the dose is titrated upward.

13.4.4.2 Study F1J-MC-HMCJ ("HMCJ"): Dose Response Study of Duloxetine Versus Placebo in the Treatment of Fibromyalgia Syndrome

This was a Phase 3, multi-center, randomized, double-blind, parallel-groups, placebo-controlled trial designed to assess the efficacy and safety of duloxetine as measured by the average pain item of the Brief Pain Inventory (BPI-Modified Short Form) and Patient's Global Impressions of Improvement (PGI-Improvement) in patients with American College of Rheumatology (ACR)-defined primary FM, with or without major depressive disorder (MDD). The study was conducted at 38 US centers from 6/16/05-11/16/06.

Study participants were male and female outpatients ≥18 years of age who met the criteria for fibromyalgia as defined by the ACR: widespread aching pain in all four quadrants of the body and skeleton for >3 months duration and ≥11 of 18 tender points under digital palpitation examination an approximate force of 4 kg/cm2. A score of ≥4 on the average pain item of the BPI at Visit 1 and Visit 2 was required for entry.

Eligible patients were randomized 2:1:2:2 to duloxetine 20 mg QD (to be increased to 60 mg QD after three months), duloxetine 60 mg once daily (QD), duloxetine 120 mg QD, or placebo, stratified into two groups: patients with current MDD and patients without current MDD. Medication was administered as 20 mg, 30 mg and 60 mg duloxetine capsules and matching placebo. Patients assigned to 20 mg QD were treated with 20 mg QD for 15 weeks and then were blindly switched to 60 mg QD for the continuation phase of 13 weeks. Patients assigned to 60 mg QD began with one week of 30 mg QD followed by 14 weeks of 60 mg QD ("acute phase") and another 13 weeks on the same dose ("continuation phase"). Those who were assigned to the 120 mg QD condition spent one week on 30 mg QD, one week on 60 mg QD, and then 13 weeks on 120 mg QD ("acute phase") and another 13 weeks on the same dose in the continuation phase. All subjects completing the continuation phase could continue to the extension phase.

Those continuing to the extension phase were switched to 120 mg QD for 28 weeks, followed by a three week taper.

Study visits occurred at 1, 2, 4, 8, 11, 15, 19, 23, 28, 32, 40, 48, and 56 weeks of treatment and at week 58 during the discontinuation phase. Efficacy assessments included BPI and patient global assessment of improvement performed at each visit during the acute therapy phase and the continuation phase, and twice during the 28-week extension phase, and the Fibromyalgia Impact Questionnaire (FIQ) performed approximately monthly.

The Hamilton Depression scale (HAM-D) was used to assess severity of depression for the purposes of exploring relationships between pain relief and the effect of duloxetine on depression.

A total of 520 patients were randomized (144 patients in the placebo group, 79 patients in the duloxetine 20 QD group, 150 in the duloxetine 60 QD group, and 147 patients in the duloxetine 120 QD group). Most of the patients were women (95% of overall enrollment) and the treatment groups ranged from 91% to 97% female. This discrepancy would be more concerning if the overall enrollment of male patients were not extremely low. It is unlikely that differential response in men vs. women would influence the outcome given the very low enrollment. The patients were primarily (84%) Caucasian, with a median age of 53 years (broadly similar across groups). From 23% to 28% of each group met criteria for MDD, and nearly half of the patients had a history of antidepressant use. Baseline severity of pain and FM impact were similar (median FIQ score, 52-56; median BPI average pain, 6-7).

The table below, constructed from the sponsor's study report, illustrates patient disposition for the first three month ("acute") phase. Because Lilly was informed that studies of 6-months' duration were no longer required for approval, emphasis is placed on the results from this initial three-month phase of the study.

