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APPLICATION NUMBER:
022516Orig1s000

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type sNDA
Application Number(s) 22-516
Priority or Standard Standard

Submit Date(s) May 15, 2009
Received Date(s) May 15, 2009
PDUFA Goal Date March 15, 2010
Division / Office DAARP

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Review Completion Date February 2, 2010

Established Name Duloxetine hydrochloride
(Proposed) Trade Name Cymbalta
Therapeutic Class Selective serotonin and
norepinephrine reuptake
inhibitor (SNRI)
Applicant Eli Lilly and Company

Formulation(s) Oral Capsule
Dosing Regimen 60 mg once daily
Indication(s) Treatment of chronic pain
Intended Population(s) Adults

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

This application does not support the efficacy of Cymbalta[®] (duloxetine hydrochloride) for the treatment of chronic pain. However, replicated evidence, sufficient to support the efficacy of Cymbalta 60 mg as a treatment of chronic low back pain (CLBP) was presented within this application and approval for this supplemental indication is recommended.

To support the chronic pain indication, in addition to the findings of efficacy for the previously approved pain indications for diabetic peripheral neuropathy pain (DPNP) and fibromyalgia (FM), the applicant has submitted five new clinical trials, three in CLBP and two in osteoarthritis (OA).

The Division's efficacy analyses showed that duloxetine was superior to placebo for the treatment of CLBP in two trials, one for the fixed 60 mg duloxetine dose (HMGC) and one for the combined 60 to 120 mg dose (HMEN). Continuous responder curves showed statistically significant separation from placebo in both trials. For patient global impression of improvement (PGI-Improvement), performed as a secondary gatekeeper analysis to address multiple comparisons, duloxetine-treated patients demonstrated statistically significant improvement when compared with placebo in both trials.

For the treatment of OA pain, duloxetine was shown to be superior to placebo in one trial for the combined 60 to 120 mg duloxetine dose (HMFG). For PGI-Improvement, no superiority to placebo was demonstrated in this trial and according to the pre-specified gatekeeper strategy for sequential testing, the WOMAC physical function analysis could not be performed.

The effect size for the positive trials was small. Analysis for the 60 mg only duloxetine dose versus placebo at the end of the flexible-dose trials (HMFG and HMEN) was negative. A mean plot analysis of the pain scores comparing placebo, duloxetine 60 mg, and duloxetine 120 mg, showed that the 120 mg dose confers no additional benefit over the 60 mg dose for patients who did not respond to duloxetine 60 mg. In addition, safety analyses confirmed that the 120 mg duloxetine dose is associated with a higher incidence of adverse events.

Advice given to the applicant by DAARP in 2005 included that additional trials in two appropriate chronic pain populations such as CLBP, OA, or visceral pain could be adequate to support a broader chronic pain indication. However, during the past several years the Division has been actively working to create a policy that presents

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requirements for a broader chronic pain indication based on scientific knowledge. It has been a difficult process, involving discussion with higher level management internally as well as consulting with academic experts in the pain field. The goal is to write an official guidance for the broad chronic pain indication that would clearly outline the appropriate steps for obtaining such a novel indication. A workshop was held recently with academic experts in the pain field who advised that substantial evidence of efficacy across multiple painful conditions with different pathophysiologic mechanisms would be necessary to support a chronic pain indication. The panel discussed neuropathic pain of central and peripheral origin, visceral pain, non-inflammatory and inflammatory arthritides, back pain, fibromyalgia, cancer pain, musculoskeletal pain, pain associated with sickle cell disease, and pelvic pain as a potential pain models. In addition it was felt that a consideration should be given for the number of negative trials.

The sponsor was able to support, in replicated trials, the efficacy of duloxetine for the treatment of DPN, FM pain, and now CLBP. In clinical practice, neuromodulatory medications, such as antidepressants and anticonvulsants, are commonly used to treat pain associated with DPN and FM. Back pain can be caused by a wide variety of factors. These include structural problems of the back (mechanical causes), inflammation, muscle and soft tissue injury, and importantly psychological/social factors. These psychological/social factors include development of adaptation to chronic low back pain and effective coping skills, pre-existing depression, anxiety and stress. Therefore, an antidepressant can influence the patient's own perception of their particular situation, pain intensity, and the overall outcome. On the other hand, standard analgesics (NSAIDs and opioids) continue to be used as first line therapy for OA pain. The sponsor presents one positive flexible-dose trial, and one negative fixed-dose trial. Another, fixed-dose, 60 mg duloxetine versus placebo trial was submitted to IND 63,615 in April of 2009 and is ongoing. The pathophysiologic mechanisms of OA pain are different from the above mentioned conditions and only one positive trial is not sufficient to demonstrate efficacy for the osteoarthritis indication, and as a result, there is not adequate evidence across multiple pain models for approval of Cymbalta for chronic pain.

In summary, the evidence from the data presented in this NDA is not adequately compelling to support that Cymbalta (duloxetine hydrochloride) would be an effective treatment for different types of painful conditions that fall under the umbrella of chronic pain, such as visceral, post-surgical, cancer, and other neuropathic pain categories. Trials to explore the efficacy of Cymbalta across additional pain models must be conducted in order to obtain sufficient evidence that Cymbalta is efficacious in the treatment of chronic painful conditions with different pathophysiologic mechanisms.

1.2 Risk Benefit Assessment

The drug has shown efficacy in the treatment of chronic low back pain. Balanced against this benefit, the drug presents risks of several common, but non-serious adverse effects, including nausea, headache, dry mouth, insomnia, fatigue, constipation, diarrhea, dizziness, somnolence, hyperhidrosis and anorexia. In addition, duloxetine is associated with several more serious risks, most notably hepatotoxicity, increased risk of bleeding when co-administered with aspirin, NSAIDs, warfarin or other anticoagulants, and the development of serotonin syndrome.

Based on a review of both pre and post-marketing cases, the Division of Psychiatric Products (DPP) is considering adding the hepatotoxicity warnings to a Box Warning.

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. In addition, in order to assure that the benefits of the drug outweigh the risks, a Medication Guide only REMS is necessary for approval of Cymbalta.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

Due to the risks of suicidality and hepatotoxicity associated with Cymbalta, the Agency has determined that a Medication Guide-only REMS must be part of the approval for this product. The REMS will include a Medication Guide, and a Timeline for REMS assessments.

1.4 Recommendations for Postmarket Requirements and Commitments

(b) (4)

Pending final action, if duloxetine receives a specific indication for CLBP or OA, pediatric waivers for studying these conditions may be granted after discussion with the pediatric review committee (PERC) since neither condition occurs frequently enough in the pediatric population for studies to be feasible.

The European Medicines Agency (EMA) pediatric committee has determined that there is no need to study duloxetine in pediatric patients. The Division is currently gathering information to understand the basis for the EMA's decision.

2 Introduction and Regulatory Background

2.1 Product Information

Duloxetine hydrochloride is a selective serotonin (5-HT) and norepinephrine (NE) reuptake inhibitor (SSNRI) which also has minor inhibition of dopamine reuptake. In the United States it was initially approved for the treatment of major depressive disorder (MDD) on August 3, 2004, and subsequently for indications of the pain associated with diabetic peripheral neuropathy (DPNP) on September 3, 2004, generalized anxiety disorder (GAD) and maintenance treatment of major depression in 2007, and fibromyalgia (FM) on June 13, 2008. The product is marketed in the US by Eli Lilly under the brand name Cymbalta®. Overseas, duloxetine is also approved for treatment of stress urinary incontinence (SUI) and international names include Yentreve, Xeristar, and Ariclam.

2.2 Tables of Currently Available Treatments for Proposed Indications

Several products from the NSAID class and opioid analgesics are available on the market for the indication of treatment of chronic pain.

2.3 Availability of Proposed Active Ingredient in the United States

Duloxetine is approved and marketed in the United States for treatment of MDD, GAD, and DPNP. Dosage forms include 20, 30, and 60 mg enteric coated capsules.

2.4 Important Safety Issues With Consideration to Related Drugs

Serious adverse events and important issues associated with the use of duloxetine and other SNRIs include suicidal thinking and behavior in children, adolescents, and young adults (a box warning for antidepressants), withdrawal symptoms, anxiety, and elevation in blood pressure. All of these issues have been well-described in previous iterations of the product label.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

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

On May 15, 2008, a NDA application for the management of chronic pain (NDA 22-333) was submitted to the Division. This NDA application was subsequently withdrawn on November 26, 2008.

Key milestones in the clinical development program are noted below.

Pre-IND meeting (7-Sep-2005)	The proposed indication at that time was CLBP. The Division recommended that a broader pain indication be considered: <ul style="list-style-type: none"> • For support, conduct studies in two appropriate pain populations (i.e. CLBP + visceral or GI pain) • One positive study in each population would be sufficient
	Regarding the study design, the applicant was informed that fixed-dose trials are encouraged: <ul style="list-style-type: none"> • Data from flexible-dose study alone would not be sufficient to provide evidence of efficacy for any one particular dose • 12-week trial duration is acceptable
	The Division informed the applicant that: <ul style="list-style-type: none"> • LOCF is not considered appropriate imputation method for pain trials, and if used, must be supported by sensitivity analyses. • Reduction in pain at the end of treatment compared to baseline is an acceptable primary outcome. • Regarding the secondary endpoints: <ul style="list-style-type: none"> ○ Validated measures should be used :(i.e. instead of SDS use RMDQ) ○ 30% ↓ in 24h average pain score at end of treatment is reasonable for a definition of response
	The applicant was asked to stratify patients at randomization and perform subgroup analyses with regards to: <ul style="list-style-type: none"> • presence or absence of radiculopathy • presence or absence of MDD

	<p>The applicant was asked to explore a range of doses in their efficacy trials.</p>
<p>Teleconference (7-March-2006)</p>	<p>The applicant was informed that:</p> <ul style="list-style-type: none"> • One CLBP and one OA study would be sufficient for chronic pain indication • Regarding the imputation strategy for the primary analysis: <ul style="list-style-type: none"> ○ LOCF is not acceptable ○ BOCF is acceptable ○ Continuous responder analysis using multiple cutoffs to define responders is also acceptable <ul style="list-style-type: none"> – All dropouts should be classified as non-responders • Inclusion of only QTF nomenclature Class 1 and 2 CLBP patients is acceptable to exclude radiculopathy <p>OA trial should include reasonable number of patients without chronic NSAID use Otherwise may result in label for “adjunctive therapy”</p>
<p>Pre-sNDA (18-Oct-2007)</p>	<p>Regarding their proposal for the primary analysis method, the applicant was informed that:</p> <ul style="list-style-type: none"> • MMRM is reasonable if missing data occur randomly. In pain trials missing data are treatment related and MMRM would not address the concern of missing data and therefore is not an acceptable method for the primary analysis. • The proposed secondary BOCF would be acceptable as a primary analysis method. <p>The Division informed the applicant that the safety analysis sets should be comprised of:</p> <ul style="list-style-type: none"> • Primary: controlled CLBP and OA trials • All controlled trials except CLBP and OA • Uncontrolled trials across all indications: <ul style="list-style-type: none"> – Applicant should include OL extension trials in the controlled dataset • Data from the uncontrolled phase will be flagged. <p>Because data from the HMFG and HMEN “back-up” efficacy trials will be submitted with the 120-day Safety update and this update may contain data from half of the chronic pain trials, the applicant was asked to:</p> <ul style="list-style-type: none"> • Update the ISE and ISS accordingly <p>The Division also informed the applicant that:</p> <ul style="list-style-type: none"> • Review of the safety data from the above studies

	<p>during the first review cycle will depend on availability of resources, but will not be a filing issue.</p> <p>Regarding the NDA content, the applicant was asked to:</p> <ul style="list-style-type: none"> • Provide narratives for all deaths, SAEs and D/C for the chronic pain trials • Include ISS and ISE in Module 5: <ul style="list-style-type: none"> ○ It is acceptable to link SCS and SCE to ISS and ISE ○ ISE should include discussion of data from all the trials that support chronic pain indication • Provide a written summary for the post marketing experience <ul style="list-style-type: none"> ○ For this section of the NDA it is not acceptable to reference the PSUR <p>The applicant was informed that:</p> <ul style="list-style-type: none"> • Combined AE table across all indications will not be suitable for the label • Cymbalta use can be promoted only for disease states that were studied
<p>NDA 22-333 Acknowledgment of withdrawal letter (16-Dec-2008)</p>	<p>“The preliminary review of the submitted efficacy studies showed that these studies fail to support findings of efficacy for Cymbalta for the proposed indication.”</p>

GI-Gastrointestinal
 LOCF-Last Observation Carried Forward
 BOCF- Baseline Observation Carried Forward
 MMRM-Mixed Modal Repeated Measures
 SDS-Sheehan Disability Scale
 RMDQ-Roland Morris Disability Questionnaire
 MDD-Major Depressive Disorder
 QTF-Quebec Task Force
 PSUR-Periodic Safety Update Report
 SCS-Summary of Clinical Safety
 SCE-Summary of Clinical Efficacy
 ISS-Integrated Summary of Safety
 ISE-Integrated Summary of Efficacy

2.6 Other Relevant Background Information

Not applicable.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The application for NDA 22-516 was submitted in eCTD format. The navigation of the application was easy, links were active, table of contents and bookmarks for the original protocols were provided, datasets with definition tables were provided, narratives for subjects who died, experienced serious adverse events (SAE) or discontinued due to safety issues were provided. The integrated summary of safety and efficacy (ISS and ISE) were located in Module 2. Module 5 contained only the tables for the controlled-DLX and all-DLX exposures analysis sets.

During the review process, the following issues with the presentation of the safety and efficacy findings were identified that made the review of certain sections difficult and created problems with the interpretation of data:

- Analysis of safety data including patient disposition, adverse events, laboratory data (including hepatic safety), and early discontinuations, were not performed by treatment group and duloxetine dose received.
- Analyses of hepatic-related adverse events and liver function test (LFT) abnormalities by dose were performed for subjects with normal baseline LFT values.
- Efficacy analysis for the comparison of duloxetine 60 mg only dose versus placebo at Week 13, using BOCF and mBOCF imputation strategies and continuous responder analyses (BOCF) were not provided.

These deficiencies were communicated to the applicant and the additional information/analysis requested was submitted in a timely manner.

The Division of Scientific Investigations (DSI) inspected Drs. Henk Mulder's (HMEN), Dr. Yuri Belenkov's (HMFG), Dr. Boris Bart's (HMFG), Dr. Bruce's Rankin (HMGC) and Dr. Kyle Patrick's (HMGC) sites. These particular sites were selected for inspection because of:

- Enrollment of large number of subjects.
- For Dr. Bart's site (HMFG), the calculated means and ranges for the change from baseline to week 13 of BPI scores for each treatment group showed that the mean difference is relatively large and the ranges do not overlap.

DSI Findings

The inspection of Dr. Henk Mulder's site for protocol HMEN, Dr. Bruce Rankin's site for HMGC, and Dr. Kyle Patrick's site for HMGC, found no serious regulatory violations.

The inspection of the two Russian sites (Dr. Yuri Belenkov and Dr. Boris Bart) for

protocol HMFG confirmed the deviations described by the sponsor in “Protocol Violations” section of the F1J-MC-HMFG clinical study report (refer to Section 5.3.3 of this review). Because the frequency of these protocol violations was similar across treatment groups, it is unlikely that the violations greatly impacted the primary efficacy results.

3.2 Compliance with Good Clinical Practices

The submitted CLBP and OA efficacy and safety trials appeared to be conducted under acceptable ethical standards. There were minor protocol violations which were not considered to have an influence on the trial results (see Section 5.3 for details).

3.3 Financial Disclosures

Applicant provided financial information for the principal and sub-investigators who participated in the CLBP and OA efficacy studies. There were no financial incentives considered to adversely affect the integrity of the data.

The investigators who reported to have disclosable information for accrued equity between \$30,000 and \$69,000 were:

[Redacted] (b) (4)

Additional statistical analysis, completed by the applicant, found that the cumulative effect [Redacted] (b) (4), had no impact on the outcome of [Redacted] (b) (4) study.

[Redacted] (b) (4)

Additional statistical analysis, completed by the applicant, found that the cumulative effect [Redacted] (b) (4) had no impact on the outcome of [Redacted] (b) (4) study.

[Redacted] (b) (4)

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

There are no new CMC issues or information submitted for this previously approved formulation of Cymbalta.

4.2 Clinical Microbiology

Not applicable.

4.3 Preclinical Pharmacology/Toxicology

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

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

No new clinical pharmacology information was included in this submission.

4.4.2 Pharmacodynamics

No new information was included in this submission.

4.4.3 Pharmacokinetics

No new information was included in this submission.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

The table below lists the primary chronic pain trials included in this application.

Table 1: Primary Chronic Pain Trials

Clinical Review
 {Insert Reviewer Name}
 {Insert Application Type and Number}
 {Insert Product Trade and Generic Name}

Trial	Design	Number of patients, sex and age	Duration of treatment	Test Product
F1J-MC-HMEP Duloxetine 60 to 120 mg vs Placebo in the Treatment of Patients with OA Knee Pain	Parallel, double-blind, randomized, placebo-controlled with re-randomization at Week 7.	N=231 111 dlx, 120 pbo M and F Age at least 40	13 weeks	Duloxetine 60 mg QD PO 120 mg QD PO
F1J-MC-HMFG Duloxetine 60 to 120 mg vs. Placebo in the Treatment of Patients with OA Knee Pain	Parallel, double-blind, randomized, placebo-controlled with dose-escalation	N=256 128 dlx, 128 pbo M and F Age at least 40	13 weeks	Duloxetine 60 mg QD PO 120 mg QD PO
F1J-MC-HMEN – Acute Therapy Phase: Effect of Duloxetine 60 mg to 120 mg Once Daily in Patients with CLBP	Parallel, double-blind, randomized, placebo-controlled with dose-escalation	N= 236 115 dlx 60/120 QD, 121 pbo M and F Age at least 18	13 weeks + 9 months extension phase (long-term analyses set)	Duloxetine 60 mg QD PO 120 mg QD PO
F1J-MC-HMEO Duloxetine versus Placebo in the Treatment of CLBP	Parallel, double-blind, randomized, fixed-dose, placebo-controlled	N=404 59 dlx 20 mg QD, 116 dlx 60 mg QD, 112 dlx 120 mg QD, 117 pbo M and F Age at least 18	13 weeks	Duloxetine 20 mg QD PO 60 mg QD PO 120 mg QD PO

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F1-MC-HMGC Duloxetine 60 mg versus placebo in patients with CLBP	Parallel, double-blind, randomized, fixed-dose, placebo-controlled	N=401 198 DLX 60 mg QD 203 placebo M and F Age at least 18	12 weeks	Duloxetine 60 mg QD PO
----------------------------------------------------------------------------	--------------------------------------------------------------------	------------------------------------------------------------------------	----------	------------------------

(Source: Adapted from applicant's Table 2.7.4.1 from Summary of Clinical Safety, pp. 12-13)

To support the indication for chronic pain, in addition to the OA and CLBP trials, the applicant included a summary of efficacy and safety findings from the trials conducted to support the approved indications for diabetic peripheral neuropathy pain and fibromyalgia.

Table 2: Fibromyalgia and DPN trials

Indication	Study	Total daily Dose	Duration of Placebo-Controlled Phase	Status in the US
DPN	HMAW	20mg, 60 mg, 120 mg	12 weeks	Indication approved (NDA 21-733)
	HMAVa	60 mg, 120 mg	12 weeks	
	HMAVb	60 mg, 120 mg	12 weeks	
Fibromyalgia	HMBO	120 mg	12 weeks	Indication approved (b) (4)
	HMCA	60 mg, 120 mg	12 weeks	
	HMCJ	20mg, 60 mg, 120 mg	12 weeks/24 weeks	
	HMEF	60 mg-120 mg	24 weeks	

(Source: Applicant's Table 2.7.3.2 from Summary of Clinical Efficacy, p. 16)

5.2 Review Strategy

The review of efficacy focused on four pivotal trials, HMEP, HMEN, HMFG and HMGC, which the applicant found to provide evidence of efficacy. The HMEO trial (fixed dose trial in CLBP population), failed to show efficacy and is not reviewed in detail.

The review of safety focused on data from the primary chronic pain trials in OA and CLBP population. In addition these findings were compared to the safety profile of duloxetine in other indications.

5.3 Discussion of Individual Studies/Clinical Trials

5.3.1 Protocol HMEP

Title: “Duloxetine 60 to 120 mg versus placebo in the treatment of patients with osteoarthritis knee pain.”

Objectives:

Primary: To assess the efficacy of duloxetine 60 to 120 mg once daily compared with placebo on the reduction of pain severity as measured by the weekly mean of the 24-hour average pain scores in patients with osteoarthritis (OA) knee pain during a 13-week, double-blind treatment period using an 11-point Likert scale patient diary.

