CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-148

SUMMARY REVIEW

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

Summary Review for Regulatory Action

Date	June 13, 2008
From	Bob A. Rappaport, M.D. Director Division of Anesthesia, Analgesia and Rheumatology Products
Subject	Division Director Summary Review
NDA #	22-148
Applicant Name	Eli Lilly
Date of Submission	August 14, 2007
PDUFA Goal Date	June 13, 2008
Proprietary Name / Established (USAN) Name	Cymbalta Duloxetine
Dosage Forms / Strength	20 mg, 30 mg and 60 mg Delayed-release capsules
Proposed Indication	For the management of fibromyalgia
Action:	approval

Material Reviewed/Consulted OND Action Package, including:	
Medical Officer Review	Ricardo E. Dent, M.D.
Statistical Review	Joan Buenconsejo, Ph.D.; Dionne Price, Ph.D.
Consultative Reviews	Marc Stone, M.D., Division of Psychiatric Products; Richardae Araojo, Pharm.D., Karen Feibus, M.D., Lisa Mathis, M.D., Maternal Health Team
Pharmacology Toxicology Review	N/A
CMC Review/OBP Review	N/A
Microbiology Review	N/A
Clinical Pharmacology Review	Emmanuel O. Fadiran, R.Ph., Ph.D., Suresh Doddapaneni, Ph.D., Jogarao V. Gobburu, Ph.D.
DDMAC	N/A
DSI	Sherbert Samuels, R.N., M.P.H., Constance Lewin, M.D., Ph.D.
CDTL Review	Celia Jaffe Winchell, M.D.
OSE/DMEDP	N/A
OSE/DAEA	N/A
OSE/DRISK	N/A
OSE/DEPI	N/A

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

1. Introduction

Cymbalta is a selective serotonin and norepinephrine reuptake inhibitor that was initially approved for the treatment of major depressive disorder and for the treatment of the pain associated diabetic peripheral neuropathy in 2004. This was followed by approvals for generalized anxiety disorder and maintenance treatment of major depressive disorder in 2007. Eli Lilly has now submitted a supplemental application for the management of fibromyalgia [redacted] This application has been submitted as a Type 6 NDA as the approved application is held by the Division of Psychiatry Products (DPP). The referenced application is NDA 21-427.

The review team has concluded that this application provides evidence of the efficacy of Cymbalta when used to treat fibromyalgia. However, a review of the post-marketing safety data performed by the Mark Stone, M.D., a safety reviewer in DPP, that was completed towards the end of our review cycle resulted in increased concerns regarding the hepatoxicity associated with exposure to Cymbalta and the need for stronger labeling to address that concern, as well as the possibility of the need for further studies to evaluate the efficacy of lower doses. I will briefly review the findings of the review team and their recommendations for labeling and post-marketing safety evaluations, and the regulatory history pertinent to our recommended indication and labeling claims structure, and focus my discussion on the significant issue of severe hepatoxicity and its relationship to the choice of appropriate doses.

2. Background

Fibromyalgia (FM) is a chronic condition that primarily affects women, although it is occasionally seen in men, children and adolescents. FM is a syndrome consisting of musculoskeletal pain, fatigue and disordered sleep, with pain as the most prominent feature. It is also frequently associated with a variety of neuropsychiatric complaints including depression, anxiety, and cognitive difficulties.

Prior to the formation of the current Division of Anesthesia, Analgesia and Rheumatology Products (DAARP), INDs for FM were under the purview of the former Division of Anti-Inflammatory, Analgesic and Ophthalmology Drug Products (DAAODP). DAAODP allowed two possible indications for FM, "for the management of the pain of FM" and "for the management of FM syndrome." However, based upon extensive internal discussion involving the rheumatology and pain clinical review staff in DAARP and the former and current directors of the Office of New Drug Evaluation II, we have proposed a new paradigm for the indication and labeling claim structure for products intended to treat FM. This paradigm allows a single indication, "for the management of FM," but also allows the inclusion of other components of the FM syndrome in the Clinical Trials section of the product labeling when appropriately designed and analyzed studies provide compelling evidence that a treatment effect has been established for these components, and that that effect is essentially independent of the treatment effect for the pain component. This new paradigm was communicated to all sponsors who were in the process of developing products for FM, including Eli Lilly, in May of 2007.

3. CMC

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

4. Nonclinical Pharmacology/Toxicology

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

5. Clinical Pharmacology/Biopharmaceutics

From Dr. Fadiran's review, pages 2 to 3:

> 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.