	Placebo N = 144	DLX 20 QD N = 79	DLX 60 QD N = 150	DLX 120 QD N = 147
Completed acute phase	84 (58%)	49 (62%)	97 (65%)	95 (65%)
Discontinued				
Adverse Event	17 (12%)	8 (10%)	22 (15%)	32 (22%)
Patient decision	10 (7%)	8 (10%)	11 (7%)	6 (4%)
Physician decision	1 (1%)	1 (1%)	1 (1%)	
Lost to follow-up	13 (9%)	3 (4%)	7 (5%)	7 (5%)
Protocol Violation	5 (3%)	1 (1%)	3 (2%)	2 (1%)
Lack of Efficacy	14 (10%)	8 (10%)	9 (6%)	5 (3%)
Exclusion Criteria		1 (1%)		

Medication exposure and compliance are summarized below by Dr. Buenconsejo:

In Study HMCJ, 39% of patients in placebo group, 53% patients in the duloxetine 20 mg QD, 40% in the duloxetine 60 QD group, and 47% in duloxetine 120 QD group received at least 105 days of study medication during the 3-month acute therapy phase. The median durations of exposure were almost similar for all treatment groups: 103 days in placebo, 105 days in duloxetine 20 QD, 104 days in duloxetine 60 QD, and 104 days in duloxetine 120 QD group. In general, patients were compliant with study drug administration during the study. In addition, at least 60% in the placebo group, 70% in the duloxetine 20 QD group, 69% in the duloxetine 60 QD group, and 69% in the duloxetine 120 QD group remained compliant at Visit 8 (i.e. Week 12 of the 3-month therapy phase).

Approximately 10% of the patients took prohibited concomitant medications, and there was some imbalance across treatment groups. However, analysis of response rates with and without these patients confirm the drug effect.

Results: Applicant's analysis

Lilly analyzed the change from baseline to endpoint in the BPI average pain score, using last-observation-carried-forward as an imputation strategy for missing data. The PGI-I was also analyzed using a similar approach. The table below is constructed from Lilly's Table 2.5.4.2 (clinical summary).

Treatment Group	BPI average pain score			PGI-I score	
	Baseline	LS Mean Change	p-value	LSMean at Endpoint	p-value
Placebo	6.57	-1.38		3.39	
DLX 20 QD	6.74	-1.92	.097	2.85	.009
DLX 60 QD	6.46	-2.00	.022	3.04	.044
DLX 120 QD	6.41	-2.31	<.001	2.89	.004

Results: Reviewer's analysis

Dr. Buenconsejo explored the results using different imputation strategies, and also used various responder-analysis approaches.

A summary table of effects of duloxetine on average pain scores based on Dr. Buenconsejo's reanalysis of the data is shown below. The conclusions depend, to some degree, on the imputation strategy selected. However, as shown below, consistent results in other analyses point to an effect of duloxetine:

Brief Pain Inventory Average Pain Score Mean Change from Baseline to Endpoint at Endpoint: All Randomized Patients in the 3-Month Therapy, HMCJ

	BPI Average Pain Score (BOCF)			BPI Average Pain Score (LOCF/BOCF)	
Placebo	6.58	-1.1		-1.2	
Duloxetine 20 mg QD	6.77	-1.6	0.135†	-1.9	0.039†
Duloxetine 60 mg QD	6.49	-1.6	0.065	-1.8	0.036
Duloxetine 120 mg QD	6.39	-1.7	0.036	-1.8	0.038

†unadjusted p-value.