Secondary Gatekeeper Objectives: A gatekeeper strategy was to have been employed to sequentially test and compare improvement between duloxetine 60 to 120 mg QD- and placebo-treated patients on:

- PGI-I physical function subscale
- WOMAC physical function subscale

Additional Secondary Objectives:

- Efficacy of duloxetine 60 to 120 mg QD versus placebo measured by:
 - Weekly mean of the 24-hour worst pain score
 - Clinical Global Impression of Severity (CGI-S)
 - WOMAC pain and stiffness subscales
 - Brief Pain Inventory (BPI) - Severity and Interference
 - Response to treatment, as defined by a 30% and a 50% reduction of weekly mean score in 24-hour average pain severity ratings computed from diary scores
- Impact of treatment with duloxetine 60 to 120 mg QD versus placebo on patient-reported health outcomes, as measured by
 - EuroQoL Questionnaire-5 Dimension (EQ-5D) version of the EuroQoL instrument
 - Medical Outcomes Study Short Form-36 (SF-36)
- To evaluate whether reduction in pain, as assessed by the weekly average pain intensity scores during the treatment phase, is a direct analgesic effect of duloxetine and is independent of treatment effect on mood, as measured by the total score of the Beck Depression Inventory - II (BDI-II), or anxiety as measured by Hospital Anxiety and Depression Scale (HADS) anxiety subscale (HADS-A).

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{Insert Reviewer Name}

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- To compare the effect of treatment with duloxetine 60 mg for 12 weeks to the effect of treatment with duloxetine 60 mg for 6 weeks followed by treatment with duloxetine 120 mg for 6 weeks measured by
 - reduction of 24-hour average pain
 - response to treatment
 - adverse events reported as reason for discontinuation
- Safety of duloxetine versus placebo.

Trial Design

This was to have been a multicenter, randomized, double-blind, parallel group, placebo controlled trial with three study periods: Screening Phase (1 week), Double-blind Treatment Phase (13 weeks), and Taper Phase (2 weeks). The study would be conducted in approximately 29 centers in the United States, Puerto Rico, and Romania.

The maximum duration of trial medication administration was to have been 15 weeks.

Trial Population

The eligibility criteria were to have been:

- Male or female, ≥ 40 years of age.
- Meet the American College of Rheumatology (ACR) clinical and radiographic criteria for the diagnosis of OA of the knee with pain for ≥ 14 days of each month for 3 months prior to study entry.
- Mean baseline week score of 4 or greater on the 24-hour average pain score.
- Acceptable method of contraception for females of child-bearing potential during the study and for 1 month following the last dose of the study.
- At least 70% compliance with the diary between Visit 1 and Visit 2.

Subjects were to have been excluded for:

- Diagnosis of psychosis, bipolar disorder, schizoaffective disorder, or major depressive disorder
- Judged clinically by the investigator to be at suicidal risk or as identified by a score of 2 or greater on question 9 of the Beck Depression Inventory-II (BDI-II) prior to starting study drug.
- Serious medical or psychiatric illness
- History of recurrent seizures
- Uncontrolled narrow-angle glaucoma.
- Acute liver injury or severe cirrhosis
- Known hypersensitivity to duloxetine
- Confounding painful condition that may interfere with assessment of the index joint
- Inflammatory arthritis
- Have received intrarticular hyaluronate or steroids, joint lavage, or other invasive therapies to the knee in the past 6 months.

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- Have had knee arthroscopy of the index knee within the past year or joint replacement of the index knee at anytime.
- Prior synovial fluid analysis showing a white blood cell (WBC) $\geq 2000\text{mm}^3$ that is indicative of a diagnosis other than OA.
- History of substance abuse or dependence within the past year, excluding nicotine and caffeine.
- Taking any of the prohibited medications for use during the trial
- Treatment with a monoamine oxidase inhibitor (MAOI) within 14 days of randomization or within 5 days of discontinuation of study drug.
- Non-ambulatory or require the use of crutches or a walker.
- Therapy with investigational drug within 30 days of study entry
- Participation in another trial of duloxetine or previously withdrawn from this study
- Previous exposure to duloxetine.

Trial Medications

Eligible subjects were to have been randomly assigned to duloxetine or placebo treatment at Visit 2 at 1:1 ratio stratified by NSAID use. At Visit 4, duloxetine-treated patients would be randomly re-assigned at 1:1 ratio to stay on 60 mg QD or escalate their dose to 120 mg QD.

The following table illustrates the treatment regimens administered during the different trial phases.

Table 3: Treatment regimens - HMEP

Table HMEP.4.1. Treatment Regimens

Study Phase	Blinding	Treatment	Dosage Form and Strength	Frequency	Dose Duration	Packaging
Screening	Screening	None	N/A	N/A	N/A	N/A
Titration	Double-blind	Duloxetine	30 mg (30 mg X 1 capsule); Placebo	QD	1 week	Blister Packs or Bottles
Double-Blind Treatment Phase	Double-blind	Duloxetine	60 mg (60 mg duloxetine X 1 capsule and placebo X 1 capsule); 120 mg (60 mg duloxetine X 2 capsules); Placebo	QD	12 weeks	Blister Packs or Bottles
Taper/Discontinuation	Double-blind	Duloxetine	30 mg (30 mg duloxetine X 1 capsule and 1 placebo capsule); 60 mg (30 mg duloxetine X 2 capsules); Placebo	QD	2 weeks	Blister Packs or Bottles

(Source: Applicant’s Table from 16.1.1 Study Report, p. 850)

Prohibited therapies:

Narcotic analgesic agents were not to have been allowed during the trial.

Analgesics allowed for use during the trial:

Acetaminophen or NSAID use was to have been permitted at stable doses during the trial.

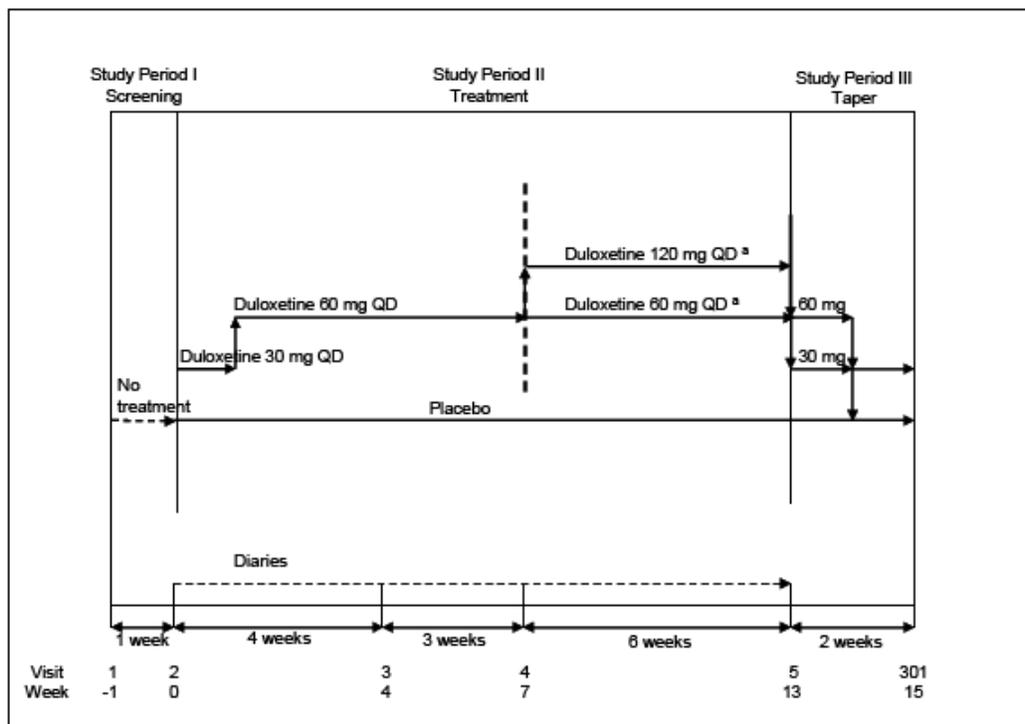
Episodic use of short-acting analgesics like acetaminophen and codeine were to have been allowed for acute injury or surgery or for rescue from an OA knee pain flare.

“Episodic use” was to have been defined as no more than 3 consecutive days and not to exceed 20 total days during the trial.

Trial Conduct

Eligible subjects were to have been randomly assigned in a 1:1 ratio stratified by NSAID use to receive placebo or duloxetine 60 mg QD. Patients randomly assigned to duloxetine 60 mg QD would start on duloxetine 30 mg QD for 1 week and then titrate up to duloxetine 60 mg QD.

Figure 1 : Trial schematic- HMEP



(Source: Applicant's Figure from 16.1.1 Study Report, p. 842)

After seven weeks of treatment (Visit 4) patients receiving duloxetine 60 mg QD were to have been re-randomized in a 1:1 ratio to either duloxetine 60 mg QD or duloxetine 120 mg QD for an additional six weeks.

Both the initial randomization and re-randomization were to have been performed by a computer-generated random sequence using an interactive voice response system (IVRS). After initial randomization and re-randomization, the IVRS dispensed the appropriate bottles containing double-blind study drug to each patient. Site personnel confirmed they obtained the correct bottle by entering into the IVRS the confirmation number found on the bottle.

At the end of the 13-week treatment period or at the time of early withdrawal, patients were to enter a 2-week taper phase.

Trial Procedures

The following table presents the time of events and assessments planned to be taken.

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Study Schedule, Protocol F1J-MC-HMEP

Visit	1	2	3	4	5	V301	ET
	Day -7	Day 0+2d	Day 28+2d	Day 49+2d	Day 91+2d	Day 105+2d	Visits 3-5
Clinical Assessments							
Description							
Informed Consent	X						
Demographics	X						
Medical History	X						
Physical Exam	X						
Historical Illness	X						
Habits	X						
Vitals and Weight	X	X	X	X	X	X	X
MINI	X						
ECG	X						
X-ray of the index knee	X ^d						
Weight and Sitting Blood Pressure and Heart Rate	X	X	X	X	X	X	X
Supine and Standing Blood Pressure and Heart Rate (orthostatic)		X			X		X
Adverse Events/Pre-existing Conditions	X	X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X
Dispense Drug		X	X	X	X ^c		X ^c
Compliance			X	X	X	X	X
Efficacy Measures							
HADS		X			X		X
PGI-Improvement			X	X	X		X
11-point Likert Scale Patient Diary ^{a,b}	X	X	X	X	X		X
PGI-Severity		X					
CGI-Severity		X	X	X	X		X
WOMAC		X	X	X	X		X
BDI-II	X	X	X	X	X	X	X
BPI		X	X	X	X		X
Labs							
Chemistry	X		X	X	X		X
Hematology	X						
Urinary Drug Screen	X						
Pregnancy Test	X						
Health Outcomes							
EQ-5D		X			X		X
SF-36		X			X		X

Abbreviations: BDI-II – Beck Depression Inventory – II; BPI = Brief Pain Inventory; CGI-Severity = Clinical Global Impressions of Severity; ECG = electrocardiogram; EQ-5D = Euro-Qol Questionnaire – 5 Day; ET = Early Termination; HADS = Hospital Anxiety and Depression Scale; MINI = Mini International Neuropsychiatric Interview; PGI-Improvement = Patient’s Global Impressions of Improvement; PGI-Severity = Patient’s Global Impressions of Severity; SF-36 = 36-item Short-Form Health Survey; V = visit; WOMAC = Western Ontario and McMaster Universities.

^a Patient should begin diary the day of Visit 1.

^b Patient should complete diary approximately the same time every day.

^c Drug only dispensed to patients entering Taper Phase.

^d X-ray of the index knee for patients who have not had an x-ray, computed tomography scan (CT-Scan), or magnetic resonance imaging (MRI) in the past showing osteophytes

(Source: Applicant’s table from Study Report, pp. 827-829)

Discontinuation Criteria

The following discontinuation criteria were to have been applied for this protocol:

- Clinically significant adverse event or laboratory abnormalities
- Patient is judged to be at high suicidal risk
- Pregnancy
- Treatment with therapeutic agent indicated for OA

Statistical Analysis

Primary efficacy variable

- The primary efficacy variable was to have been the change in 24 hour average pain score, expressed as weekly mean, of the Brief Pain Inventory (BPI), from Baseline to endpoint (last non-missing observation).

Pain scores were to have been recorded in a patient diary once a day as an average pain over 24 hours. The 11-point Likert scale was to have been used to rate the pain severity. The baseline pain score was to have been calculated as the average score from the week prior to randomization. The endpoint score was to have been calculated as the average weekly score from the last week of available observations.

Secondary efficacy variables

- Percentage of subjects with 30% and 50% reduction in the 24-hour average pain (11-point Likert)
- Patient's Global Impressions of improvement (PGI - Improvement) assessed at Visits 3, 4, 5, and end of treatment
- Patient's Global Impressions of disease severity (PGI – Severity) assessed at Visit 2
- Clinical Global Impressions of disease severity (CGI – Severity) assessed at Visits 3, 4, 5, and end of treatment
- WOMAC pain, stiffness, physical function subscales assessed at Visits 3, 4, 5, and end of treatment
- Severity of pain and the interference of pain on function measured by the Brief Pain Inventory scale (BPI) at Visits 3, 4, 5, and end of treatment visit
- Suicidal risk using the Beck Depression Inventory-II (BDI-II) at each clinic visit
- Anxiety and depression using the Hospital Anxiety and Depression Scale (HADS) assessed at Visits 2, 5, and end of treatment
- Health outcome using Euro-Qol Questionnaire (EQ-5D) assessed at Visits 2, 5, and end of treatment
- Quality of life using Short-Form Health Survey (SF-36) assessed at Visits 2, 5, and end of treatment

Safety variables

- Adverse events
- Discontinuation due to adverse events
- Changes in vital signs measurements, laboratory evaluations, and physical examination findings

Safety analysis was to include all patients with baseline data.

Statistical analysis methods

All analyses were to have been conducted on an intent-to-treat basis with subjects with no post-baseline pain scores excluded. Statistical tests of efficacy variables were to have been presented as 2-sided p-values. Statistical comparisons were to have been performed at the 0.05 level of significance. No adjustments for multiple comparisons were to have been made.

Efficacy analyses were performed for Study Period II (Treatment phase, Week 0 through Week 13, duloxetine 60 mg QD versus placebo) and after re-randomization (Treatment phase Week 7 through Week 13, duloxetine 60 mg QD versus duloxetine 120 mg QD).

A likelihood-based, mixed-effect repeated measures (MMRM) analysis was to have been used to analyze the primary efficacy variable. All patients with data from baseline and at least one post-baseline visit were to have been included in the analysis. The model was to include fixed categorical effects of treatment, NSAID use, investigator, week and treatment-by-week interactions, and continuous fixed covariates of baseline score and baseline by-week interaction. Mean change in the primary efficacy variable was to have been also analyzed using a last-observation carried-forward (LOCF) approach and baseline-observation-carried-forward (BOCF) approach. The analysis of variance (ANOVA) model was to have been used to analyze continuous variables, with terms for treatment and investigator. The stratifying variable of NSAID use was to have been added to the analysis of covariance (ANCOVA) with baseline values added as a covariate.

A gatekeeper strategy was to have been used to sequentially test the secondary objectives to compare improvement between duloxetine- and placebo-treated patients on the PGI-I and the WOMAC physical function subscale, using the ANCOVA model and LOCF approach.

The analysis of the re-randomized patients at Visit 4 was to have been performed using the ANCOVA model with terms of baseline, treatment, and investigator. Response rates (30% and 50% reduction in pain score) between 60 mg QD and 120 mg QD groups were to have been compared using Fisher's exact test.

Sample size calculation

A sample size of 230 subjects was calculated assuming a study power of approximately 80% to detect a treatment difference of 1.0 point in the mean change of the primary variable and 85% to detect a treatment group difference of 25% in response rate based on data from duloxetine studies of diabetic peripheral neuropathic pain.

Protocol Amendments

The protocol was amended only once, 13 December 2006. The changes included the following:

- Additional language explaining osteophyte diagnostic criteria was added

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- X-ray was added to the schedule of events
- Intrarticular injection exclusion changed from six to three months
- NSAID user was defined as a patient taking NSAID for > 14 days per month for three months prior to study entry

Trial Results

Protocol violations

Overall 60% of all randomized subjects reported at least one protocol violation. Noncompliance to diary regimen was the most frequent protocol violation followed by noncompliance to study medication.

Because the frequency of these protocol violations was similar across treatment groups, it is unlikely that the violations greatly impacted the primary efficacy results.

The types and numbers of violations are shown on the table below:

Table 4: Protocol violations by treatment group – HMEP

Violation Type *	---Placebo---		-DLX60/120QD--		----TOTAL----	
	N=120		N=111		N=231	
	n	(%)	n	(%)	n	(%)
Exclusionary Con. Med. Taken	10	(8.33%)	10	(9.01%)	20	(8.66%)
Inclusion/Exclusion	6	(5.00%)	2	(1.80%)	8	(3.46%)
Non compliance to diary regimen	35	(29.17%)	39	(35.14%)	74	(32.03%)
Non compliance to study drug regimen	17	(14.17%)	16	(14.41%)	33	(14.29%)

(Source: Applicant's table from the original NDA 22-333 submission, July 8, 2008 Amendment, p. 14)

Enrollment/ Subject disposition

Of the 231 randomized patients, 120 were assigned to the placebo group, and 111 were assigned to the duloxetine group.

A total of 89 (80%) of the 111 patients originally assigned to the duloxetine 60 mg a day group, completed seven weeks of treatment and were re-randomized at Week 7, 46 to the 60 mg QD group and 43 to the duloxetine 120 mg QD group. At Week 7, 103 (85.8%) from the placebo group remained to continue the trial.

A total of 173 (74.9%) patients completed the study: 96 (80.0%) in the placebo group and 77 (69.4%) in the duloxetine group. One hundred and three (85.8%) of the placebo and 89 (80.2%) of the 60 mg duloxetine treated subjects completed the first seven weeks of treatment. The 89 subjects assigned to the active treatment were re-randomized at Week 7 in 1:1 ratio to 60 mg or 120 mg duloxetine. Of the re-randomized subjects, 39 (84.8%) of the duloxetine 60 mg QD group and 38 (88.4%) of the duloxetine 120 mg QD group completed the last six weeks of the treatment period.

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The disposition for the 231 randomized subjects is summarized on the table below. Across all groups, 25% of patients discontinued the trial. The most frequently reported reason was discontinuation due to adverse event, 13.5% for the duloxetine-treated patients versus 5.8% for the placebo-treated patients. The discontinuation rate due to lack of efficacy was similar between the placebo and duloxetine-treated patients.

Table 5: Subject disposition - HMEP

**Table HMEP.10.1. Reasons for Discontinuation
 All Randomized Patients
 Treatment Phase**

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Primary Reason for Discontinuation	PLACEBO (N = 120) n (%)	DLX60/120qD (N = 111) n (%)	Total (N = 231) n (%)
Completed	96 (80.00)	77 (69.37)	173 (74.89)
DC due to ANY reason	24 (20.00)	34 (30.63)	58 (25.11)
Adverse Event	7 (5.83)	15 (13.51)	22 (9.52)
Subject Decision	9 (7.50)	8 (7.21)	17 (7.36)
Lack of Efficacy	3 (2.50)	2 (1.80)	5 (2.16)
Physician Decision	2 (1.67)	3 (2.70)	5 (2.16)
Lost to follow up	0 (0.00)	4 (3.60)	4 (1.73)
Protocol Violation	1 (0.83)	2 (1.80)	3 (1.30)
Entry Criteria Not Met	1 (0.83)	0 (0.00)	1 (0.43)
Sponsor Decision	1 (0.83)	0 (0.00)	1 (0.43)

(Source: Applicant's table from Study Report 10.1, p. 64)

Analysis of discontinuation by dose, prior to re-randomization (first 7 weeks) and after re-randomization (Week 7 to Week 13) is presented on the table below:

Table 6: Discontinuations by dose, first 7 weeks and last 6 weeks - HMEP

	First 7 weeks of Study		Second 6 weeks of Study		
	Placebo n (%)	DLX60 n (%)	Placebo n (%)	DLX60 n (%)	DLX120 ^b n (%)
Study HMEP ^a	N= 120	N= 111	N= 103	N= 46	N= 43
Any Reason	17 (14.2)	22 (19.8)	7 (6.8)	7 (15.2)	5 (11.6)
Adverse Event	5 (4.2)	9 (8.1)	2 (1.9)	2 (4.3)	4 (9.3)
Subject/Physician Decision	8 (6.6)	7 (6.3)	3 (2.9)	4 (8.7)	0 (0)
Lack of Efficacy	2 (1.7)	2 (1.8)	1 (1.0)	0 (0)	0 (0)

(Source: Applicant's table 2.7.4.21, CSS, p.68)

More patients in the duloxetine 60 mg treatment group (8.1%) discontinued during the first seven weeks of treatment due to adverse event compared to placebo (4.2%). For the same period, discontinuations due to lack of efficacy were similar between the two groups.