The general clinical pharmacology and biopharmaceutics considerations for this product are already adequately described in the approved label.

6. Clinical Microbiology

No clinical microbiology data were necessary for this application.

7. Clinical/Statistical-Efficacy

The efficacy of Cymbalta for FM was demonstrated in two adequate and well-controlled clinical trials, HMCJ (Study J) and HMCA (Study A). These trials were double-blind, placebo-controlled, parallel-group studies in adult patients with FM. Patients were treated for three months in Study A and six months in Study J. 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), with the endpoint at three months. Both studies demonstrated a statistically significant treatment effect for the proposed 60-mg per day dose.

Although the sponsor initially planned to study the efficacy of only the 60- and 120-mg doses, DAAODP asked them to study a lower dose in order to demonstrate a "minimally effective dose." While we would not require this of most drug development programs today, the data that the sponsor did obtain from one of their studies that included a 20-mg dosing arm demonstrated a similar treatment effect for this lower dose compared to the higher doses. The efficacy data also demonstrated no apparent improvement in treatment effect for the 120-mg dose compared to the 60-mg dose.

A summary of the data from Dr. Buenconsejo's analyses that supports the above conclusions regarding dosing, and which Dr. Winchell included on pages 10 and 11 of her review, are reproduced below. Dr. Buenconsejo's reanalysis of the BPI endpoint results incorporates more conservative strategies for imputation of missing data than the analysis performed by the sponsor. Her decision to use these imputation methodologies was based on the well established policy of the Division (that Lilly has been aware for a number of years) that a drug

product that is used primarily to treat pain is only considered to be effective if the side effects caused by that drug are tolerable and patients are able to remain on the drug.

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

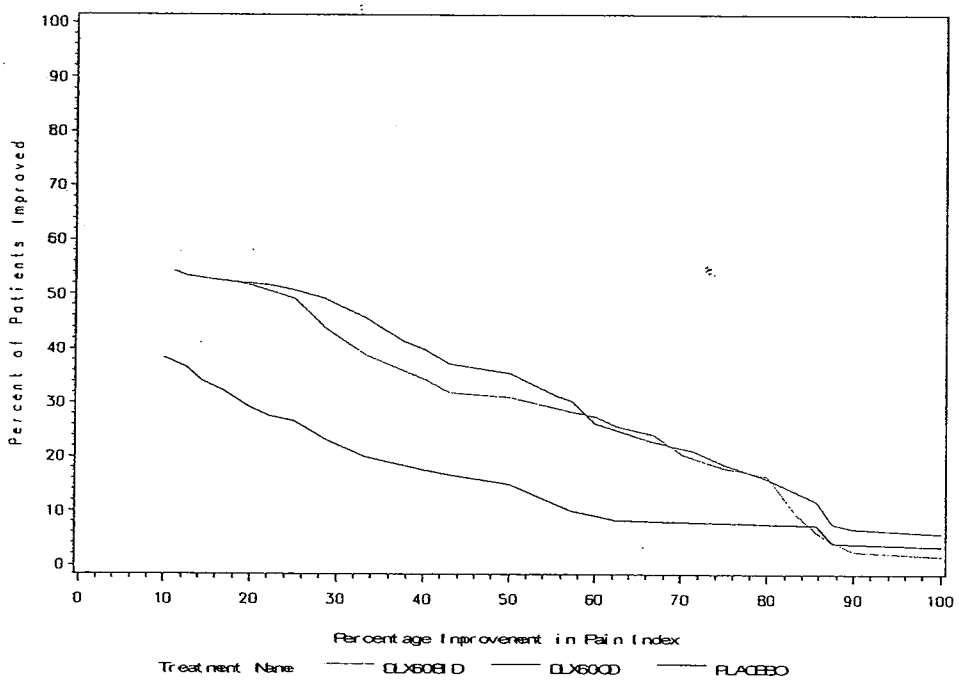
†unadjusted p-value.