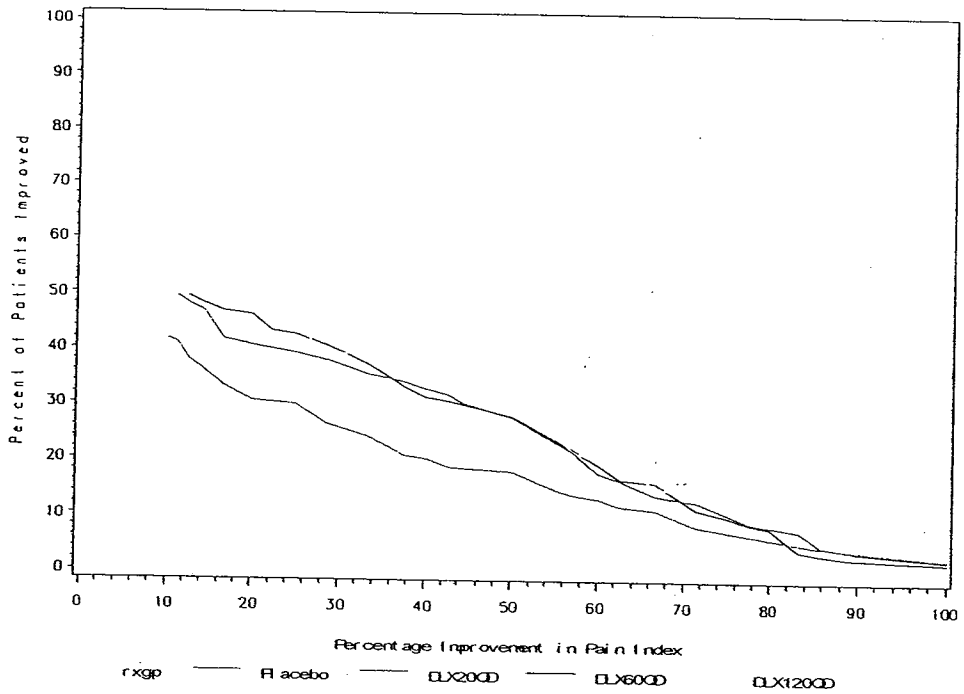
The table below illustrates Dr. Buenconsejo's calculation of responder rates using two different definitions of treatment response. In addition to showing the superiority of duloxetine 60 mg or 120 mg over placebo, this tabulation illustrates the numerical, although not statistically significant, similarity between the response rates on the 20 mg QD dose and the higher doses. Furthermore, it displays the lack of apparent benefit of 120 mg over 60 mg.

Responder Analysis of Brief Pain Inventory Average Pain Score at Endpoint: All Randomized Patients in the 3-Month Therapy, HMCJ

	≥ 30% Improvement in Pain			≥ 50% Improvement in Pain	
Treatment Group	N	n(%)	p-value	n(%)	p-value
Placebo	144	37 (26%)		26 (18%)	
Duloxetine 20 mg QD	79	28 (35%)	0.126	22 (28%)	0.089
Duloxetine 60 mg QD	150	56 (37%)	0.032	42 (28%)	0.043
Duloxetine 120 mg QD	147	57 (39%)	0.017	44 (30%)	0.018

Dr. Buenconsejo also constructed curves showing the proportion of patients considered responders across the full range of possible response definitions. These are shown below. In this figure, the placebo group is clearly different from the duloxetine groups, but little difference across duloxetine doses is apparent.

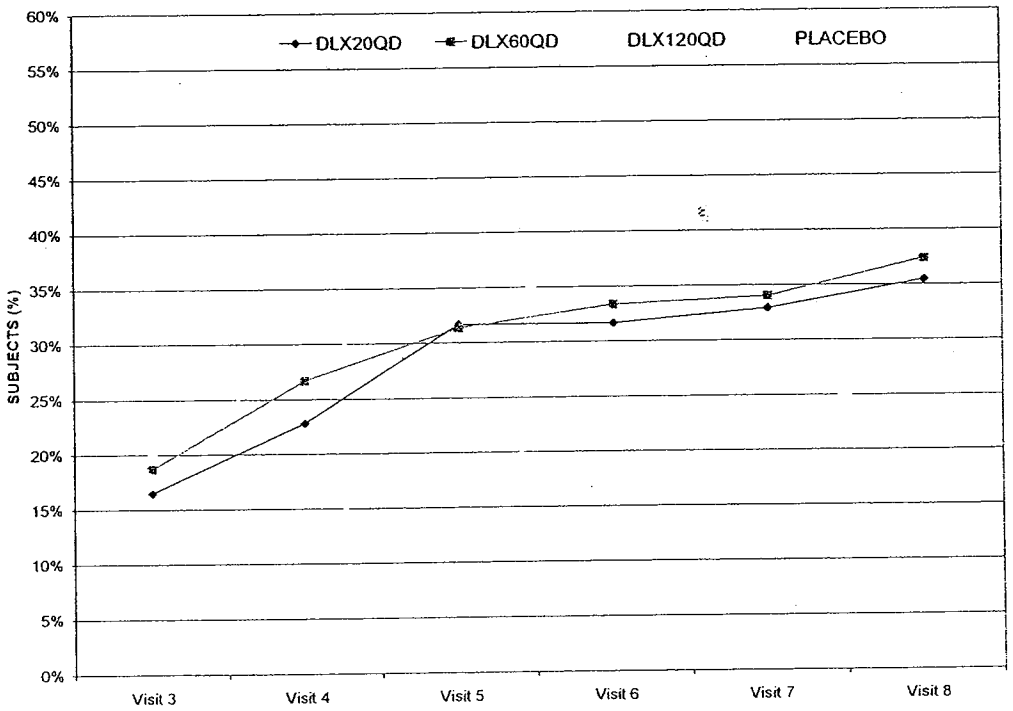
Overall Response Profile for Study HMCJ at 3 months