After re-randomization, most patients who discontinued due to adverse events were from the 120 mg QD duloxetine group (9.3%) compared to the 60 mg QD dose group (4.3%) and placebo (1.9%). One subject (1%) discontinued due to lack of efficacy from the placebo group, and no subjects discontinued for this reason from the duloxetine 60 mg and 120 mg treatment groups.

The following table illustrates the drop-out rate by study week for the placebo and duloxetine treatment groups.

Table 7: Drop outs by treatment group and study week – HMEP

Drop out week	Placebo N=120	Duloxetine 60- 120 mg/d N=111	Total N=231
	n (%)		
Week 4	8 (6.7%)	19 (17.1%)	27 (11.7%)
Week 7	9 (7.5%)	3 (2.7%)	12 (5.2%)
Week 13	7 (5.8%)	12 (10.8%)	19 (8.2%)

(Source: Adapted from Applicant’s table 10.3 from Study report for HMEP, pp. 68-69)

The placebo-treated patients’ drop-out rate was similar throughout the duration of the double-blind treatment while the duloxetine-treated patients tended to discontinue treatment relatively early (17% at Week 4) or late (11% at Week 13) during the double-blind treatment compared to only 3% of the subjects who discontinued at the middle of this period (Week 7).

Extent of exposure

The mean study drug exposure was 79.6 days with 61.0% of patients receiving study drug for at least 13 weeks, 62.5% for the placebo and 59.3% for the duloxetine-treated patients.

Overall, no significant differences were observed between the duloxetine and the placebo treatment groups in terms of study drug exposure.

The table below shows the extent of exposure to study drug for all randomized patients:

Table 8: Study drug exposure for all randomized patients – HMEP

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Variable	PLACEBO (N = 120)	DLX60/120QD (N = 111)	Total (N = 231)
Duration of Exposure (Days)			
NO. SUBJECTS	120	108	228
MEAN	82.20	76.65	79.57
STD	21.31	29.77	25.76
MAXIMUM	106.00	109.00	109.00
MEDIAN	91.00	91.00	91.00
MINIMUM	6.00	1.00	1.00
Patient Years	27.01	22.66	49.67
Duration of Exposure -n(%)			
NO. SUBJECTS	120	108	228
>0	120 (100.0)	108 (100.0)	228 (100.0)
>=28	114 (95.0)	95 (88.0)	209 (91.7)
>=49	106 (88.3)	91 (84.3)	197 (86.4)
>=91	75 (62.5)	64 (59.3)	139 (61.0)
>=105	2 (1.7)	2 (1.9)	4 (1.8)

(Source: Applicant's table 12.1 form Study report for HMEP, p. 162)

The table below shows the extent of exposure to study drug for patients who were re-randomized at Visit 4 (Week 7) to 60 mg QD or 120 mg QD. The mean study drug exposure was 39.3 days with 67.0% of patients receiving study drug for at least 6 weeks, 65.2% for the DLX 60 mg /day group and 69% for the DLX 120 mg/day group.

Table 9: Study drug exposure for all re-randomized patients – HMEP

Variable	DLX60QD (N = 46)	DLX120QD (N = 43)	Total (N = 89)
Duration of Exposure (Days)			
NO. SUBJECTS	46	42	88
MEAN	38.83	39.90	39.34
STD	11.09	8.47	9.89
MAXIMUM	53.00	58.00	58.00
MEDIAN	42.00	42.00	42.00
MINIMUM	1.00	3.00	1.00
Patient Years	4.89	4.59	9.48
Duration of Exposure -n(%)			
NO. SUBJECTS	46	42	88
>0	46 (100.0)	42 (100.0)	88 (100.0)
>=7	45 (97.8)	41 (97.6)	86 (97.7)
>=14	42 (91.3)	40 (95.2)	82 (93.2)
>=28	41 (89.1)	40 (95.2)	81 (92.0)
>=42	30 (65.2)	29 (69.0)	59 (67.0)

(Source: Applicant's table 12.2 form Study report for HMEP, p. 164)

Demographics

Overall, the average age of subjects was 62.3 years and was similar between the placebo and duloxetine-treated patients. The mean height of the duloxetine group was significantly greater than that of the placebo group. This difference is not expected to have interfered with the interpretation of data.

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There were no significant differences between the duloxetine and placebo groups for age, sex and duration of OA since diagnosis, or duration of OA pain since onset as illustrated on the following table:

Table 10: Patient Demographic Characteristics and Disease Severity at Baseline - HMEP

Parameter	Placebo N=120	DLX 60 to 120 mg/d N=111	Total N=231
	n (%)		
Sex			
Male	39 (32.5)	41 (37)	80 (34.6)
Female	81 (67.5)	70 (63)	151 (65.4)
Race			
White	100 (83.3)	94(84.7)	194 (84)
Black	6 (5)	6 (5.4)	12 (5.2)
Hispanic	10 (8.3)	9 (8.1)	19 (8.2)
Asian	3 (2.5)	0	3 (1.3)
Age			
Mean	62.5	62.7	62.3
Minimum	43.8	40.2	40.2
Maximum	86.7	82	86.7
Weight (kg)			
Mean	85.7	85.6	85.6
Minimum	53	50	50
Maximum	127	129	129
Height (cm)			
Mean	164.7	167	165.8
Minimum	134	150	134
Maximum	188	193	193
Duration of OA since Dx (in years)			
Mean	7	6.94	7.01
Minimum	0.05	0.02	0.02
Maximum	37	40	40
Duration of OA pain since onset (in years)			
Mean	9.3	9.04	9.17
Minimum	0.24	0.33	0.24
Maximum	39	40	40
Weekly Mean of 24h average pain			

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at baseline (11 PT Likert)			
Mean	6.18	6.10	6.14
Minimum	4	3.63	3.63
Maximum	9.56	9.75	9.75

(Source: Adapted from Applicant’s table 11.1 from Study report for HMEP, pp. 73-75)

Baseline medical characteristics and concomitant therapy

Medical history and concomitant diseases were similar between the placebo and duloxetine treatment groups. With regards to the concomitant medication use, a significantly greater number of patients in the duloxetine group was taking lisinopril than patients in placebo (13.5% versus 5%).

Applicant’s efficacy analysis

Results Overview

Primary analysis

The applicant found with respect to the primary efficacy variable that the MMRM primary analysis demonstrated a statistically significant improvement from baseline to endpoint in the weekly 24-hour average pain score for the duloxetine 60-120 mg group compared to placebo. The LSMean at Week 13 difference between the placebo and DLX 60-120 was 0.84 with $p < 0.001$.

Additional LOCF analysis of mean change from baseline to endpoint in 24-hour average pain score was found to demonstrate statistically significant pain reduction for duloxetine compared to placebo (LSMean difference of 0.70, $p=0.006$). Using the BOCF approach the difference was not found to be statistically significant (LSMean difference of 0.45, $p=0.086$).

In a post hoc analysis, the applicant used mBOCF imputation strategy defining two categories of reasons for dropout:

- Treatment-related: “Adverse events” and “Lack of efficacy”
- Non-treatment-related: Any other reason

The results from this mBOCF analysis showed that the duloxetine-treated patients had statistically significant greater improvement compared with placebo-treated patients (LSMean difference of 0.74, $p=0.047$).

Secondary analyses

Secondary analyses of the 30% and 50% response rates at endpoint were found to demonstrate statistically greater response rates in the duloxetine group compared with the placebo group using the LOCF imputation strategy, but not when BOCF was used.

In the analysis of patients re-randomized to duloxetine 60 mg QD or 120 mg QD, the applicant found statistically greater 24-hour average pain reduction based on LOCF mean change analysis of the weekly mean change from patient diaries when compared

duloxetine 120 mg QD re-randomized patients with those re-randomized to duloxetine 60 mg QD. No statistically significant differences were observed between duloxetine 60 mg QD and 120 mg QD for the MMRM analysis of the weekly 24-hour average pain score or the 30% and 50% response rates at endpoint.

The secondary gatekeeper assessments for PGI-I and the WOMAC (LOCF and MMRM only) physical function subscale were found to demonstrate significantly greater improvement for the duloxetine compared to the placebo-treated patients.

The path analysis was found to demonstrate that improvements in pain scores were due to a direct analgesic effect independent of changes in mood as measured by BDI-II or anxiety as measured by the HADS-A subscale.

Analysis of primary efficacy endpoint

The primary efficacy measure for this study was the BPI 24-hour average pain item on the 11-point Likert scale expressed as the weekly mean from patient diaries. Mixed-effects model repeated measures (MMRM) was the pre-specified primary analysis testing the null hypothesis that the difference in the 24-hour average pain score between the duloxetine and placebo treatment groups at the last time point of the treatment phase is 0.

The applicant found that at Week 13 (Visit 5) there was a statistically significant greater decrease (improvement) in the average pain score in the duloxetine group (2.92 points) compared to the placebo group (2.08 points). The LSMean difference between the placebo and duloxetine 60/120 mg was 0.84 with a p-value of < 0.001.

In addition to the primary MMRM analysis, the applicant performed sensitivity analyses on the primary efficacy measure, including ANCOVA model based on LOCF, BOCF, and mBOCF. For the LOCF and mBOCF analysis, the applicant found that patients treated with duloxetine 60 mg to 120 mg for 13 weeks demonstrated significantly greater pain reduction than placebo-treated patients. The difference in LSMean pain score between the duloxetine 60/120QD and placebo using LOCF was -0.70 with a p-value of 0.006. The difference in LSMean pain score between the duloxetine 60/120QD and placebo using mBOCF was -0.51 with a p-value of 0.047. Using the BOCF approach, the difference was not statistically significant.

The table below illustrates the difference in pain score reduction between duloxetine 60/120 QD and placebo for the different analysis. In addition the table compares the results between data collected from patient diaries, expressed as weekly mean score and data collected as single day BPI report at study visits.

Table 11: Difference in LSMean 24-hour average pain score (from patient diaries and the BPI), DLX60/120 - Placebo, All Randomized Patients - HMEP

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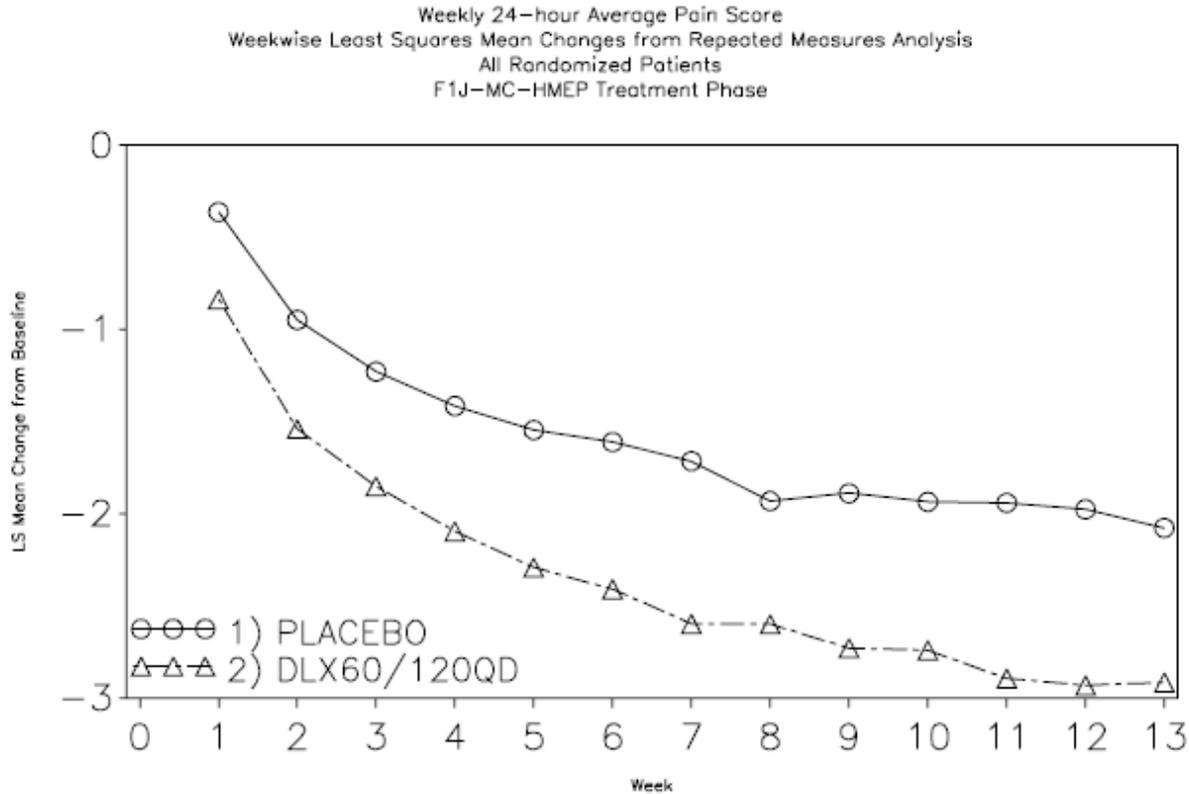
	HMEP		
	Endpoint LSMean	Treatment Difference	p-value
Weekly mean 24-hour average pain (Diary)			
MMRM: DLX 60/120 Placebo	-2.92	-0.84	<.001
	-2.08		
LOCF: DLX 60/120 Placebo	-2.64	-0.70	0.006
	-1.93		
BOCF: DLX 60/120 Placebo	-2.20	-0.45	0.086
	-1.75		
mBOCF: DLX 60/120 Placebo	-2.39	-0.51	0.047
	-1.88		
24-hour average pain (BPI collected at study visits)			
MMRM: DLX 60/120 Placebo	-3.01	-1.12	<.001
	-1.89		
LOCF: DLX 60/120 Placebo	-2.82	-0.97	<.001
	-1.85		
BOCF: DLX 60/120 Placebo	-2.31	-0.10	0.024
	-1.68		
mBOCF: DLX 60/120 Placebo	-2.58	-0.74	0.010
	-1.84		

(Source: Adapted from Applicant's tables 2.7.3.8 and 2.7.3.10 from CSE, pp. 44-48)

Graphical representation of the data, presented below, by week and LSMean change from repeated measures analysis show separation between the duloxetine 60/120 QD and placebo group for the entire duration of the 13 week period.

Figure 2: Weekly LSMean changes from repeated measures analysis - HMEP

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(Source: Applicant’s figure 14.1 from Study report for HMEP, p. 372)

Secondary efficacy endpoints

Because there were no adjustments for the multiple secondary analyses, any p-values associated with secondary efficacy variables should be interpreted as descriptive statistics only.

- Percentage of subjects with 30% and 50% reduction in the 24-hour average pain (11-point Likert)

The applicant’s analysis of 30% and 50% response rate at endpoint demonstrated statistically greater response rate in the duloxetine 60/120 QD group compared with the placebo group with the LOCF imputation strategy but not when BOCF was used.

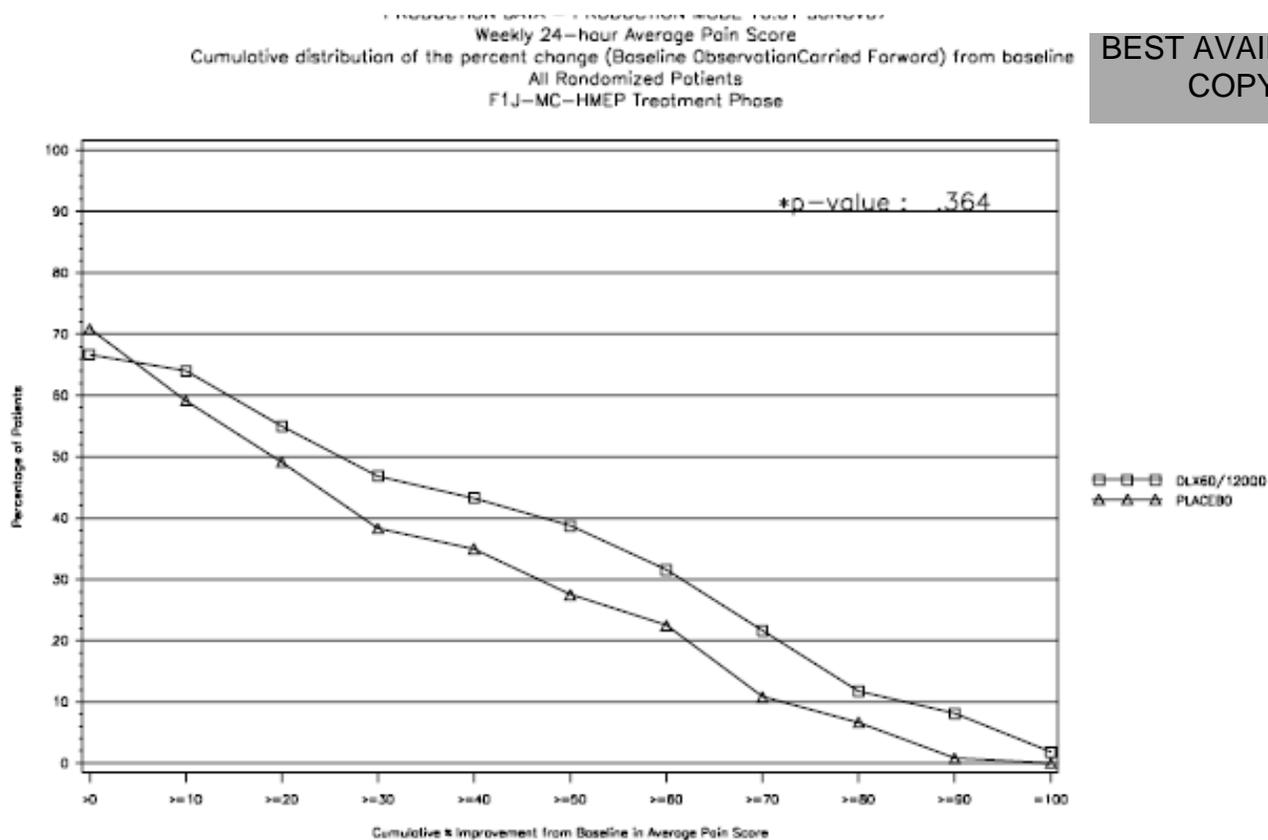
Table 12: Proportion of treatment responders – 30% and 50% improvement from Baseline to Endpoint using LOCF - HMEP

Treatment	N	30% improvement n (%)	p-value	50% improvement n (%)	p-value
Placebo	119	53 (44.5)	0.033	35 (29.4)	0.006
DLX 60/120	108	64 (59.3)		51 (47.2)	

QD					
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(Source: Adapted from Applicant's tables 14.13 and 14.15 from Study Report, pp. 377-379)

Figure 3: Cumulative distribution of the percent change from Baseline (BOCF) - HMEP



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(Source: Applicant's figure 14.3, HMEP Study Report, p.375)

- Patient's Global Impressions of improvement (PGI - Improvement) and WOMAC physical function.

The applicant employed a gatekeeper strategy, using LOCF imputation, for sequentially testing the following:

- To evaluate duloxetine 60 to 120 mg QD versus placebo on patients' perceived improvement during the 13-week treatment phase as measured by PGI-Improvement.
- To evaluate duloxetine 60 to 120 mg QD versus placebo on the change in patients' functioning during the 13-week treatment phase as measured by the WOMAC physical function subscale.

For both assessments, the applicant found that duloxetine 60/120 QD treated patients demonstrated significantly greater improvement when compared with placebo-treated patients, LSMean difference of -0.53, p=0.001 for the PGI-I and LSMean difference of -1.41, p=0.003 for the WOMAC physical function.

- The applicant found that duloxetine treatment resulted in significant reduction in pain severity on analysis of the 24-hour average pain score collected from the BPI instrument at study visits (LSMean -0.97, p<0.001), the weekly mean of the worst pain score collected from patient diaries (LSMean difference -1.06, p=<0.001), and the WOMAC pain (LSMean difference of 1.61, p<0.001), SF-36 pain (LSMean difference of 0.71, p=0.006).
- The applicant also found that duloxetine treatment resulted in significant improvement in patients' general well-being as measured by CGI-Severity (LSMean difference 0.36, p=0.001) and significant improvement in quality of life as measured by patient-rated health outcomes, including the EQ-5D domains for mobility, self-care, usual activities, pain/discomfort, and anxiety/depression (LSMean difference of 0.08, p<0.001).
- Quality of life using Short-Form Health Survey (SF-36) did not show significant improvement for the mental, physical, and general health function.