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

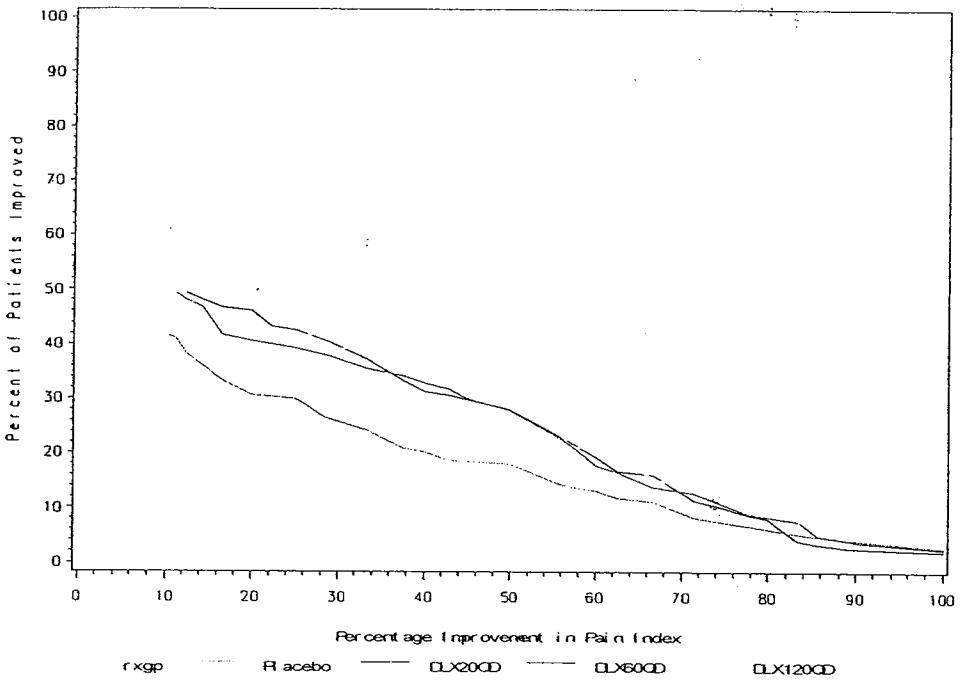
Dr. Buenconsejo also constructed cumulative responder function curves which show the proportion of responders across the full range of response definitions. While the curves for both studies show a clear treatment effect for the Cymbalta groups compared to placebo, there is little difference between the 60- and 120-mg dose groups. These graphic representations from page 38 of Dr. Buenconsejo's review are reproduced below:

Figure 1: Overall Response Profile for Study HMCA



Appears This Way
On Original

Figure 2: Overall Response Profile for Study HMCJ at 3 months



Dr. Buenconsejo also explored the sponsor's proposed claim that some subjects responded to treatment as early as Week One (Visit 3). Her analysis of the responder data for 30% improvement does support this claim and her graphs of this data from pages 44 and 45 of her review are reproduced below:

Figure 3: Proportion of Responders by Week (30% Improvement) – Study HMCA

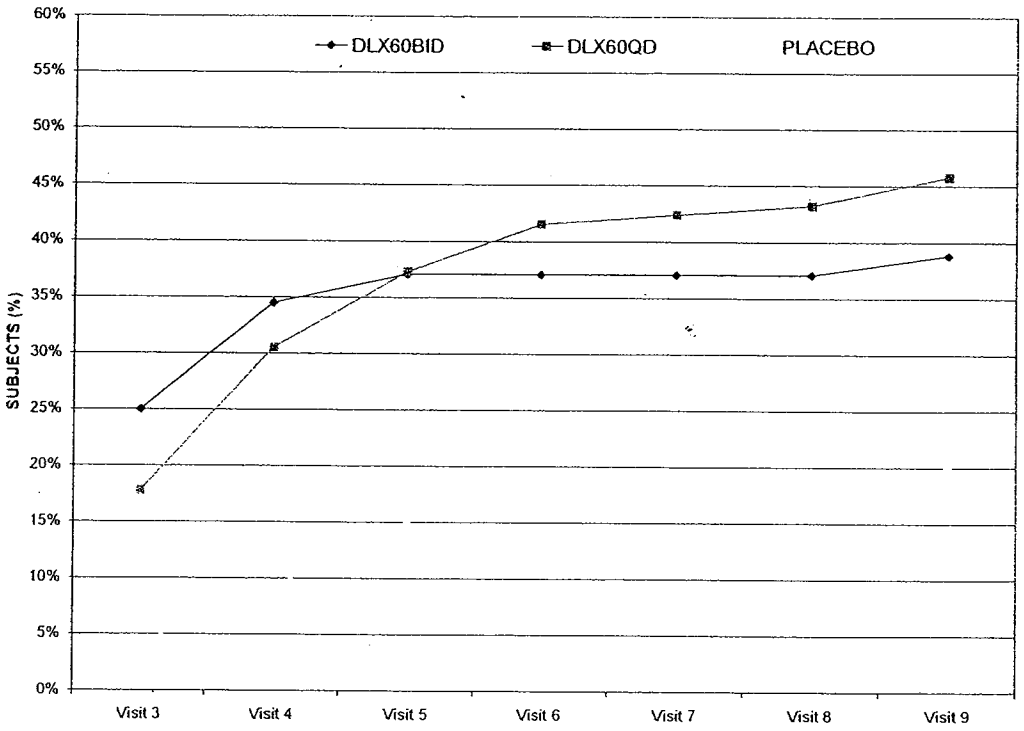
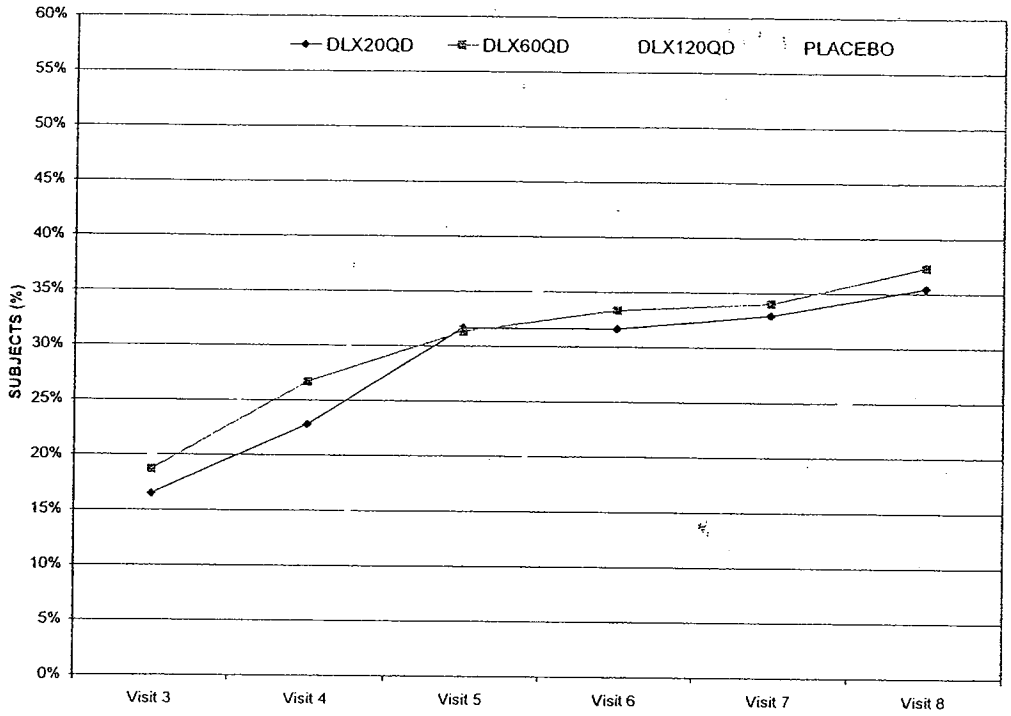


Figure 4: Proportion of Responders by Week (30% Improvement) – Study HMCJ



Of note, the fact that the results are similar for Study A in which subjects began the 60-mg dose at the start of the trial and Study J in which subjects began the study with a week at 30 mg before titrating up to 60 mg, taken in conjunction with the improved tolerability (discussed below under **Safety**), support the use of a titration step in dosing for all patients.

The key secondary endpoints were the Fibromyalgia Impact Questionnaire (FIQ) and the Global Impression of Improvement (PGI). The results of the endpoint analyses of these measures demonstrated improvements for the 20-, 60- and 120-mg doses for the PGI, and improvements for the higher doses with a marginal result for the 20-mg dose for the FIQ. These analyses held up even with conservative imputation strategies.

[redacted] While their own analysis of the BPI data in Study J demonstrated a statistically significant treatment effect for all three dose arms compared to placebo, this analysis was performed with LOCF as the imputation strategy. When Dr. Buenconsejo reanalyzed this data with more conservative imputation strategies, the study failed [redacted]
A summary of this analysis from page 48 of Dr. Buenconsejo's review is reproduced below:

Table 1: Brief Pain Inventory Average Pain Score Mean Change from Baseline to Endpoint (Six Months): All Randomized Patients in the 6-Month Therapy Phase Placebo-Controlled Study: F1J-MC-HMCJ

Treatment Group	BPI Average Pain Score (BOCF)			BPI Average Pain Score (LOCF/BOCF)		BPI Average Pain Score (LOCF/BOCF)*	
	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.