Dr. Buenconsejo also explored the time-course of treatment response. Lilly proposed to claim that "Separation from placebo on the BPI average pain score occurred at one week and persisted throughout the 12 weeks of the study." Because the time point at which

group mean scores in the treatment group differ from those in the placebo group has little clinical implication, she instead looked at those patients who were considered responders at the 3-month time point and plotted how many had responded by Week 1, 2, 3, etc. This analysis demonstrated that quite a few patients did experience a treatment response (30% reduction in pain) as early as Week 1.

Proportion of Responders by Week (30% Improvement) – Study HMCJ



Other endpoints assessed in the efficacy studies included function (Fibromyalgia Impact Questionnaire; FIQ) and global impression of improvement (PGI). Dr. Buenconsejo notes that:

> ... it is difficult to draw any conclusions from the analyses of these endpoints because multiplicity adjustments were not applied to these endpoints.

Nonetheless, the trends are notable and a treatment effect on these endpoints is apparent. The tables below summarize the results of the analyses of FIQ and patient global assessments. Note that WOCF indicates "worst observation carried forward" as there was no baseline score for the patient global impression of change.

Fibromyalgia Impact Questionnaire Total Score Change from Baseline to Endpoint*: All Randomized Patients in the 3-Month Therapy Phase HMCJ

	FIQ Total Score (BOCF)			FIQ Total Score (LOCF/BOCF)	
Treatment Group	Baseline	LSMean Change	p-value†	LSMean Change	p-value†
Placebo	53.0	-8.0		-9.1	
Duloxetine 20 mg QD	54.0	-11.1	0.130	-13.3	0.053
Duloxetine 60 mg QD	51.7	-12.1	0.017	-12.9	0.032
Duloxetine 120 mg QD	51.7	-11.7	0.030	-12.7	0.048

*negative implies improvement
†unadjusted p-value

PGI-Improvement at Endpoint: All Randomized Patients in the 3-Month Therapy Phase HMCJ

			PGI Improvement Score (LOCF)		PGI Improvement Score (WOCF)	
Study	Treatment Group	N	LSMean Change	p-value	LSMean Change	p-value
HMCJ**	Placebo	139	3.4		3.6	
	Duloxetine 20 mg QD	77	2.9	0.012†	3.1	0.010†
	Duloxetine 60 mg QD	143	3.0	0.026	3.1	0.009
	Duloxetine 120 mg QD	142	2.9	0.004	3.0	0.002

**GLM Model: PGIImp=Treatment+Pool Investigator
†unadjusted p-value.

Results: 6-month Timepoint

Lilly's own analysis, using LOCF, does support an effect of duloxetine at the 6-month time point.

Brief Pain Inventory Average Pain Score Mean Change from Baseline to Endpoint (Six Months) and PGI Improvement at Endpoint: All Randomized Patients in the 6-Month Therapy Phase Study HMCJ

	BPI Average Pain Score (LOCF)			PGI-Improvement (LOCF)		
Treatment Group	Baseline	LSMean Change	p-value	Baseline	LSMean Endpoint	p-value
Placebo	6.57	-1.4		4.06	3.4	
Duloxetine 20 mg QD	6.74	-2.3	0.018	4.20	2.8	0.006
Duloxetine 60 mg QD	6.46	-1.9	0.041	3.78	3.1	0.108
Duloxetine 120 mg QD	6.41	-2.1	0.003	3.82	2.9	0.012

Source: Clinical Study Report HMCJ, page 128 and 130

However, reanalysis by Dr. Buenconsejo using different imputation strategies does not support this conclusion. Her results are shown below:

Brief Pain Inventory Average Pain Score Mean Change from Baseline to Endpoint (Six Months): All Randomized Patients in the 6-Month Therapy Study HMCJ