Other efficacy endpoints

The applicant found that patients re-randomized to duloxetine 120 mg QD at Week 7 had significantly greater 24-hour average pain reduction based on LOCF, mean change analysis of the weekly mean change from patient diaries when compared with those re-randomized to duloxetine 60 mg QD (LSMean difference of 0.87, p=0.039). MMRM analysis did not show a statistically significant difference.

Analysis of response rate for 30% and 50% improvement using LOCF imputation failed to show statistical difference between the 60 and the 120 mg duloxetine groups.

Table 13: Efficacy analysis of patients re-randomized to duloxetine 60 or 120 mg QD - HMEP

Measure	Analysis	DLX 60 QD N=46	DLX 120 QD N=43	p-Val
Weekly mean change in 24-hour average pain score ^{a,b}	LOCF (Mean [SE])	-2.47 (0.29)	-3.34 (0.33)	.039
	MMRM (Mean [SE])	-2.49 (0.30)	-3.24 (0.34)	.080
Response rates	LOCF 30% (%)	57.8	76.2	.075
	LOCF 50% (%)	51.1	54.8	.831

(Source: Applicant's tables 2.7.3.1, CSE Appendix, p. 7)

5.3.2 Protocol HMEN

Title: “Effect of duloxetine 60 mg to 120 mg once daily in patients with chronic low back pain.”

Objectives

Primary: To assess the efficacy of duloxetine 60 to 120 mg once daily compared with placebo on the reduction of pain severity as measured by weekly mean of the 24 hour average pain scores in patients with chronic low back pain (CLBP) during a 13-week, double-blind treatment period using an 11-point Likert scale and an electronic patient diary.

Secondary Gatekeeper Objectives: A gatekeeper strategy was to have been employed to sequentially test and compare improvement between duloxetine 60 to 120 mg QD- and placebo-treated patients on:

- PGI-I physical function subscale
- Improvement of functioning as measured by the Roland Morris Disability Questionnaire (RMDQ-24)

Additional Secondary Objectives

- Efficacy of duloxetine 60 mg QD versus placebo as measured by the same outcome measures used to compare duloxetine 60/120 versus placebo.
- Efficacy of duloxetine 60 to 120 mg QD versus placebo measured by:
 - Weekly mean of the 24-hour night, and worst pain score computed from electronic diary scores
 - Clinical Global Impression of Severity (CGI-S)
 - Brief Pain Inventory (BPI) - Severity and Interference
 - Athens Insomnia Scale (AIS)
 - Response to treatment, as defined by a 30% and 50% reduction of BPI average pain scores
- Impact of treatment with duloxetine 60 to 120 mg QD versus placebo on patient-reported health outcomes, as measured by:
 - EuroQoL Questionnaire-5 Dimension (EQ-5D) version of the EuroQoL instrument
 - Medical Outcomes Study Short Form-36 (SF-36)
 - Work Productivity and Activity Impairment Instrument (WPAI)
- To evaluate whether reduction in pain, as assessed by the weekly average pain intensity scores during the treatment phase, is a direct analgesic effect of duloxetine and is independent of treatment effect on mood, as measured by the total score of the Beck Depression Inventory - II (BDI-II), or anxiety as measured by Hospital Anxiety and Depression Scale (HADS) anxiety subscale (HADS-A)

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- Safety of duloxetine versus placebo

Extension Phase Objectives

- To evaluate whether the treatment effect of duloxetine 60 QD to 120 mg QD was maintained over a 41-week period in patients with CLBP as measured by change from baseline to endpoint in BPI average pain.
- To evaluate the maintenance effect of duloxetine 60 mg QD to 120 mg QD during the extension treatment phase as measured by:
 - BPI
 - CGI-Severity
 - Roland Morris Scale
 - AIS
 - WPAI
 - BDI

Trial Design

This was to have been a multicenter, randomized, double-blind, parallel group, placebo controlled trial with 5 study periods: Screening Period (1 week), Double-Blind Treatment Period (13 weeks), Taper or Titration Period (2 weeks), Double-Blind Extension Period (39 week), and Taper Period (2 weeks). The study would be conducted in approximately 20 centers in Brazil, France, Germany, the Netherlands, and Mexico.

Trial Population

The eligibility criteria were to have been:

- Male or female, ≥ 18 years of age.
- Low back pain (T-6 or below) present on most days for the preceding six months or longer meeting the following disease diagnostic criteria:
 - Trial candidates must not have:
 - neurological radicular signs
 - presumptive compression of a spinal nerve root on a simple radiogram
 - compression of a spinal nerve root confirmed by specific imaging techniques
 - Pain must not radiate below the knee, and must not be due to neurogenic claudication (spinal stenosis).
 - Pain must be either restricted to low back or associated with radiation to the proximal portion of the lower limb only (Class 1 and 2 per Quebec Task Force on Spinal Disorders)
 - Absence of spinal fracture, spondylolisthesis grade 3 or 4, tumor, abscess or acute pathology in the low back/abdominal regional must be confirmed by historical record of imaging studies
- Mean baseline week score of 4 or greater on the 24-hour average pain score
- Acceptable method of contraception for females of child-bearing potential during the study and for 1 month following the last dose of the study

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- At least 70% compliance with the diary between Visit 1 and Visit 2

Subjects would be excluded for:

- History of more than one low back surgery, or low back surgery 12 months prior to study entry
- Have received epidural steroids, facet block, nerve block or other invasive procedures aimed to reduce low back pain within the past month prior to Visit 1
- Diagnosis of psychosis, bipolar disorder, schizoaffective disorder, or major depressive disorder
- Are judged clinically by the investigator to be at suicidal risk or as identified by a score of 2 or greater on question nine of the Beck Depression Inventory-II (BDI-II) prior to starting study drug
- Serious medical or psychiatric illness
- Uncontrolled narrow-angle glaucoma, seizures, thyroid disease, and hypertension.
- Acute liver injury or severe cirrhosis
- Known hypersensitivity to duloxetine
- History of substance abuse or dependence within the past year, excluding nicotine and caffeine
- Taking any of the prohibited medications for use during the trial
- Treatment with a monoamine oxidase inhibitor (MAOI) within 14 days of randomization or within 5 days of discontinuation of study drug
- Non-ambulatory or require the use of crutches or a walker
- Therapy with investigational drug within 30 days of study entry
- Previous exposure to duloxetine

Trial Medications

Duloxetine 60 mg QD, duloxetine 120 mg QD, and placebo were to have been the treatments administered to patients during this trial.

Prohibited Therapies

Opioids, antidepressants and anticonvulsant medications, acupuncture, chiropractic maneuvers, transcutaneous electrical nerve stimulation (TENS), or similar procedures would not be allowed during the trial.

Analgesics allowed for use during the trial

Acetaminophen and NSAID use was to have been permitted at stable doses during the trial.

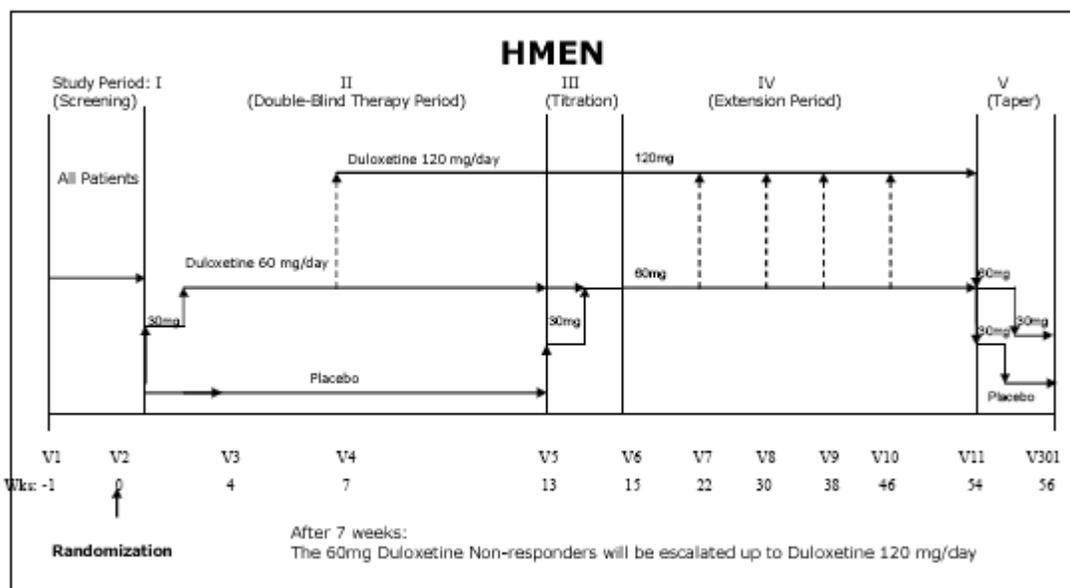
Episodic use of short-acting analgesics like acetaminophen and codeine were to have been allowed for management of breakthrough chronic low back pain (rescue therapy) or acute conditions unrelated to low back. “Episodic use” was to have been defined as no more than three consecutive days and not to exceed 20 total days during the trial.

Trial Conduct

Eligible subjects were to have been randomly assigned in a 1:1 ratio stratified by NSAID use to receive placebo or duloxetine 60 mg QD. Patients randomly assigned to duloxetine 60 mg QD would start on duloxetine 30 mg QD for 1 week and then titrate up to duloxetine 60 mg QD.

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Figure 4: Trial schematic- HMEN



(Source: Applicant’s Figure from 9.1 HMEN Report, p. 29)

After seven weeks of treatment (Visit 4) patients who did not meet response criteria, defined as at least 30% reduction in weekly mean of the BPI average score compared to baseline, were to have their dose increased to 120 mg QD for the remainder of the study. At the end of the Double-blind Treatment Period, patients receiving placebo were to have been randomized to 60 mg QD with dose titration over two weeks. Those patients unable to tolerate their starting dose or their treatment dose would be discontinued from the trial.

During the Double-Blind Extension Period, all patients in the study were to have been taking either duloxetine 60 mg QD or duloxetine 120 mg QD. Patients who entered the extension treatment phase taking duloxetine 60 mg QD and did not meet response criteria (defined as at least 30% pain reduction on the BPI) were to have had their doses increased to 120 mg QD beginning at Visit 7, 8, 9 or 10, depending on when the patient failed to meet the response criteria. Patients taking duloxetine 120 mg were not to have been allowed to return to the duloxetine 60-mg QD dose. Patients who were not tolerating duloxetine 60 mg QD or duloxetine 120 mg QD during the extension treatment

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phase, and who had taken duloxetine 60 mg QD for at least 2 weeks, were to have been discontinued from the trial.

During the last two weeks of the trial, all patients receiving either duloxetine 60 mg QD or duloxetine 120 mg QD were to have their respective doses gradually reduced.

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Trial Procedures

The following table presents the time of events and assessments planned to be taken.

Study Schedule, Protocol F1J-MC-HMEN

Visit	1	2	3	4	5	6	7	8	9	10	11	V301	ET
Week	-1	0	4	7	13	15	22	30	38	46	54	56>W1	>W1
Days From Visit 2		-	28 +/- 2	49 +/- 4	91 +/- 4	105 +/- 2	154 +/- 4	210 +/- 4	266 +/- 4	322 +/- 4	378 +/- 4	392 +/- 2	
Description													
Informed Consent	X												
Demographics	X												
Medical History	X												
Physical Exam	X												
Historical Illness	X												
MINI	X												
Habits	X												
Height	X											X	X
Weight	X	X	X	X	X	X	X	X	X	X	X	X	X
ECG	X												
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X	X
Supine/Standing BP and HR (orthostatic)		X			X			X			X		X
Pre-existing conditions	X												
Adverse Events		X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X
Urinary Drug Screen	X												
Serum Pregnancy Test ^a	X												
Chemistry	X		X		X		X	X	X	X	X		X
Hematology	X												
Hepatitis Panel ^c	X												
HgbA1c	X										X		X
Fasting Glucose	X				X			X			X		X
Lipid Profile	X				X			X			X		X
Electronic Patient Diary		X	X	X	X								X
BDI-II	X	X	X	X	X	X	X	X	X	X	X	X	X
HADS		X			X						X		X
PGI-Severity		X											
PGI-Improvement			X	X	X								X
CGI-Severity		X	X	X	X	X	X	X	X	X	X		X
BPI		X	X	X	X	X	X	X	X	X	X		X
Roland Morris Scale		X			X						X		X
WPAI		X			X						X		X
EQ-5D		X			X						X		X
SF-36		X			X						X		X
Athens insomnia scale		X			X						X		X
Dispense Drug		X	X	X	X	X	X	X	X	X	X		
Return Drug			X	X	X	X	X	X	X	X	X	X	X
X-Ray ^b	X												

(Source: Applicant’s table from HMEN Study Report, Attachment, pp. 57-58)

Discontinuation Criteria

The following discontinuation criteria were to have been applied for this protocol:

- Clinically significant adverse event or laboratory abnormalities
- Patient is judged to be at high suicidal risk

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- Pregnancy
- Treatment with therapeutic agent indicated for CLBP

Statistical Analysis

Primary efficacy variable

- The primary efficacy variable was to have been the change in BPI 24 hours average pain score from Baseline to endpoint (last non-missing observation), expressed as weekly mean, and collected from electronic patient diaries.

Pain scores were to have been recorded in a patient diary once a day as an average pain over 24 hours. The 11-point Likert scale was to have been used to rate the pain severity. The baseline pain score was to have been calculated as the average score from the week prior to randomization. The endpoint score was to have been calculated as the average weekly score from the last week of available observations.

- Extension Phase: Change from baseline (last non-missing observation during Visit 3 to Visit 5) to endpoint (last non-missing observation during Visit 6 to Visit 11) in BPI average pain.

Secondary efficacy variables

- Percentage of subjects with 30% and 50% reduction in the 24-hour average pain (11-point Likert)
- Patient's Global Impressions of improvement (PGI - Improvement)
- Patient's Global Impressions of disease severity (PGI – Severity)
- Clinical Global Impressions of disease severity (CGI – Severity)
- Severity of pain and the interference of pain on function measured by the Brief Pain Inventory scale (BPI)
- Suicidal risk using the Beck Depression Inventory-II (BDI-II)
- Anxiety and depression using the Hospital Anxiety and Depression Scale (HADS)
- Health outcome using Euro-QoL Questionnaire (EQ-5D) assessed at Visits 2, 5, and end of treatment
- Quality of life using Short-Form Health Survey (SF-36) assessed at Visits 2, 5, and end of treatment
- Sleep assessment using The Athens Insomnia Scale (AIS)
- Effect of general health and symptom severity on work productivity and regular activities using Work Productivity and Activity Impairment Instrument (WPAI)

Safety variables

- Adverse events
- Discontinuation due to adverse events

- Changes in vital signs measurements, laboratory evaluations, and physical examination findings

Safety analyses were to include all patients with baseline data.

Statistical analysis methods

All analyses were to have been conducted on an intent-to-treat basis. Statistical tests of efficacy variables were to have been presented as 2-sided p-values. Statistical comparisons were to have been performed at the 0.05 level of significance. No adjustments for multiple comparisons were to have been made.

A likelihood-based, mixed-effect repeated measures (MMRM) analysis was to have been used to analyze the primary efficacy variable. All patients with data from baseline and at least one post-baseline visit were to have been included in the analysis. The model was to include fixed categorical effects of treatment, NSAID use, investigator, week and treatment-by-week interactions, and continuous fixed covariates of baseline score and baseline by-week interaction. Similar to HMEP trial, mean change in the primary efficacy variable was to have been analyzed using a last-observation carried-forward (LOCF) and baseline-observation-carried-forward (BOCF) approaches. The analysis of variance (ANOVA) model was to have been used to analyze continuous variables, with terms for treatment and investigator. The stratifying variable of NSAID use was to have been added to the analysis of covariance (ANCOVA) with baseline values added as a covariate.

A gatekeeper strategy was to have been used to sequentially test the secondary objectives to compare improvement between duloxetine- and placebo-treated patients on the PGI-I and the Roland Morris total score, using the ANCOVA model and LOCF approach.

Path analysis was to have been used to test if the change in 24 average pain severity was due to improvement of BDI-II or Hospital Anxiety Depression Scale –Anxiety subscale (HADS-A), or due to a direct analgesic effect of the treatment and not dependent upon the improvement in depression and anxiety symptoms.

Sample size calculation

A sample size of 230 subjects (115 patients per arm) was calculated based on the results from Study HMEP for a study power of approximately 80% to detect a treatment difference of 1.0 in the mean change from baseline to endpoint in the weekly mean 24 hour average pain severity between duloxetine and placebo treatment groups.

Statistical Analysis for the Extension Phase

All patients in the 41-week, double-blind, uncontrolled extension treatment phase with a baseline visit and at least one post-baseline visit were included in the efficacy analyses. All patients in the extension treatment phase were included in the safety analyses.

The main efficacy objective of the extension treatment phase was to evaluate whether the treatment effect of duloxetine 60 QD to 120 mg QD was maintained over a 41-week period in patients with CLBP as measured by change from baseline to endpoint in BPI average pain. The null hypothesis that the treatment effect of duloxetine was not maintained during the extension treatment phase was to have been tested by evaluating a one-sided 97.5% CI of the change from baseline to endpoint for patients in the extension treatment phase who responded to duloxetine 60 mg QD to 120 mg QD (acute phase duloxetine responders). In this analysis, baseline was defined as the last non-missing observation during Visit 3 to Visit 5, and endpoint was defined as the last non-missing observation during Visit 6 to Visit 11. When the upper bound of the one-sided 97.5% CI was less than or equal to the non-inferiority margin of 1.5 points on BPI average pain, the null hypothesis was rejected at the significance level of 0.025. A similar analysis was also to be performed for patients in the extension treatment phase who responded to duloxetine 60 mg QD as the last dose during the acute treatment phase (acute phase 60 mg QD duloxetine responders). For this second analysis, patients who titrated from duloxetine 60 mg QD to 120 mg QD during the acute treatment phase were to have been excluded. Only patients who achieved greater than or equal to a 30% reduction on BPI average pain, after 13 weeks of acute duloxetine treatment, were to have been included in both analyses.

For BPI average pain, change from baseline (the end of the acute treatment phase) to endpoint (the end of the extension treatment phase) was to have been summarized for all randomized patients in the extension treatment phase, with within-group, t test p-values.

A similar analysis was also to be performed by the initial group assignments in the acute treatment phase and the last dose in the extension treatment phase. The groups were as follows:

- Placebo in the acute phase and DLX 60 mg QD in the extension treatment phase
- Placebo in the acute phase and DLX 120 mg QD as the last dose in extension phase
- DLX 60 mg QD as the last dose in the acute phase and DLX 60 mg QD as the last dose in extension treatment phase
- DLX 60 mg QD as the last dose in the acute phase and DLX 120 mg QD as the last dose in extension treatment phase
- DLX 120 mg QD as the last dose in the acute phase and DLX 120 mg QD as the last dose in extension phase

For BPI (severity and interference) and CGI-Severity, MMRM analysis was to have been conducted for all patients in the extension treatment phase using data collected in the extension treatment phase. For BPI average pain, a similar MMRM analysis was to have been performed for all patients who entered the extension treatment phase using

data collected during the entire study (both acute treatment phase and extension treatment phase).

For patients who discontinued early, the LOCF approach was to have been used to impute the missing data.

The percentage of patients meeting response criteria during the extension treatment phase were to have been summarized using three response definitions: (1) $\geq 30\%$ reduction from baseline to endpoint for BPI average pain; (2) $\geq 50\%$ reduction from baseline to endpoint for BPI average pain; and (3) sustained response.

Protocol Amendments

The protocol was approved submitted? by the applicant on August 3rd, 2006. The first subject was enrolled on January 24, 2007. The original protocol was amended three times.

1. Amendment A (November 6, 2006). The most pertinent changes included the following:
 - Electronic diary completion prior to randomization clarified.
 - Episodic use of some short-acting analgesics was changed.
 - Schedule of events and laboratory tests were updated.
2. Amendment B (February 5, 2007). Minor changes were made:
 - NSAID use was clarified
 - All references to Boehringer Ingelheim (BI) were removed from the protocol.
3. Amendment C (January 23, 2008). The most pertinent changes included the following:
 - The primary efficacy measure was changed from the 24-hour average pain score collected from patient diaries to the Brief Pain Inventory (BPI) 24-hour average pain score collected at study visits. The applicant's rationale for this change was that in the two completed pain studies (HMEP in osteoarthritis knee pain and HMEO in chronic low back pain), overall electronic patient diary compliance over 13 weeks was low (68% and 49%, respectively). Because of the greater than anticipated missing diary data, these studies no longer had adequate power for the pre-specified effect size.
 - Statements regarding study power were revised based on the new primary outcome measure of BPI average pain score and data from the two completed chronic pain studies.
 - mBOCF was added as additional secondary analysis of BPI average pain score.
 - Secondary efficacy analyses, including response rate and subgroup analyses, and path analysis of direct analgesic effect were changed to be based on the BPI average pain score.