From Dr. Buenconsejo's review, page 32:

> In Study HMEH, patients were randomized to receive either duloxetine 120 mg QD or 60 mg QD at Week 8. This was carried out to patients who responded to treatment (response defined as a $\geq$ 50% reduction from Week 0 (baseline) to Week 8 in the BPI 24-hour average pain score) as well as to non-responders. Of the 350 patients who entered the open-label phase, 339 patients had a baseline and an endpoint BPI average pain score values, while 43 patients discontinued from the study. Of the 339 patients who had BPI score at baseline and post-baseline, 118 patients (35%) were considered BPI responders at Visit 4 (Week 8). 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.

Drs. Winchell and Buenconsejo attempted a number of analyses to understand why subjects appeared to fail to experience continued effectiveness at six months. Unfortunately, these analyses were inconclusive.

Additionally, Drs. Winchell and Buenconsejo analyzed the data from Study HMEH to see whether subjects who were non-responders to initial treatment had responded to up titration. Their analysis clearly demonstrated that these non-responders were no more likely to respond at 52 weeks of treatment when titrated up to 120 mg than the subjects who continued on 60 mg. Dr. Winchell's table documenting the results of this analysis from page 20 of her review is reproduced below:

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%)

Drs. Winchell and Buenconsejo evaluated whether there was a difference in the results on the BPI between these two groups. The results of their analysis were somewhat inconclusive, but there did seem to be a trend for patients with MDD to have a greater magnitude of change than those without MDD.

8. Safety

Drs. Dent and Winchell found no new safety concerns specific to the FM patient population based on their review of the data from the clinical studies submitted in this application. However, during our review cycle Dr. Marc Stone, a safety reviewer in DPP, was performing a review and analysis of the post-marketing hepatotoxicity data for the product. From page 14 of Dr. Stone's review:

> To summarize, the results of this process indicate that the incidence of reports of liver failure that are plausibly due to duloxetine is higher than comparable rates for paroxetine [used in Dr. Stone's analysis as a control]... The similarity of background reporting rates, as measured by reports that, after imputation and factor analysis, are considered to be

unlikely to be drug-induced or have inadequate information, suggests that this is not a result of biases in reporting.

On June 4, 2008, DPP issued a supplement request letter for increased warning language regarding the hepatotoxicity findings based on Dr. Stone's review. Based on the language included in DPP's request, we asked that the following be included in the label for approval of the FM application:

> There have been reports of hepatic failure, sometimes fatal, in patients treated with Cymbalta. These cases have presented as hepatitis with abdominal pain, hepatomegaly and elevation of transaminase levels to more than twenty times the upper limit of normal with or without jaundice, reflecting a mixed or hepatocellular pattern of liver injury. Cymbalta should be discontinued in patients who develop jaundice or other evidence of clinically significant liver dysfunction and should not be resumed unless another cause can be established.
>
> Cases of cholestatic jaundice with minimal elevation of transaminase levels have also been reported. Other postmarketing reports indicate that elevated transaminases, bilirubin and alkaline phosphatase have occurred in patients with chronic liver disease or cirrhosis.

The sponsor was initially reluctant to include this language in their label without significant modification. However, after extensive discussion with the Division and Dr. Stone, the sponsor agreed to include this language in their label.

Additionally, based on the fact that the FM is composed primarily of women of child bearing potential, the clinical review team determined that a pregnancy registry would be an important tool for monitoring for any pregnancy-related toxicities associated with Cymbalta's use in this patient population. The Division consulted the Maternal Health Team (MHT) to see if they agreed with this determination and, if so, for recommendations on the design of the registry. The following comments have been reproduced from their response to our consult:

> There are no human data available on the effects of Cymbalta use during pregnancy. Based on animal data, duloxetine may cause fetal harm. While there are no human data on Cymbalta use during pregnancy, there are numerous case reports and epidemiological studies on the use of SSRIs during pregnancy. There are documented and labeled class effects for SSRIs and SNRIs that involve a withdrawal-like syndrome in the neonatal period. However, current available data on potential embryofetal toxicities are conflicting.
>
> Cymbalta is currently approved for the treatment of MDD, GAD, and Diabetic Peripheral Neuropathic Pain, and is currently under review for the ——— of FM. MDD, GAD, and FM are all conditions that commonly occur in women of child bearing potential. Even with limited data, the possibility exists that women with these conditions, who are of childbearing potential, may conceive while on Cymbalta therapy, resulting in inadvertent exposure to the drug. During pregnancy, women with these conditions may fail other available therapies. A clinician may choose to prescribe Cymbalta after considering the risks and benefits associated with treatment for both the mother and her embryo/fetus. Therefore, a pregnancy registry is needed to monitor maternal and fetal exposures to Cymbalta during pregnancy and associated pregnancy and fetal outcomes.