	BPI Average Pain Score (BOCF)			BPI Average Pain Score (LOCF/BOCF)		BPI Average Pain Score (LOCF/BOCF)*	
Treatment Group	Baseline	LSMean Change	p-value	LSMean Change	p-value	LSMean Change	p-value
Placebo	6.58	-1.1		-1.2		-1.2	
Duloxetine 20 mg QD/60 mg QD	6.77	-1.9	0.018	-2.2	0.003	-2.2	0.004
Duloxetine 60 mg QD	6.49	-1.4	0.391	-1.7	0.048	-1.7	0.057
Duloxetine 120 mg QD	6.39	-1.4	0.251	-1.7	0.093	-1.6	0.121

* Eight patients who dropped out at Visit 11 retained their Visit 11 score.

Responder Analysis of Brief Pain Inventory Average Pain Score at Endpoint: All Randomized Patients in the 6-Month Therapy Phase Placebo-Controlled Study: F1J-MC-HMCJ

		≥ 30% Improvement in Pain			≥ 50% Improvement in Pain	
Study	Treatment Group	N	n(%)	p-value	n(%)	p-value
HMCJ	Placebo	144	37 (26%)		21 (15%)	
	Duloxetine 20/60 mg QD	79	30 (38%)	0.056	24 (30%)	0.005
	Duloxetine 60 mg QD	150	42 (28%)	0.656	33 (22%)	0.101
	Duloxetine 120 mg QD	147	47 (32%)	0.237	34 (23%)	0.063

In order to understand why the drug appears to work for the first three months but no longer demonstrates statistically significant effects at six months, Dr. Buenconsejo and I explored the possible reasons for this outcome. If large numbers of dropouts for various reasons occurred over the second three months, the BOCF imputation strategy which assigns a "nonresponder" status to each dropout could obscure a result in patients who remained on-study. To determine whether the apparent lack of efficacy at the 6-month time point was simply a result of our data imputation strategy combined with patients dropping out over time, we examined the fate of patients who were considered responders at the three-month point. At the 6-month time-point, 61% of the original 56 responders to 60 mg/day of duloxetine still met the 30% improvement from baseline criteria. As shown in the table below, a similar proportion of the patients in the 120 mg/day remained in the responder category, but sustained response was more common among patients switched from 20 mg to 60 mg, and among placebo-treated patients.

Responder Status (30% improvement) Endpoint based on responder status at three months: All Randomized Patients in the 6-Month Therapy Phase, HMCJ

	Responders at 3 months			NonResponders at 3 months	
Treatment Group	N	Remained Responders at 6 months	Became non-responders at 6 months	N	Became responders at 6 months
Placebo	37	27 (73%)	10 (27%)	107	10 (9%)
Duloxetine 20/60 mg QD	28	22 (79%)	6 (21%)	51	8 (16%)
Duloxetine 60 mg QD	56	34 (61%)	22 (39%)	94	8 (9%)
Duloxetine 120 mg QD	57	35 (61%)	22 (39%)	90	12 (13%)

The remaining patients fell into two categories—patients who discontinued, and patients who continued on drug but whose pain scores increased to the point that they no longer met the responder definition. Both are coded as non-responders in a BOCF analysis. To understand more fully what actually happened, we identified those patients who were coded as becoming nonresponders based on *observed* information: either an endpoint pain score that was no longer 30% below baseline, or a discontinuation due to lack of efficacy. We found that the drug "stopped working" for 22% of placebo responders between months 3 and 6, vs. 29% of duloxetine 60 mg QD responders and 26% of duloxetine 120 mg QD responders. It is also notable that some patients who were not considered responders at the 3 month timepoint experienced sufficient improvement in pain to be considered responders at 6 months, but this was as common among placebo-treated patients as among those treated with 60 mg/day of duloxetine. To some extent, this represents fluctuation in severity of illness, and it is difficult to draw conclusions about these findings other than to report them in the label.

13.4.4.3 Protocol F1J-MC-HMEH: See Dr. Dent's Review

Also note data quality concerns for Site 202 in section 12.

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

/s/

Celia Winchell
5/2/2008 02:50:02 PM
MEDICAL OFFICER