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- The comparison of duloxetine 60 mg QD with placebo was deleted from the list of secondary objectives. The applicant determined that Study HMEN is not optimally designed to compare duloxetine 60 mg QD with placebo, given that the 60 mg QD dose was not a true fixed dose arm.

Trial Results

Protocol Violations

Study visit interval interruption resulting in a lack of study drug supply was the most frequent protocol violation followed by noncompliance to diary regimen.

Because the frequency of these protocol violations was similar across treatment groups, it is unlikely that the violations greatly impacted the primary efficacy results.

The types and numbers of violations are shown on the table below:

Table 14: Protocol Violations - HMEN

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Violation Type *	---Placebo---		-DLX60/120qD--		----TOTAL-----	
	N=121 n	(%)	N=115 n	(%)	N=236 n	(%)
Exclusionary Con. Med. Taken	6	(4.96%)	2	(1.74%)	8	(3.39%)
Inclusion/Exclusion	1	(0.83%)	1	(0.87%)	2	(0.85%)
Non compliance to diary regimen	68	(56.20%)	67	(58.26%)	135	(57.20%)
Non compliance to study drug regimen	17	(14.05%)	14	(12.17%)	31	(13.14%)
Study visit interval resulting in a lack of study drug	108	(89.26%)	97	(84.35%)	205	(86.86%)

(Source: Applicant's table from the original NDA 22-333 submission, July 8, 2008 Amendment, p. 12)

Enrollment/ Subject disposition

Of the 236 randomized patients, 121 were assigned to the placebo group, and 115 were assigned to the duloxetine group. A total of 94 (81.7%) of the 115 patients originally assigned to the duloxetine 60 mg per day group, completed six weeks of treatment. At Week 7, of 94 patients, 27 (28.7%) required up-titration of duloxetine to 120 mg QD because of insufficient response (< 30% pain score reduction compared to baseline). Sixty seven patients continued on 60 mg QD duloxetine dose for the remainder of the treatment phase.

A total of 180 (76.3%) patients completed the study: 96 (79.3.0%) in the placebo group and 84 (73%) in the duloxetine group.

The disposition for the 236 randomized subjects is summarized on the table below. Across all groups, 22.9% of patients discontinued the trial. The most frequently reported reason was discontinuation due to adverse event, with a significantly higher

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rate for the duloxetine-treated patients, 13.9% versus 5.8% for the placebo-treated patients. The discontinuation rate due to lack of efficacy was slightly higher for the placebo-treated patients (4.1% for placebo vs. 2.6% for DLX).

Table 15: Subject disposition - HMEN

Primary Reason for Discont.	HMEN trial	
	Placebo	DLX 60/120
	N=121 (%)	N=115 (%)
Completed	81.0	73.0
Discont. Due to any reason	19.0	27.0
Adverse Event	5.8	13.9
Subject Decision	5.0	7.0
Lack of Efficacy	4.1	2.6
Lost to follow up	0.8	0.9

(Source: Adapted from applicant's table 2.7.3.8 from Amendment 3, p. 16)

Analysis of discontinuation by dose prior of re-randomization (first 7 weeks) and after re-randomization (last 6 weeks) is presented on the table below. The final data lock of November 20, 2008 including data of the entire study was used for this analysis.

Table 16: Discontinuation by dose, first 7 weeks and last 6 weeks – HMEN

	First 7 weeks of Study		Second 6 weeks of Study		
	Placebo n (%)	DLX60 n (%)	Placebo n (%)	DLX60 n (%)	DLX120 ^b n (%)
Study HMEN ^a	N= 121	N= 115	N= 109	N= 64	N= 27
Any Reason	12 (9.9)	24 (20.9)	11 (10.1)	5 (7.8)	2 (7.4)
Adverse Event	4 (3.3)	13 (11.3)	3 (2.8)	2 (3.1)	1 (3.7)
Subject/Physician Decision	3 (2.5)	6 (5.2)	4 (3.7)	2 (3.1)	0 (0)
Lack of Efficacy	2 (1.7)	3 (2.6)	3 (2.8)	0 (0)	0 (0)

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(Source: Applicant's table 2.7.4.21 form CSS, p. 68)

Significantly more patients administered duloxetine 60 mg QD discontinued overall (21% vs. 10%) and due to an AE (11% vs. 3%) after the first seven weeks of treatment compared to patients administered placebo. No significant differences were observed during the last six weeks.

The following table illustrates the drop-out rate by study week for the placebo and duloxetine treatment groups.

Table 17: Drop outs by treatment group and study week – HMEN

Drop out week	Placebo N=120	Duloxetine 60- 120 mg/d N=111	Total N=231
	n (%)		
Week 4	10 (8.3%)	18 (15.7%)	28 (12.1%)
Week 7	2 (1.7%)	6 (5.2%)	8 (3.5%)
Week 13	11 (9.1%)	7 (6.1%)	18 7.8(%)

(Source: Adapted from Applicant's table 10.3 from Study report for HMEP, pp. 68-69)

The duloxetine-treated patients tended to discontinue treatment relatively early during the double-blind treatment phase (15.7% at Week 4 compared to 5.2% at Week 7 and 6.1% at Week 13). The early discontinuations were mainly due to adverse events (9.6% at Week 4).

The table below illustrates the disposition of patients during the extension phase. Of the 181 patients entering the extension treatment phase, 28 (33.7%) DLX_DLX60/120-treated patients and 36 (36.7%) PLA_DLX60/120-treated patients discontinued from the study extension treatment phase. The primary reason for study discontinuation was the subject's decision for DLX_DLX60/120-treated patients (12%) and an adverse event for PLA_DLX60/120-treated patients (13.3%).

Table 18: Subject disposition – HMEN Extension Phase

Table HMEN.10.1. Reasons for Study Discontinuation
 All Randomized Patients
 Extension Treatment Phase

Primary reason for discontinuation	PLA_DLX60/120	DLX_DLX60/120	Total
	(n = 98)	(n = 83)	(n = 181)
	n (%)	n (%)	n (%)
Completed	62 (63.3)	55 (66.3)	117 (64.6)
DC DUE TO ANY REASON	36 (36.7)	28 (33.7)	64 (35.4)
Subject Decision	9 (9.2)	10 (12.0)	19 (10.5)
Adverse Event	13 (13.3)	5 (6.0)	18 (9.9)
Lack of Efficacy	6 (6.1)	3 (3.6)	9 (5.0)
Protocol Violation	4 (4.1)	5 (6.0)	9 (5.0)
Lost to follow up	2 (2.0)	4 (4.8)	6 (3.3)
Physician Decision	2 (2.0)	1 (1.2)	3 (1.7)

(Source: Applicant's table HMEN 10.1 from study report, p. 45)

Extent of exposure

The mean study drug exposure was 80 days with 58.5% of patients receiving study drug for at least 13 weeks, 62.0% for the placebo and 54.8% for the duloxetine-treated patients.

Overall, no significant differences were observed between the duloxetine and the placebo treatment groups study drug exposure.

The table below shows the extent of exposure to study drug for all randomized patients:

Table 19: Study drug exposure for all randomized patients – HMEN

Table HMEN.12.1. Study Drug Exposure All Randomized Patients Double-Blind Treatment Phase		BEST AVAILABLE COPY	
Variable	PLACEBO (N = 121)	DLX60/120QD (N = 115)	Total (N = 236)

Duration of Exposure (Days)			
NO. SUBJECTS	121	115	236
MEAN	82.60	77.43	80.08
STD	46.39	30.96	39.63
MAX	145.00	125.00	145.00
MEDIAN	91.00	91.00	91.00
MIN	-362.00	-13.00	-362.00
Patient Years	27.36	24.38	51.74
Duration of Exposure -n(%)			
NO. SUBJECTS	121	115	236
>0	120 (99.2)	114 (99.1)	234 (99.2)
>=28	114 (94.2)	100 (87.0)	214 (90.7)
>=49	110 (90.9)	95 (82.6)	205 (86.9)
>=91	75 (62.0)	63 (54.8)	138 (58.5)
>=105	8 (6.6)	6 (5.2)	14 (5.9)

(Source: Applicant's table 12.1 form Study report for HMEP, p. 156)

The table below illustrates the study drug exposure during the extension phase. Of the 181 patients in the extension treatment phase, 98 PLA_DLX60/120-treated patients were exposed to duloxetine for an average of 224.5 days, and 83 DLX_DLX60/120-treated patients were exposed to duloxetine for an average of 243.4. Overall, 120 of 181 (66.3%) patients had at least 270 days of treatment during the extension treatment phase.

Table 20: Study drug exposure – HMEN Extension Phase

**Table HMEN.12.1. Study Drug Exposure
 All Randomized Patients
 Extension Treatment Phase**

Variable	PLA_DLX60/120 (N = 98)	DLX_DLX60/120 (N = 83)	Total (N = 181)
Duration of Exposure (Days)			
NO. SUBJECTS	98	83	181
MEAN	224.49	243.37	233.15
STD	94.47	84.82	90.42
MAXIMUM	336.00	369.00	369.00
MEDIAN	281.00	285.00	283.00
MINIMUM	1.00	42.00	1.00
Patient Years	60.23	55.30	115.54
Duration of Exposure -n(%)			
NO. SUBJECTS	98	83	181
>0	98 (100.0)	83 (100.0)	181 (100.0)
>=14	94 (95.9)	83 (100.0)	177 (97.8)
>=60	89 (90.8)	78 (94.0)	167 (92.3)
>=120	77 (78.6)	71 (85.5)	148 (81.8)
>=180	71 (72.4)	66 (79.5)	137 (75.7)
>=240	64 (65.3)	61 (73.5)	125 (69.1)
>=270	61 (62.2)	59 (71.1)	120 (66.3)

(Source: Applicant's table HMEN 12.1, from study report, p. 121)

The table below shows a summary of duloxetine dose escalation from Visit 6 to Visit 11 during the extension treatment phase. At Visit 11, 37% of patients stayed on DLX 60 mg QD, and 27.6% of patients stayed on duloxetine 120 mg QD. During the extension treatment phase 21.5% and 13.8% of patients discontinued the study or were lost to follow up while on DLX 60 mg QD and duloxetine 120 mg QD, respectively. It is of note that at Visits 8 and 9 most patients on DLX 60 mg had their dose increased to 120 mg QD. The rate of discontinuations/lost of follow up for the two dose groups at all visits was similar except for Visit 7 when 7.5% of DLX 60 mg treated patients versus 1.7% of DLX 120 mg treated patients discontinued from the trail.

Table 21: Duloxetine dose escalation – HMEN Extension Phase

**Table HMEN.12.2. Summary of Duloxetine Dose Escalation
 All Randomized Patients
 Extension Treatment Phase**

Visit	Total No. of Patients at each visit	Continued on DLX60QD n (%)	Continued on DLX120QD n (%)	Increased to DLX120QD n (%)	D/c or Lost fup on DLX60QD n (%)	D/c or Lost fup on DLX120QD n (%)
6	181	149 (82.3)	25 (13.8)	0 (0.0)	7 (3.9)	0 (0.0)
7	174	136 (78.2)	22 (12.6)	0 (0.0)	13 (7.5)	3 (1.7)
8	158	98 (62.0)	46 (29.1)	33 (20.9)	5 (3.2)	9 (5.7)
9	144	80 (55.6)	54 (37.5)	13 (9.0)	5 (3.5)	5 (3.5)
10	134	73 (54.5)	54 (40.3)	4 (3.0)	3 (2.2)	4 (3.0)
11	127	67 (52.8)	50 (39.4)	0 (0.0)	6 (4.7)	4 (3.1)

(Source: Applicant's table HMEN 12.1, from study report, p. 122)

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Overall, the average age of subjects was 51.5 years and similar between the placebo and duloxetine-treated patients. The majority of patients were female and Caucasian.

There were no significant differences between the duloxetine and placebo groups for age, sex and baseline illness characteristics as illustrated on the following table:

Table 22: Patient Demographic Characteristics and Disease Severity at Baseline - HMEN

Parameter	Placebo N=120	DLX 60 to 120 mg/d N=111	Total N=231
	n (%)		
Sex			
Male	48 (39.7)	44 (38.3)	92 (40.0)
Female	73 (60.3)	71 (61.7)	144 (61.0)
Race			
White	91 (75.2)	85 (74.0)	176 (74.6)
Black	6 (5)	6 (5.2)	12 (5.1)
Hispanic	21 (17.4)	23 (20.0)	44 (18.6)
Asian	2 (1.7)	0	2 (0.9)
Age			
Mean	51.2	51.8	51.5
Minimum	21.2	20.0	20.0
Maximum	79.6	84.6	84.6
Weight (kg)			
Mean	76.0	76.2	76.1
Minimum	42.4	45.1	42.4
Maximum	114.8	120.2	120.2
Height (cm)			
Mean	167.4	166.0	166.7
Minimum	146.0	145.0	145.0
Maximum	197.0	197.0	197.0
Duration of CLBP since onset (in years)			
Mean	9.5	8.8	9.2
Minimum	0.6	0.5	0.5
Maximum	42.0	44.0	44.0
BPI Average Pain			
Mean	6.0	6.0	6.0
Minimum	2.0	2.00	2.00
Maximum	10.0	10.0	10.0
NSAID use No. of			

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patients			
No	82 (76.8)	80 (70.0%)	162 (68.6%)
Yes	39 (32.2)	35 (30.4%)	74 (31.4)

(Source: Adapted from Applicant's table 11.1 and 11.2 from Study report for HMEN, pp. 59-62)

Baseline medical characteristics and concomitant therapy

Medical history and concomitant diseases were similar between the placebo and duloxetine treatment groups. With regards to the concomitant medication use, there were no significant differences between groups.

The demographic and baseline illness characteristics for the extension phase were similar to those presented for the acute treatment phase.

Applicant's efficacy analysis

Overview

On the primary MMRM analysis of the 24-hour average pain score as recorded on the BPI instrument at study visits, the applicant found that patients treated with duloxetine 60 mg to 120 mg for 13 weeks demonstrated significantly greater improvement than placebo-treated patients.

The LSMean at Week 13 difference between the placebo and DLX 60-120 was .082 with $p < 0.004$.

The additional LOCF analysis of mean change from baseline to endpoint in 24-hour average pain score was found by the applicant to demonstrate statistically significant pain reduction for duloxetine compared to placebo (LSMean difference of -0.64, $p=0.019$). Using the BOCF and mBOCF approach the difference was also found to be statistically significant (LSMean difference of -0.61, $p= 0.019$ for BOCF and LSMean difference of -0.55, $p= 0.041$ for mBOCF).

In a secondary analysis of 30% and 50% response rate at endpoint using the LOCF imputation strategy no significant difference between treatment groups was observed. When BOCF approach was used, a statistically greater 50% response rate was demonstrated for the duloxetine group compared with the placebo group.

In the analysis of patients re-randomized to duloxetine 60 mg QD or 120 mg QD at Visit 4 (Week 7), the applicant found statistically greater 24-hour average pain reduction based on LOCF mean change analysis of the weekly mean change from patient diaries when compared duloxetine 120 mg QD re-randomized patients with those re-randomized to duloxetine 60 mg QD. No statistically significant differences were observed between duloxetine 60 mg QD and 120 mg QD on the MMRM analysis of the weekly 24-hour average pain score or the 30% and 50% response rates at endpoint.

The secondary gatekeeper assessments for PGI-I and the RMDQ-24 hour total score were found to demonstrate significantly greater improvement for the duloxetine compared to the placebo-treated patients.

The path analysis conducted by the applicant was found to demonstrate that improvements in pain scores were due to a direct analgesic effect independent of improvement in mood and/or anxiety symptoms.

During the 41-week, uncontrolled, double-blind extension treatment phase, the applicant found that DLX 60 to 120 mg QD demonstrates maintenance of effect on pain reduction in CLBP patients.

Primary efficacy endpoint

The applicant found that the results from Study HMEP and Study HMEO revealed lower-than-expected diary compliance, and amended the primary endpoint of Study HMEN to 24-hour average BPI pain item on the 11-point Likert scale collected as a single-day report at study visits instead of the weekly average score collected from patient diary. Mixed-effects model repeated measures (MMRM) was the pre-specified primary analysis.

The applicant found that at Week 13 (Visit 5) there was a statistically significant greater decrease (improvement) in the average pain score in the duloxetine 60/120 mg QD group (2.32 points) compared to the placebo group (1.50 points). The LSMean difference between the placebo and duloxetine 60/120 mg was 0.82 with a p-value of 0.004.

In addition to the primary MMRM analysis, the applicant performed additional sensitivity analyses on the primary efficacy measure, including ANCOVA model based on LOCF, BOCF, and mBOCF. On all of the three additional analyses, the applicant found that patients treated with duloxetine 60 mg to 120 mg for 13 weeks demonstrated significantly greater pain reduction than placebo-treated patients. The difference in LSMean pain score between the duloxetine 60/120QD and placebo using LOCF was -0.64 with a p-value of 0.019. LSMean pain score difference using BOCF was -0.61 with a p-value of 0.019 and using the mBOCF it was -0.55 with a p-value of 0.041.

The table below illustrates the difference in pain score reduction between duloxetine 60/120 QD and placebo for the different analyses. In addition the table compares the results between data collected from patient diaries, expressed as weekly mean score and data collected as single-day BPI reports collected at study visits.

Table 23: Difference in LSMean 24-hour average pain score (from patient diaries and the BPI), DLX60/120 - Placebo, All Randomized Patients – HMEN

	HMEN
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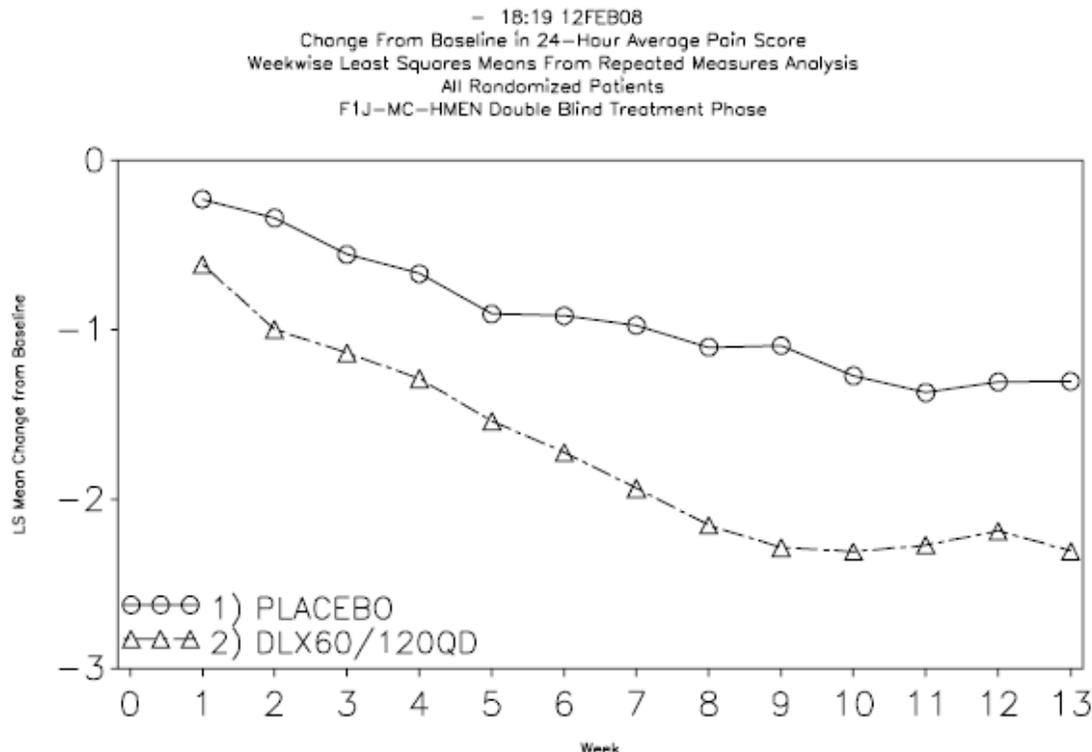
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	Endpoint LSMean	Treatment Difference	p-value
Weekly mean 24-hour average pain (Diary)			
MMRM: DLX 60/120 Placebo	-2.31	-1.00	<.001
	-1.31		
LOCF: DLX 60/120 Placebo	-2.08	-0.77	0.002
	-1.30		
BOCF: DLX 60/120 Placebo	-1.82	-0.58	0.019
	-1.24		
mBOCF: DLX 60/120 Placebo	-1.91	-0.63	0.012
	-1.28		
24-hour average pain (BPI collected at study visits)			
MMRM: DLX 60/120 Placebo	-2.32	-0.82	0.004
	-1.50		
LOCF: DLX 60/120 Placebo	-2.09	-0.64	0.019
	-1.45		
BOCF: DLX 60/120 Placebo	-1.86	-0.61	0.019
	-1.25		
mBOCF: DLX 60/120 Placebo	-1.91	-0.55	0.041
	-1.35		

(Source: Adapted from Applicant's tables 2.5.4.2 and 2.5.4.3, Clinical overview, pp. 26-28)

Graphical representation of the data, presented below, by week and LSMean change from repeated measures analysis show separation between the duloxetine 60/120 QD and placebo group for the entire duration of the 13 week period.