The MHT recommends that the sponsor develop and maintain a prospective, observational pregnancy exposure registry conducted in the United States that compares the pregnancy and fetal outcomes of women exposed to duloxetine (for any indication) during pregnancy to an unexposed control population.

The registry should be conducted as a post-marketing requirement for this application. The outcomes of the registry should include major and minor congenital anomalies, spontaneous abortions, stillbirths, elective terminations, and other serious adverse pregnancy outcomes. These outcomes should be assessed throughout pregnancy. Infant outcomes should be assessed through at least the first year of life.

We have determined that this pregnancy registry may be included as a Post-Marketing Requirement under the authorities granted to the Agency by the Food and Drug Administration Amendments Act.

9. Advisory Committee Meeting

The Division determined, early in the review cycle, that an advisory committee meeting was not necessary for this application as there was apparent evidence of efficacy and there was no apparent new safety concern. The increased concern regarding hepatoxicity surfaced late in the course of the review and has been adequately addressed via conservative language in the product labeling.

10. Pediatrics

Studies in pediatric patients under 13 years of age will be waived as the population of FM patients in this age category is extremely small and it would be unlikely that adequate studies could be performed. Studies in pediatric FM patients between the ages of 13 and 17 years of age will be deferred, as those studies are currently unavailable and the need for data from pediatric studies should not preclude approval of this application for adult FM patients.

11. Other Relevant Regulatory Issues

There are no other unresolved relevant regulatory issues.

12. Labeling

In addition to discussion regarding the addition of stronger warning language for the hepatotoxicity associated with Cymbalta, the Division also discussed with Lilly their request to

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action

Approval

- Risk Benefit Assessment

The sponsor has demonstrated that Cymbalta at a dose of 60 mg per day is safe and effective for the management of FM in adult patients. However, post-marketing data has shown that Cymbalta is associated with cases of serious hepatoxicity which appears to be dose-related, and there is preliminary data to support that lower doses of the drug may be effective for this indication. While we are approving Cymbalta 60 mg per day for the management of FM, it will be important to obtain additional data on lower doses of the product. The sponsor has agreed to perform an adequate and well-controlled study of the efficacy of a lower dose of Cymbalta as a Post-Marketing Commitment. Also, although the current agreed upon label includes reasonable warning language regarding the hepatoxicity of Cymbalta, careful surveillance will be necessary in the post-marketing environment to assure that further risk management strategies are not necessary. In addition, it will be essential to monitor the effects of this product on pregnancy in this population that primarily consists of women of child bearing potential. The sponsor has agreed to undertake a pregnancy exposure registry study as a Post-Marketing Requirement.

- Recommendation for Post-Marketing Risk Management Activities

As noted above, the sponsor has agreed to perform the following study as a Post-Marketing Requirement:

A prospective, observational pregnancy exposure registry study conducted in the United States that compares the pregnancy and fetal outcomes of women exposed to Cymbalta during pregnancy to an unexposed control population. The registry will detect and record major and minor

congenital anomalies, spontaneous abortions, stillbirths, elective terminations, and any serious adverse pregnancy outcomes. These events will be assessed among the enrolled women throughout the pregnancy. The events will also be assessed among infants through at least the first year of life. Annual interim reports will be submitted until FDA has acknowledged that sufficient data has been collected.

Additionally, as noted above under **Pediatrics**, the sponsor will be required to perform an appropriately designed study of Cymbalta in pediatric patients with FM from 13 to 17 years of age to assess the efficacy, safety and dosing for these patients.

- Recommendation for other Post-Marketing Study Commitments

The sponsor has agreed to perform a study to define the efficacy of a lower dose of Cymbalta for the management of FM as a Post-Marketing Commitment. This study will be a randomized, double-blind, placebo-controlled trial of Cymbalta at a dose of 20 – 30 mg per day for the management of fibromyalgia.

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/s/

Bob Rappaport
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MEDICAL OFFICER