Figure 5: Weekly LSMean changes from repeated measures analysis - HMEN



(Source: Applicant’s figure 14.5 from study report for HMEN, p. 280)

Secondary efficacy endpoints

Because there were no adjustments for the multiple secondary analyses, any p-values associated with secondary efficacy variables should be interpreted as descriptive statistics only.

- Percentage of subjects with 30% and 50% reduction in the 24-hour average pain (11-point Likert)

The applicant’s analysis of 30% and 50% response rate at endpoint failed to demonstrate statistically significant difference in response between the duloxetine 60/120 QD group and the placebo group for LOCF and BOCF 30% response, and LOCF 50% response rate. Significantly more patients in the duloxetine treatment group were found to have 50% response rate compared with patients in the placebo treatment group with the BOCF imputation.

Table 24: Proportion of treatment responders – 30% and 50% improvement from Baseline to Endpoint using LOCF - HMEN

Treatment	N	30% improvement n (%)	p-value	50% improvement n (%)	p-value

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Placebo	115	46 (40.0)	0.06	31 (27.0)	0.087
DLX 60/120 QD	109	58 (53.2)		42 (38.5)	

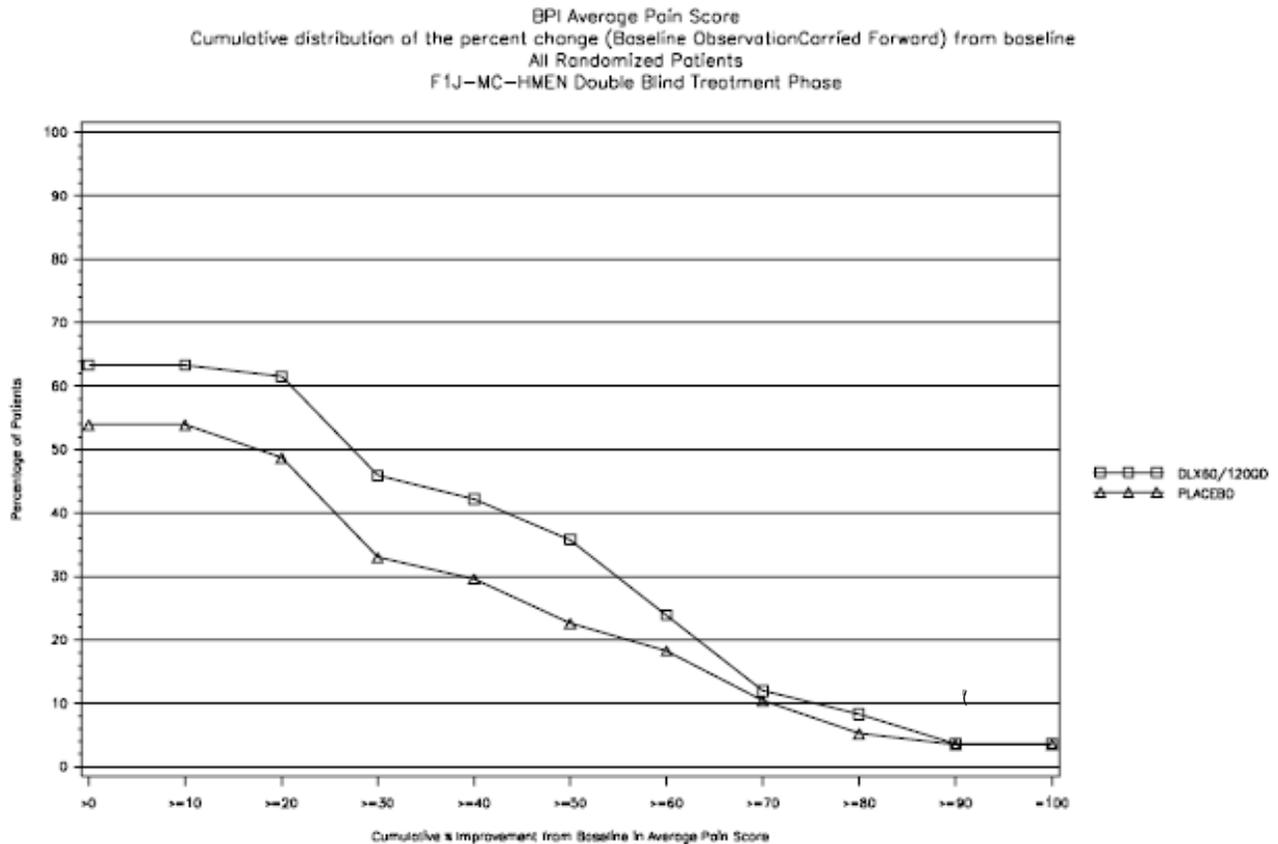
(Source: Adapted from Applicant's tables 14.7 and 14.8 from Study Report, pp.251 - 252)

Table 25: Proportion of treatment responders – 30% and 50% improvement from Baseline to Endpoint using BOCF - HMEN

Treatment	N	30% improvement n (%)	p-value	50% improvement n (%)	p-value
Placebo	115	38 (33.0)	0.056	26 (22.6)	0.039
DLX 60/120 QD	109	50 (45.9)		39 (35.8)	

(Source: Adapted from Applicant's tables 14.10 and 14.11 from Study Report, pp. 254-255)

Figure 6: Cumulative distribution of the percent change from Baseline (BOCF) – HMEN



(Source: Applicant's figure 14.1, Study Report, p. 249)

- Patient's Global Impressions of improvement (PGI - Improvement) and CLBP and its interference with activities of daily living (RMDQ-24)

The applicant employed a gatekeeper strategy, using LOCF imputation, for sequentially testing the following:

- The comparison of duloxetine 60 mg QD versus placebo on patients' perceived improvement as measured by PGI-Improvement
- The comparison of duloxetine 60 mg QD versus placebo on the improvement of functioning as measured by the RMDQ-24, a questionnaire addressing CLBP and its interference with activities of daily living

For both assessments, the applicant found that duloxetine 60/120 QD treated patients demonstrated significantly greater improvement when compared with placebo-treated patients. LS Mean difference of -0.41, $p=0.014$ for the PGI-I and LS Mean difference of -1.67, $p=0.009$ for the RMDQ-24.

- The applicant found that duloxetine treatment resulted in significant reduction of the BPI worst pain score collected from patient diaries (LSMean difference -0.76, p=0.011)
- The applicant found no significant difference between treatment groups for the patients' general well-being as measured by CGI-Severity (LSMean difference -0.21, p=0.092) and quality of life as measured by the European Quality of Life Questionnaire – 5 Dimensions (EQ-5D), LSmMean difference of 0.05, p=0.117
- Quality of life using Short-Form Health Survey (SF-36) did not show significant improvement for most of the domains when duloxetine was compared to placebo

Efficacy results from the Extension Phase

The efficacy findings from the open-label extension phase do not support findings of efficacy for duloxetine because there was lack of placebo control.

- The primary efficacy variable for Study HMEN was BPI average pain. The table below shows the mean change from baseline to endpoint during the extension treatment phase for BPI average pain with a one-sided 97.5% CI for DLX_DLX60/120- treated-patients who achieved greater than or equal to a 30% reduction on BPI average pain during the acute treatment phase (acute phase duloxetine responders). The mean change in BPI average pain was -0.97, and the upper bound of the one-sided 97.5% CI was -0.45, which was less than the prespecified, non-inferiority margin of 1.5 points (p<.001).

Table 26: Change in BPI average pain from baseline to endpoint for acute phase DLX responders – HMEN extension phase

Table HMEN.11.5. Brief Pain Inventory Average Pain
 Mean Change from Baseline to Endpoint
 Acute Phase Duloxetine Responders
 Extension Treatment Phase

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BPI Average Pain	Baseline						Endpoint					Change				
	N	Mean	SD	Median	Min	Max	Mean	SD	Median	Min	Max	Mean	SD	Median	Min	Max
DLX_DLX60/120	58	2.86	1.71	3.0	0.0	8.0	1.90	1.67	1.0	0.0	6.0	-0.97	1.72	-1.0	-6.0	3.0
1- sided 97.5% CI : (-, -0.45) t = -10.94 p = <.001																

(Source: Applicant's table 11.5 from study report, p.64)

- Additional analyses of the primary efficacy variable (HMEN extension phase) The table below shows the mean change from baseline to endpoint during the extension treatment phase for BPI average pain with a one-sided 97.5% CI for acute phase duloxetine 60 mg QD responders who received duloxetine 60 mg QD during the extension treatment phase (DLX60_DLX60). The mean change in BPI average pain was -0.59, and the upper bound of the one-sided 97.5% CI was 0.05, which was less than the prespecified, non-inferiority margin of 1.5 points (p<.001).

Table 27: Change in BPI average pain from baseline to endpoint for acute phase DLX 60 mg responders who stayed on DLX 60 mg during the extension phase - HMEN

BPI Average Pain		Baseline					Endpoint					Change				
Therapy	N	Mean	SD	Median	Min	Max	Mean	SD	Median	Min	Max	Mean	SD	Median	Min	Max
DLX60_DLX60	49	2.65	1.58	3.0	0.0	7.0	2.06	1.89	2.0	0.0	7.0	-0.59	1.94	-1.0	-6.0	3.0

1- Sided 97.5% CI : (--, 0.05) t = -7.56 p = <.001

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(Source: Applicant’s table 11.6 from study report, p.66)

The table below presents the mean change from baseline to endpoint during the extension treatment phase for BPI average pain severity with a two-sided, within-group t test and 95% CI for PLA_DLX60/120-treated patients, DLX_DLX60/120-treated patients, and for both groups of patients combined (overall). The mean change from baseline was statistically significantly less than zero for PLA_DLX60/120-treated patients, DLX_DLX60/120-treated patients, and overall (p<.001), demonstrating a reduction in pain for patients with CLBP during the extension treatment phase regardless of their initial treatment assignment during the acute treatment phase.

Table 28: Change in BPI average pain from baseline to endpoint for all randomized patients – HMEN extension phase

BPI Average Pain Severity		Baseline		Endpoint		Change				
Therapy	N	Mean	SD	Mean	SD	Mean	SD	95% CI	t-statistics	p-val
PLA_DLX60/120	97	4.45	2.29	3.10	2.77	-1.35	2.24	(-1.80, -0.90)	-5.95	<.001
DLX_DLX60/120	80	3.40	1.87	2.35	1.95	-1.05	1.79	(-1.45, -0.65)	-5.24	<.001
Overall	177	3.98	2.17	2.76	2.46	-1.21	2.05	(-1.52, -0.91)	-7.89	<.001

(Source: Applicant’s table 11.7 from study report, p.67)

The table that follows shows the MMRM analysis on BPI average pain for PLA_DLX60/120-treated patients, DLX_DLX60/120-treated patients, and for both groups of patients combined during the entire 54-week study duration. The LS Mean change from baseline (Visit 2) in BPI average pain was statistically significantly less than zero at each visit for PLA_DLX60/120-treated patients,

DLX_DLX60/120-treated patients, and overall, demonstrating a reduction in pain for patients with CLBP during the acute (Visit 3 and Visit 4) and extension (Visit 5 through Visit 11) treatment phases. The reduction in pain by the end of the extension treatment phase, as shown by the LS Mean change, had an increase of 116%, 53%, and 75% when compared to the end of the acute treatment phase for PLA_DLX60/120-treated patients, DLX_DLX60/120-treated patients, and overall, respectively. The figure that follows the table shows the mean changes from study baseline (Visit 2) in BPI average pain at each visit from the MMRM analysis.

Table 29: Change in BPI average pain from baseline to endpoint for all randomized patients – HMEN acute and extension phases

Table HMEN.11.8. Brief Pain Inventory Average Pain Repeated Measures Analysis All Randomized Patients in the Extension Treatment Phase Acute and Extension Treatment Phase (Concluded)

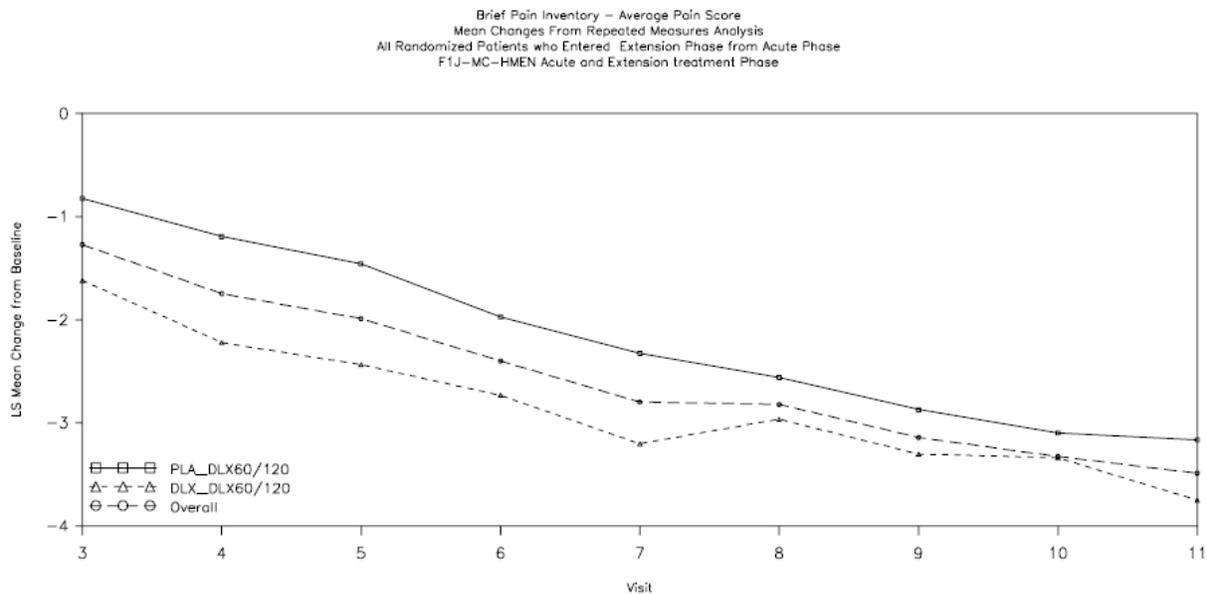
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BPI Average Pain

Therapy	Visit (Week)	N	LS Mean	LS Mean Change	SE	T	DDF	Within p-Value
1) PLA_DLX60/120	10 (46)	69	2.85	-3.09	0.28	-11.15	100	<.001
2) DLX_DLX60/120		63	2.50	-3.35	0.31	-10.96	72	<.001
3) overall		132	2.57	-3.33	0.21	-16.09	188	<.001
1) PLA_DLX60/120	11 (54)	65	2.79	-3.15	0.28	-11.09	99	<.001
2) DLX_DLX60/120		60	2.10	-3.74	0.23	-16.28	67	<.001
3) overall		125	2.41	-3.48	0.19	-17.89	185	<.001

(Source: Applicant’s table 11.8 from study report, p.69)

Figure 7: BPI average pain, mean change from MMRM – all randomized patients who entered extension phase



(Source: Applicant’s figure 11.1 from study report, p.70)

5.3.3 Protocol HMFG

Title: “Duloxetine 60 to 120 mg versus placebo in the treatment of patients with osteoarthritis knee pain.”

Objectives

The primary, secondary gatekeeper and additional secondary objectives for this trial are identical to the one described for the HMEP OA trial (see 5.3.1).

Trial Design

This was to have been a multicenter, randomized, double-blind, parallel group, placebo controlled trial with three study periods: Screening Phase (1 week), Double-blind Treatment Phase (13 weeks), and Taper Phase (2 weeks). The study would be conducted in approximately 29 centers in the United States, Canada, Greece, Russia, and Sweden

The maximum duration of trial medication administration was to have been 15 weeks.

Trial Population

The subject selection criteria for this trial are identical to the one described for the HMEP OA trial (see 5.3.1). Approximately 230 patients were to have been enrolled to the two treatment groups (115 patients per treatment group).

Trial Medications

Eligible subjects were to have been randomly assigned to duloxetine or placebo treatment at Visit 2 at 1:1 ratio stratified by NSAID use. At Visit 4, non-responders (that is, those who met the dose escalation criteria) were to have their dose escalated to 120 mg QD.

Treatment regimens for duloxetine during the Titration, Double-Blind, and Taper Phase are identical to the one described for HMEP OA trial (see 5.3.1).

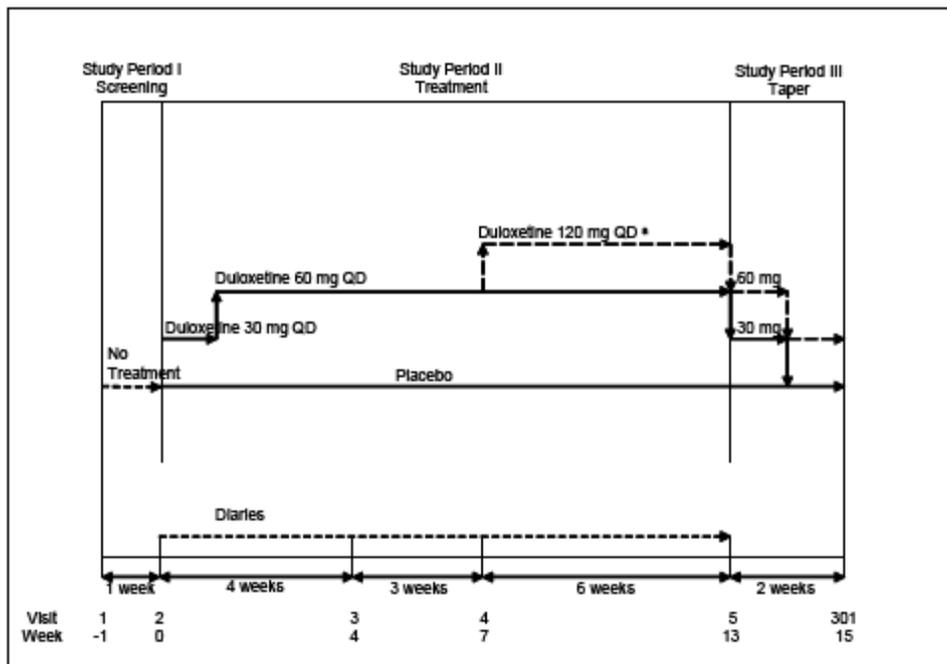
Similar to the other chronic pain trials, acetaminophen or NSAID use was to have been permitted at stable doses during the trial. Narcotic analgesics were not to be allowed for use during the trial.

Trial Conduct

The randomization, treatment administration, procedures, assessments, and discontinuation criteria for this trial are similar to those described for the HMEP OA trial. The main difference is that after seven weeks of treatment (Visit 4), subjects on duloxetine 60 mg were not to be forcedly re-randomized to 60 mg and 120 mg, but only the non-responders (responder defined as at least 30% reduction in weekly mean of the BPI average score compared to baseline) were to have their dose increased to 120 mg QD for the remaining six weeks of the double-blind treatment period (see figure below).

The dose escalation design for non-responders at Visit 4 was used by the applicant for HMEN chronic back pain trial.

Figure 8: Study design - HMFG



* Non-responders at Visit 4 will titrate up to 120 mg QD

(Source: Applicant's figure HMFG 1, Clinical study report, p.17)

Statistical Analysis

Primary efficacy variable

- The primary efficacy variable was to have been the change in 24 hour average pain score (expressed as weekly mean and computed from patients diaries) from Baseline to endpoint (last non-missing observation).

Pain scores were to have been recorded in a patient diary once a day as an average pain over 24 hours. The 11-point Likert scale was to have been used to rate the pain severity. The baseline pain score was to have been calculated as the average score from the week prior to randomization. The endpoint score was to have been calculated as the average weekly score from the last week of available observations.

Secondary efficacy variables

- Percentage of subjects with 30% and 50% reduction in the 24-hour average pain (11-point Likert)
- Patient's Global Impressions of improvement (PGI - Improvement) assessed at Visits 3, 4, 5, and end of treatment

- Clinical Global Impressions of disease severity (CGI – Severity) assessed at Visits 3, 4, 5, and end of treatment
- WOMAC pain, stiffness, physical function subscales assessed at Visits 3, 4, 5, and end of treatment
- Severity of pain and the interference of pain on function measured by the Brief Pain Inventory scale (BPI) at Visits 3, 4, 5, and end of treatment visit
- Suicidal risk using the Beck Depression Inventory-II (BDI-II) at each clinic visit
- Anxiety and depression using the Hospital Anxiety and Depression Scale (HADS) assessed at Visits 2, 5, and end of treatment
- Health outcome using Euro-QoL Questionnaire (EQ-5D) assessed at Visits 2, 5, and end of treatment
- Quality of life using Short-Form Health Survey (SF-36) assessed at Visits 2, 5, and end of treatment

Safety variables

- Adverse events
- Discontinuation due to adverse events
- Changes in vital signs measurements, laboratory evaluations, and physical examination findings

Safety analyses were to include all patients with baseline data.

Statistical analysis methods

All analyses were to have been conducted on an intent-to-treat basis with subjects with no post-baseline pain scores excluded. Statistical tests of efficacy variables were to have been presented as 2-sided p-values. Statistical comparisons were to have been performed at the 0.05 level of significance. No adjustments for multiple comparisons were to have been made.

Efficacy analyses were to have been performed for the treatment phase (Week 0 to Week 13) between duloxetine 60/120 mg QD and placebo. In addition, for duloxetine 60 mg QD non-responders who had their dose increased to 120 mg QD, analysis of the mean change from Visit 4 to Visit 5 in BPI average pain score was to have been performed.

A likelihood-based, mixed-effect repeated measures (MMRM) analysis was to have been used to analyze the primary efficacy variable. All patients with data from baseline and at least one post-baseline visit were to have been included in the analysis. The model was to include fixed categorical effects of treatment, NSAID use, investigator, week and treatment-by-week interactions, and continuous fixed covariates of baseline score and baseline by-week interaction. Mean change in the primary efficacy variable was to have been also analyzed using a last-observation carried-forward (LOCF) approach and baseline-observation-carried-forward (BOCF) approach. The analysis of

variance (ANOVA) model was to have been used to analyze continuous variables, with terms for treatment and investigator. The stratifying variable of NSAID use was to have been added to the analysis of covariance (ANCOVA) with baseline values added as a covariate.

A gatekeeper strategy was to have been used to sequentially test the secondary objectives to compare improvement between duloxetine- and placebo-treated patients on the PGI-I and the WOMAC physical function subscale, using the ANCOVA model and LOCF approach.

Sample size calculation

A sample size of 230 subjects was calculated assuming a study power of approximately 80% to detect a treatment difference of 1.0 point in the mean change of the primary variable and 85% to detect a treatment group difference of 25% in response rate based on data from duloxetine studies of diabetic peripheral neuropathic pain.

Protocol Amendments

The original protocol was approved in August 2006. Subsequently it was amended twice.

1. Amendment, dated February 5, 2007, included the following pertinent changes:

- Exclusion Criterion was changed from receipt of specific invasive therapies to the knee within the past 6 months to receipt of the specified therapies within the past 3 months.
- Changes to the language for use of NSAID as a concomitant therapy. Patients were allowed to decrease their dose or stop taking NSAIDs during the trial. If there was an increase in pain, the NSAID therapy could be restarted or the dose increased but not to exceed the baseline dose (Visit 1 dose).

2. Amendment, dated January 23, 2008, included the following important changes:

- The primary efficacy measure was changed from the 24-hour average pain score collected from patient diaries to the Brief Pain Inventory (BPI) 24-hour average pain score collected at study visits (similar to HMEN). The rationale for this change was the very low compliance with the electronic patient diary in the already completed pain trials (68% for HMEP and 49% for HMEO). Because of the greater than anticipated missing diary data, these trials no longer had adequate power for the pre-specified effect size.
- Secondary efficacy analysis, including response rate and subgroup analysis, and path analysis of direct analgesic effect were changed to be based on the BPI average pain score.
- A secondary analysis of the BPI average pain score, mBOCF analysis was added
- A secondary objective was revised (the comparison of duloxetine 60 mg QD for 12 weeks with duloxetine 60 mg QD for 6 weeks followed by duloxetine 120 mg QD for 6 weeks) to summarize only the duloxetine 60 mg QD non-responders.

Efficacy results

Protocol Violations

Trial visit interval exceeding planned visit interval was the most frequent protocol violation followed by noncompliance to diary regimen and noncompliance to study medication.

Because the frequency of these protocol violations was similar across treatment groups, it is unlikely that the violations greatly impacted the primary efficacy results.

The types and numbers of violations are shown on the table below. None of the violations was classified as major protocol violation.

Table 30: Protocol violations - HMFG

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**Table HMFG.10.3. Summary of Significant Protocol Violations
 All Randomized Patients
 Treatment Phase**

	Placebo N = 116 n (%)	DLX60/120QD N = 113 n (%)	Total N = 229 n (%)
Exclusionary Con. Med. Taken	12 (10.3)	10 (8.8)	22 (9.6)
Inclusion/Exclusion violation	3 (2.6)	1 (0.9)	4 (1.7)
Non compliance to diary regimen	48 (41.4)	50 (44.2)	98 (42.8)
Non compliance to study drug regimen	11 (9.5)	18 (15.9)	29 (12.7)
Actual visit interval exceeds planned interval	102 (87.9)	103 (91.2)	205 (89.5)

(Source: Applicant’s table HMFG 10.3 from Study Report, p. 61)

An error in patient dosing instructions was found during site compliance monitoring. A total of 26 duloxetine-treated patients who did not meet the criterion for dose escalation at Visit 4 proceeded to dose with 1 capsule from 1 of the 2 bottles dispensed versus 1 capsule from each of the 2 bottles dispensed for the remainder of the treatment period. This error led to an administration of either placebo only or duloxetine only versus administration of duloxetine 60 mg QD plus placebo from Visit 4 (Treatment Week 7) to Visit 5 (Treatment Week 13). All 26 patients were included in the analyses for this study as the error was related to site instructions versus patient compliance.

Enrollment/ Subject disposition

Of the 256 randomized patients, 128 were assigned to the placebo group, and 128 were assigned to the DLX group. At Visit 4 (Week 7), 102 (80%) out of the 128 DLX-treated patients continued on with the study; of these DLX-treated patients, 33 (32%) were considered non-responders and had their dose increased to 120 mg QD and 69

continued on 60 mg QD DLX dose for the remainder of the treatment phase. Of the 69 subjects who continued on 60 mg DLX, 3 (4.3%) discontinued treatment during the second six weeks of the trail and 6 (18.2%) of the 33 subjects who had their DLX dose increased to 120 mg QD discontinued treatment during the second six weeks of the trial.

A total of 204 (79.7%) patients completed the treatment phase: 111 (86.7%) in the placebo group and 93 (72.7%) in the duloxetine 60/120 QD group.

The disposition for the 256 randomized subjects is summarized on the table below. Across all groups, 22.9% of patients discontinued the trial. The most frequently reported reason was discontinuation due to adverse event, with a significantly higher rate for the duloxetine-treated patients, 18.8% versus 5.5% for the placebo-treated patients. The discontinuation rate due to lack of efficacy was slightly higher for the placebo compared to duloxetine-treated patients (3.9% versus 0.8%, respectively).

Table 31: Patient disposition - HMFG

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Table HMFG.10.1. Reasons for Discontinuation Comparison of Treatment Groups All Randomized Patients Treatment Phase

Primary Reason for Discontinuation	PLACEBO (N = 128) n (%)	DLX60/120QD (N = 128) n (%)	Total (N = 256) n (%)	p-Value*
Completed	111 (86.7)	93 (72.7)	204 (79.7)	.008
DC due to ANY reason	17 (13.3)	35 (27.3)	52 (20.3)	.008
Adverse Event	7 (5.5)	24 (18.8)	31 (12.1)	.002
Lack of Efficacy	5 (3.9)	1 (0.8)	6 (2.3)	.213
Subject Decision	2 (1.6)	4 (3.1)	6 (2.3)	.684
Protocol Violation	2 (1.6)	3 (2.3)	5 (2.0)	1.000
Physician Decision	0 (0.0)	2 (1.6)	2 (0.8)	.498
Entry Criteria Not Met	1 (0.8)	0 (0.0)	1 (0.4)	1.000
Lost to follow up	0 (0.0)	1 (0.8)	1 (0.4)	1.000

(Source: Applicant’s table HMFG 10.1 from study report page 56)

The disposition by treatment group and DLX dose for the first seven weeks and the last six weeks of the treatment period is presented on the table below.

Table 32: Reason for discontinuation by dose - HMFG

Table 2.7.4.21. Reason for Study Discontinuation by Dose Comparison of Data during the First 7 Weeks and the Second 6 Weeks of the Dose-Escalation Studies All Randomized Patients All Primary Chronic Pain Studies – HMEP, HMFG, HMEN, and HMEO

	First 7 weeks of Study		Second 6 weeks of Study		
	Placebo n (%)	DLX60 n (%)	Placebo n (%)	DLX60 n (%)	DLX120 ^b n (%)
Study HMFG ^a	N= 128	N= 128	N = 117	N= 69	N= 33
Any Reason	11 (8.6)	26 (20.3)	6 (5.1)	3 (4.3)	6 (18.2)
Adverse Event Subject/Physician Decision	3 (2.3)	19 (14.8)	4 (3.4)	2 (2.9)	3 (9.1)
Lack of Efficacy	0 (0)	4 (3.1)	1 (0.9)	0 (0)	2 (6.0)
	5 (3.9)	0 (0)	1 (0.9)	0 (0)	1 (3.0)

(Source: Applicant’s table from ISS, p.68)

Significantly more patients administered duloxetine 60 mg QD discontinued overall (20% vs. 9%) and due to an AE (15% vs. 2%) after the first seven weeks of treatment compared to patients administered placebo.

The discontinuation due to an AE was lower overall during the second six weeks of acute treatment compared with the first seven weeks of treatment. However, patients who had their DLX dose increased to 120 mg QD at Week 7, discontinued the trial due to an AE more frequently than patients who continued on duloxetine 60 mg QD (9% versus 3%, respectively).

The following table illustrates the drop-out rate by study week for the placebo and duloxetine treatment groups.

Table 33: Drop outs by treatment group and study week – HMFG

Drop out week	Placebo N=128	Duloxetine 60- 120 mg/d N=128	Total N=256
	n (%)		
Week 4	7 (5.5%)	21 (16.4%)	28 (11%)
Week 7	3 (2.3%)	5 (3.9%)	8 (3%)
Week 13	6 (4.7%)	9 (7.0%)	15(6%)

(Source: Adapted from Applicant’s table 10.2 form Study report for HMEP, pp. 68-69)

The duloxetine-treated patients tended to discontinue treatment relatively early during the double-blind treatment phase (16.4% at Week 4 compared to 3.9% at Week 7 and

7% at Week 13). The early discontinuations were mainly due to adverse events (13.3% at Week 4).

Extent of exposure

The mean study drug exposure was 81 days with 54.9% of patients receiving study drug for at least 13 weeks, 55.9% for the placebo and 53.9% for the duloxetine-treated patients.

Overall, no significant differences were observed between the duloxetine and the placebo treatment groups study drug exposure.

The table below shows the extent of exposure to study drug for all randomized patients.

Table 34: Study drug exposure - HMFG

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Table HMFG.12.1. Study Drug Exposure All Randomized Patients Treatment Phase			
Variable	PLACEBO (N = 128)	DLX60/120QD (N = 128)	Total (N = 256)
Duration of Exposure (Days)			
n	127	128	255
mean	85.32	76.65	80.97
std	17.70	28.30	23.97
max	113.00	105.00	113.00
median	91.00	91.00	91.00
min	8.00	0.00	0.00
sum	10836.00	9811.00	20647.00
Patient Years	29.67	26.86	56.53
Duration of Exposure -n(%)			
NO. SUBJECTS	127	128	255
=0	0 (0.0)	1 (0.8)	1 (0.4)
>0	127 (100.0)	127 (99.2)	254 (99.6)
>=28	123 (96.9)	114 (89.1)	237 (92.9)
>=49	119 (93.7)	105 (82.0)	224 (87.8)
>=91	71 (55.9)	69 (53.9)	140 (54.9)
>=105	1 (0.8)	1 (0.8)	2 (0.8)

(Source: Applicant's table from study report page 146)

Demographics

Overall, the average age of subjects was 62.5 years and similar between the placebo and duloxetine-treated patients. The placebo group had a significantly higher percentage of female patients (83.6%) compared with the duloxetine group (69.5%). There were no other significant treatment group differences.

Baseline medical characteristics and concomitant therapy

Medical history and concomitant diseases were similar between the placebo and DLX treatment groups. With regards to the concomitant medication use, there were no significant treatment differences between groups.

Applicant's efficacy analysis

Overview

On the primary MMRM analysis of the 24-hour average pain score as recorded on the BPI instrument at study visits, the applicant found that patients treated with duloxetine 60 mg to 120 mg for 13 weeks demonstrated significantly greater improvement than placebo-treated patients. The LSMean at Week 13 difference between the placebo and DLX 60-120 was -0.84 with $p < 0.001$.

The additional LOCF analysis of mean change from baseline to endpoint in the BPI average pain score was found by the applicant to demonstrate statistically significant pain reduction for duloxetine 60-120 mg compared to placebo (LSMean difference of -0.78, $p < 0.001$). Using the BOCF approach the difference was also found to be statistically significant (LSMean difference of -0.59, $p = 0.013$).

In the response rate analyses at endpoint using the LOCF and BOCF imputation strategies, statistically greater 30% response rate, but not 50% response rate, was demonstrated for the duloxetine group compared with the placebo group.

At Week 7, 33 (31.1%) of the 106 patients on DLX 60 mg QD required up titration to 120 mg QD because of insufficient response. Of this group, 27.3% met the 30% response criteria ($\geq 30\%$ reduction in BPI average pain rating from baseline to endpoint).

The secondary gatekeeper assessments for PGI-I and WOMAC physical function using BOCF did not demonstrate significantly greater improvement for the duloxetine compared to the placebo-treated patients. Only the LOCF analysis of the WOMAC physical functioning subscale showed a statistically significant improvement in the duloxetine-treated patients compared with the placebo-treated patients.

Primary efficacy endpoint

The applicant found that the results from Study HMEP and Study HMEO revealed lower-than-expected diary compliance, and amended the primary endpoint of Study HMFG to 24-hour average BPI pain item on the 11-point Likert scale collected as a single day report at study visits instead of the weekly average score collected from patient diary. Mixed-effects model repeated measures (MMRM) was the pre-specified primary analysis.

The applicant found that at Week 13 (Visit 5) there was a statistically significant greater decrease (improvement) in the average pain score in the duloxetine 60/120 mg QD group (2.72 points) compared to the placebo group (1.88 points). The LSMean

difference between the placebo and duloxetine 60/120 mg was -0.84 with a p-value of <0.001.

In addition to the primary MMRM analysis, the applicant performed sensitivity analyses on the primary efficacy measure, including ANCOVA model based on LOCF and BOCF. On all of the three additional analyses, the applicant found that patients treated with duloxetine 60 mg to 120 mg for 13 weeks demonstrated significantly greater pain reduction than placebo-treated patients. The difference in LSMean pain score between the duloxetine 60/120QD and placebo using LOCF was -0.78 with a p-value of < 0.001. LSMean pain score difference using BOCF was -0.59 with a p-value of 0.013 and using the mBOCF it was -0.68 with a p-value of 0.005.

The table below illustrates the difference in pain score reduction between duloxetine 60/120 QD and placebo for the different analysis. In addition the table compares the results between data collected from patient diaries, expressed as weekly mean score and data collected as single day BPI report collected at study visits.

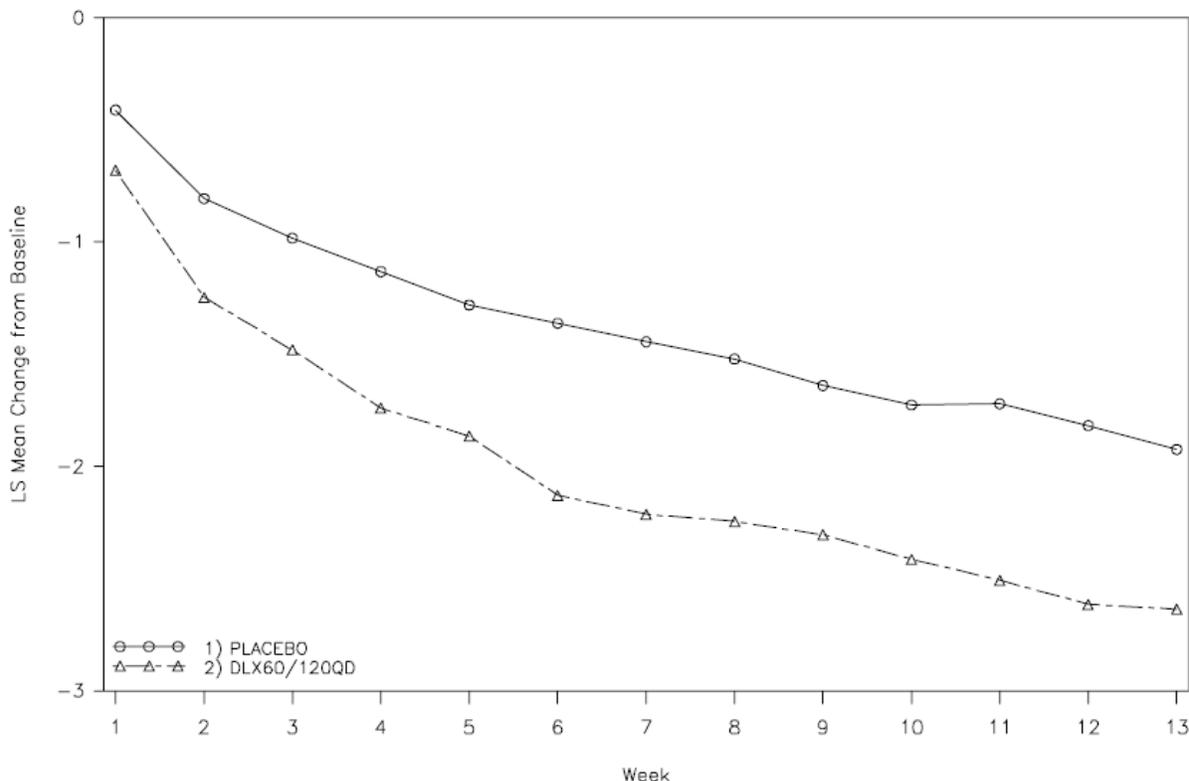
Table 35: Difference in LSMean 24-hour average pain score (from patient diaries and the BPI), DLX60/120 - Placebo, All Randomized Patients – HMFG

		HMEN		
		Endpoint LSMean	Treatment Difference	p-value
Weekly mean 24-hour average pain (Diary)				
MMRM: DLX 60/120		-2.64	-0.72	<.001
	Placebo	-1.92		
LOCF: DLX 60/120		-2.32	-0.59	0.008
	Placebo	-1.73		
BOCF: DLX 60/120		-2.02	-0.40	0.077
	Placebo	-1.62		
24-hour average pain (BPI collected at study visits)				
MMRM: DLX 60/120		-2.72	-0.84	<0.001
	Placebo	-1.88		
LOCF: DLX60/120		-2.51	-0.79	<0.001
	Placebo	-1.72		
BOCF: DLX 60/120		-2.23	-0.60	0.013
	Placebo	-1.63		

(Source: Adapted from applicant’s tables 2.7.3.10 and 2.7.3.11 from ISE, pp. 58-60)

Graphical representation of the data presented below by week and LSMean change from repeated measures analysis show separation between the duloxetine 60/120 QD and placebo group for the entire duration of the 13 week period.

Figure 9: Weekly LS Mean changes from repeated measures analysis - HMFG



(Source: Applicant's figure HMFG14.5 from study report for HMFG, p. 310)

Secondary efficacy endpoints

Because there were no adjustments for the multiple secondary analyses, any p-values associated with secondary efficacy variables should be interpreted as descriptive statistics only.

- Percentage of subjects with 30% and 50% reduction in the 24-hour average pain (11-point Likert)

The applicant's analysis of 30% and 50% response rate at endpoint failed to demonstrate statistically significant difference in response between the duloxetine 60/120 QD group and the placebo group for LOCF and BOCF 50% response rate. Significantly more patients in the duloxetine treatment group were found to have 30% response rate compared with patients in the placebo treatment group with both LOCF and BOCF imputation strategies.

Table 36: Proportion of treatment responders – 30% and 50% improvement from Baseline to Endpoint using LOCF - HMFG

Treatment	N	30%	p-value	50%	p-value
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		improvement n (%)		improvement n (%)	
Placebo	127	56 (44%)	<0.001	41 (32%)	0.68
DLX 60/120 QD	121	79 (65%)		53 (44%)	

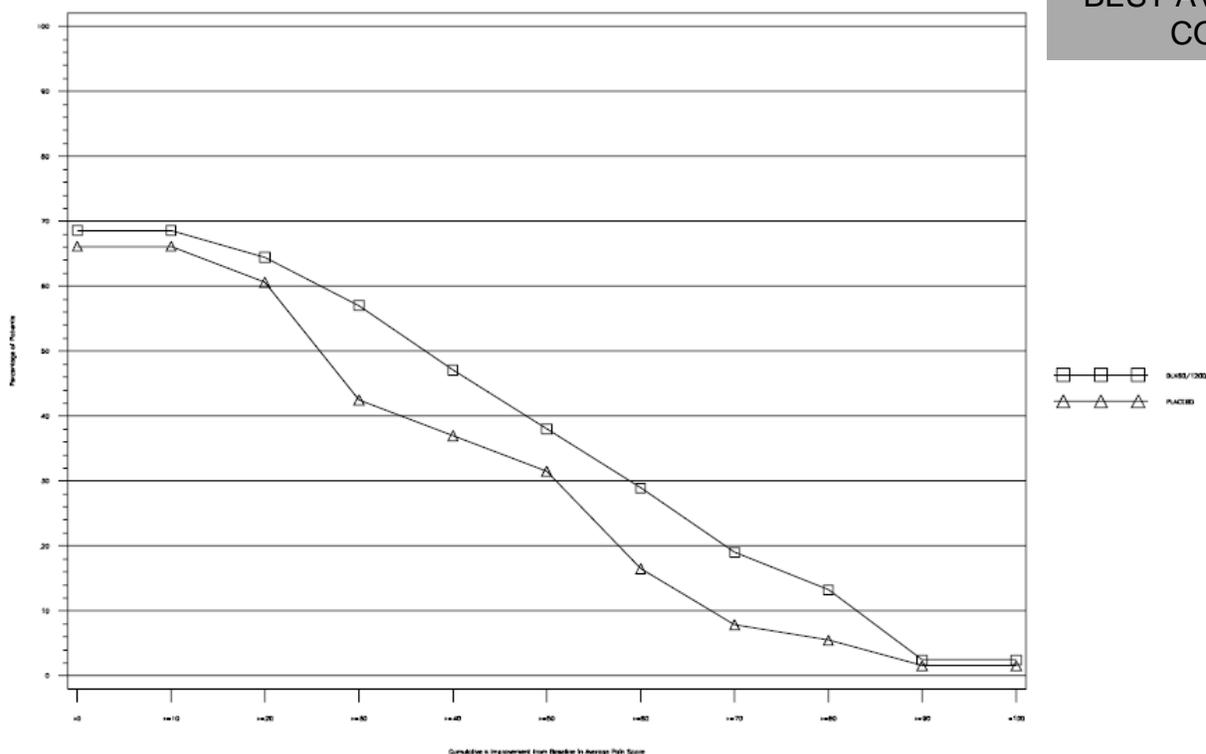
(Source: Adapted from Applicant's tables 14.10 and 14.12 from Study Report, pp. 284-286)

Table 37 : Proportion of treatment responders – 30% and 50% improvement from Baseline to Endpoint using BOCF - HMFG

Treatment	N	30% improvement n (%)	p-value	50% improvement n (%)	p-value
Placebo	127	54 (43%)	0.031	40 (32%)	0.289
DLX 60/120 QD	121	69 (57%)		46 (38%)	

(Source: Adapted from Applicant's tables 14.11 and 14.13 from Study Report, pp. 285-287)

Figure 10: Cumulative distribution of the percent change from Baseline (BOCF) – HMFG



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(Source: Applicant's figure HMFG 14.1 from study report page 281)

- Patient's Global Impressions of improvement (PGI - Improvement) and ?

The applicant employed a gatekeeper strategy, using LOCF imputation, for sequentially testing the following:

- The comparison of duloxetine 60/120 mg QD versus placebo on patients' perceived improvement as measured by PGI-Improvement.
- The comparison of duloxetine 60/120 mg QD versus placebo on the improvement of functioning as measured by the WOMAC physical function subscale

For PGI-I, the applicant did not find a statistically significant difference in improvement between the DLX 60/120 QD treated patients and the placebo-treated patients ($p=0.164$). A statistically significant greater decrease (improvement) in the mean change physical function subscale score was observed in the DLX-treated patients compared with the placebo-treated patients (LSMean difference of -3.27 , $p=0.016$).

- No statistically significant differences were observed between treatment groups in the pain and stiffness WOMAC subscale scores.
- The applicant found that duloxetine treatment resulted in significant reduction of the BPI worst pain score collected from patient diaries (LSMean difference -0.47 , $p=0.047$).
- The applicant found no significant difference between treatment groups for the patients' general well-being as measured by CGI-Severity (LSMean difference -0.30 , $p=0.009$).
- A statistically significantly greater change improvement was observed in the DLX-treated patients compared with the placebo-treated patients for the following items of the Short-Form Health Survey (SF-36): bodily pain, physical functioning, and physical role.
- Analysis of non-responders: As previously indicated, a total of 33 duloxetine-treated patients did not respond to duloxetine 60 mg QD at Visit 4 (non-responders), and had their DLX dose increased to 120 mg QD. The applicant found that for these patients, treatment with 120 mg QD resulted in a statistically significant decrease (improvement) in the BPI average pain score from Week 7 to Week 13 ($p=0.40$). No other significant changes were observed. The 30% response criteria ($\geq 30\%$ reduction in BPI average pain rating from baseline to endpoint) were met by 27.3% of the patients from this group.

5.3.4 Protocol HMGC

This fixed duloxetine 60 mg QD dose trial in CLBP was submitted with the 120-day safety update.

Title: “Effect of duloxetine 60 mg once daily versus placebo in patients with chronic low back pain.”

Objectives

Primary: To assess the efficacy of duloxetine 60 mg once daily compared with placebo on the reduction of pain severity as measured by the BPI 24-hour average pain score in patients with CLBP during a 12-week, double-blind treatment period.

Secondary Gatekeeper Objectives: A gatekeeper strategy was to have been employed to sequentially test and compare improvement between duloxetine 60 mg QD- and placebo-treated patients on:

- PGI-Improvement
- Improvement of functioning as measured by the Roland Morris Disability Questionnaire (RMDQ-24)

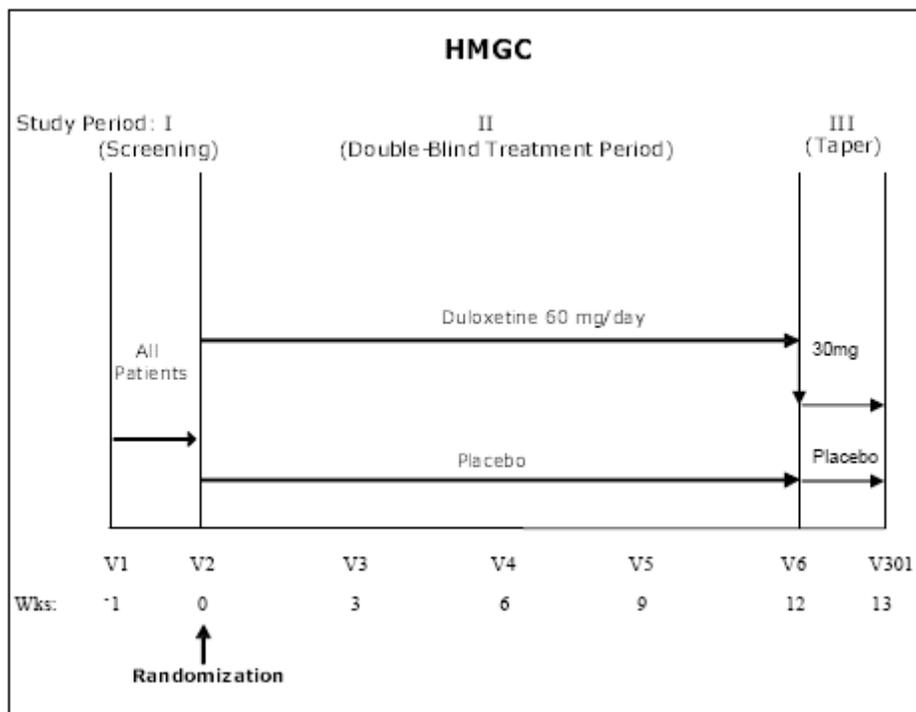
Additional Secondary Objectives:

- Efficacy of duloxetine 60 mg QD versus placebo as measured by:
 - Brief Pain Inventory (BPI) - Severity and Interference
 - Weekly mean of the 24-hour average pain, average pain at night, and worst daily pain score computed from electronic diary scores
 - Clinical Global Impression of Severity (CGI-S)
 - Sustained response to treatment
 - Cumulative distribution of BPI average pain score reduction
 - Response to treatment, as defined by a 30% and 50% reduction of BPI average pain scores
 - Profile of mood states (POMS – Brief Form)
 - Medical Outcomes Study Short Form-36 (SF-36)
 - EuroQoL Questionnaire-5 Dimension (EQ-5D) version of the EuroQoL instrument
 - Work Productivity and Activity Impairment Instrument (WPAI)
- Safety of duloxetine versus placebo.

Trial Design

This was to have been a multicenter, randomized, double-blind, parallel group, placebo controlled trial with 3 trial periods: Screening Period (1 week), Double-Blind Treatment Period (12 weeks), Taper Period (1 week).

Trial Schematic



Trial Population

The important eligibility criteria were to have been identical to HMEN trial.

Study medications

Duloxetine 60 mg QD and placebo were to have been the treatments administered to patients during this trial.

Prohibited Therapies

Opioids, antidepressants, anticonvulsant medications, NSAIDs, and acetaminophen were not to have been allowed during the trial. Patients who entered the trial receiving physical therapy were to have been allowed to continue those therapies as long as they did not change in frequency during the course of the trial.

Analgesics and therapies allowed for use during the trial

Patients who entered the trial receiving physical therapy were to have been allowed to continue this therapy as long as they did not change in frequency during the course of the trial.

Episodic use of short-acting analgesics was to have been allowed for management of breakthrough chronic low back pain (rescue therapy) or acute conditions unrelated to low back. "Episodic use" was to have been defined as no more than three consecutive days and not to exceed 20 total days during the trial.

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Trial Conduct

Eligible subjects were to have been randomly assigned in a 1:1 ratio to receive placebo or duloxetine 60 mg QD for 12 weeks. Patients who cannot tolerate duloxetine 60 mg QD, but have taken study drug for at least one week, were to have been discontinued from the study and enter Study Period III, Week 13 (taper phase, one week of DLX 30mg) to minimize discontinuation-emergent adverse events (DEAEs).

Trial Procedures

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The following table presents the time of events and assessments planned to be taken.

Study Schedule, Protocol F1J-MC-HMGC

Study Period	I			II			III	
Visit	1	2	3	4	5	6	301	ET
Days from Visit 2	-7 +/-2	0	21 +/- 2	42 +/- 2	63 +/- 2	84 +/- 2	91 +/- 2	
Study Procedure Description:								
Informed Consent	X							
Demographics	X							
Medical History	X							
Physical Exam	X							
Historical Illness	X							
Habits	X							
Height	X							
Weight/Vital signs (sitting BP and HR)	X	X	X	X	X	X	X	X
Supine/Standing BP and HR (orthostatic)		X				X		X
X-Ray ^a	X							
Adverse Events		X	X	X	X	X	X	X
Pre-existing Conditions	X							
Concomitant Medications	X	X	X	X	X	X	X	X
MINI	X							
ECG	X							
C-SSRS	X	X	X	X	X	X	X	X
Self-Harm Supplement Form	X	X	X	X	X	X	X	X
Self-Harm Follow-up Form ^b								
Study Drug:								
Interactive Voice Response System	X	X	X	X	X	X	X	X
Dispense Drug		X	X	X	X	X		
Return Drug/accountability			X	X	X	X	X	X
Compliance			X	X	X	X	X	X
Efficacy Measurements:								
11-point Likert Scale Patient Diary ^{c, d}	X	X	X	X	X	X		X
Patient Diary Compliance		X	X	X	X	X		
BPI	X	X	X	X	X	X		X
PGI-Improvement			X	X	X	X		X
PGI-Severity		X						
CGI-Severity	X	X	X	X	X	X		X
RMDQ-24		X				X		X
POMS – Brief Form		X				X		X
Health Outcomes:								
SF-36		X				X		X
EQ-5D		X	X			X		X
WPAI		X	X			X		X
Laboratory Assessments:								
Chemistry ^e	X		X	X		X		X
Hematology	X							
HgbA _{1c}	X					X		X
Urinary Drug Screen	X							
Serum Pregnancy Test ^f	X							
Serologies ^g	X							

(Source: Applicant's table from HMGC Protocol description, pp. 58-59)

Discontinuation criteria

The following discontinuation criteria were to have been applied for this protocol:

- Clinically significant adverse event or laboratory abnormalities
- Patient is judged to be at high suicidal risk
- Pregnancy
- Treatment with therapeutic agent indicated for CLBP

Statistical analysis

Primary efficacy variable

- The primary efficacy variable was to have been the change in BPI 24 hours average pain score from Baseline to endpoint (last non-missing observation), expressed as weekly mean.

Pain scores were to have been recorded in an electronic diary once a day as an average pain over 24 hours. Data were to have been collected at scheduled office visits. The 11-point Likert scale was to have been used to rate the pain severity. The baseline pain score was to have been calculated as the average score from the week prior to randomization. The endpoint score was to have been calculated as the average weekly score from the last week of available observations.

Secondary efficacy variables and additional analyses for the primary efficacy variable

Table 37: Secondary efficacy variable and additional analyses for the primary efficacy variable - HMGC

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Table HMGC.2. Additional Secondary Efficacy Analyses

Efficacy Variable	Derivation and Details	Analysis
1. Area Under the Curve of Change from Baseline in BPI Average Pain Score	The area under the curve (AUC) is the sum of each trapezoidal area between two consecutive visits.	The variable 1 will be analyzed by the ANCOVA models as described in Section 8.2.1 (using baseline BPI average pain score as covariate)
2. Change from baseline to BOCF endpoint: BPI average pain score	BPI severity for average pain	The variable 2 (includes both BOCF endpoint and modified BOCF endpoint) will be analyzed by the ANCOVA models as described in Section 8.2.1.
3. Change from baseline to LOCF endpoint: a. BPI: Severity and Interference b. Weekly mean of pain severity score on the 11-point Likert scale c. PGI-Improvement* d. CGI-Severity e. POMS-Brief Form	a. BPI severity for average pain, worst pain, least pain, and pain right now. BPI interference for general activity, mood, walking normally, normal work, relations with others, sleep, and enjoyment of life, and a mean interference score from the seven interference questions b. Weekly data will be computed from diaries according to the algorithm described below (Section 8.2.7.2) for 24-hour average pain, 24-hour worst pain, and night pain score c. CRF data. d. CRF data. e. POMS total score and subscale scores	The variables 3 a to 3.e will be analyzed by the ANCOVA models as described in Section 8.2.1.
4. All baseline and post-baseline data at the visits in the treatment phase for: a. BPI: Severity and Interference b. Weekly mean of pain severity score on the 11-point Likert scale c. PGI-Improvement* d. CGI-Severity e. POMS-Brief Form	Same as above.	Variable 4.b will be analyzed by a repeated measures analysis similar to the primary analysis of BPI average pain as described in Section 8.2.6, and visit variable will be replaced with week variable. Variables 4.a, and 4.c to 4.e will be analyzed by a repeated measures analysis similar to the primary analysis of BPI average pain as described in Section 8.2.6.
5. Categorical variable: a. 30% Response rate (LOCF) b. 30% Response rate (BOCF) c. 50% Response rate (LOCF) d. 50% Response rate (BOCF) e. Sustained response rate f. Cumulative distribution of BPI average pain score reduction	a-b. Response: at least 30% reduction from baseline to endpoint (LOCF or BOCF) for BPI average pain score. c-d. Response: at least 50% reduction from baseline to endpoint (LOCF or BOCF) for BPI average pain score. e. Sustained response: at least 30% reduction from baseline to endpoint; with a 30% reduction from baseline at an earlier visit than the last visit, and remains at least 20% reduction from baseline in every visit in between, if there are any intervening visits (based on BPI average pain score). f. The percentage of patients who have reached each threshold of BPI average pain reduction from baseline to BOCF endpoint (from > 0% to 100% with a 10% increase) will be calculated. Discontinued patients will be considered as "no change."	For variable 5b and 5d, endpoint includes both BOCF endpoint and modified BOCF endpoint as described in Section 8.2.1. For variables 5a to 5e, proportions will be summarized by treatment group and will be analyzed by a Fisher's exact test. For variable 5f, the treatment group difference in the empirical cumulated distribution of the percentage pain reduction will be evaluated using a Kolmogoro-Smirnov test.
6. Time to event variable: a. Time to first 30% reduction in BPI average pain score b. Time to first 50% reduction in BPI average pain score c. Time-to-sustained response	a. For the patients with a 30% reduction at a visit in the treatment phase, time = days from the date of the visit that the earliest 30% reduction is observed to the randomization date. b. For the patients with a 50% reduction at a visit in the treatment phase, time = days from the visit that the earliest 50% reduction is observed to the randomization date. c. For the sustained responders defined above, time = the days from the date of the visit which is the earlier visit from which the sustained response is observed to the randomization date.	For variables 6a to 6c, the Kaplan-Meier survival curves of time to event will be calculated by treatment group. In the calculation, patients who do not have the event will be considered as right-censored observation. The comparison of the survival curves between treatment groups will be conducted by a log-rank test.

(Source: Applicant's table form HMGC protocol description, pp. 45-47)

Safety variables

- Adverse events
- Discontinuation due to adverse events
- Changes in vital signs measurements, laboratory evaluations, and physical examination findings

Safety analyses were to include all patients with baseline data.

Statistical analysis methods

All analyses were to have been conducted on an intent-to-treat basis. Statistical tests of efficacy variables were to have been presented as 2-sided p-values. Statistical comparisons were to have been performed at the 0.05 level of significance. No adjustments for multiple comparisons were to have been made.

A likelihood-based, mixed-effect repeated measures (MMRM) analysis was to have been used to analyze the primary efficacy variable. All patients with data from baseline and at least one post-baseline visit were to have been included in the analysis. The model was to include fixed categorical effects of treatment, investigator, week and treatment-by-week interactions, and continuous fixed covariates of baseline score and baseline by-week interaction. Similar to HMEN, the mean change in the primary efficacy variable was to have been analyzed using a last-observation carried-forward (LOCF), baseline-observation-carried-forward (BOCF), and modified BOCF (mBOCF) approach.

A gatekeeper strategy was to have been used to sequentially test the secondary objectives to compare improvement between duloxetine- and placebo-treated patients on the PGI-I and the Roland Morris total score, using the ANCOVA model and LOCF approach.

Sample size calculation

A sample size of 400 subjects (200 patients per arm) was calculated for a power of approximately 90% to detect a treatment difference of 0.76 points in the mean change from baseline to endpoint in the BPI average pain score severity between duloxetine and placebo treatment groups.

Protocol Amendments

The protocol was approved by the applicant on August 3rd, 2006. The first subject was enrolled on January 24, 2007. The original protocol was amended twice.

1. Amendment 1 (April 14, 2008). The most pertinent changes included the following:
 - Collection of biological samples for banking

2. Amendment 2 (April 30, 2008), to implement changes to the exclusion criteria and discontinuation from the trial, applicable to patients participating in HMGC in Brazil. The most pertinent changes included the following:

- Patients participating in an interventional medical, surgical, or pharmaceutical trial within the *last year* were excluded
- Discontinuation of the trial or trial sites has to consider the rights, safety and well-being of the patient(s) in accordance with ICH/GCP Guidelines and local regulations

Trial Results

Protocol Violations

Intake of excluded medication was the most frequent protocol violation followed by exclusion criteria violation.

Because the frequency of these protocol violations was similar across treatment groups, it is unlikely that the violations greatly impacted the primary efficacy results.

The types and numbers of violations are shown on the table below.

Table 38: Protocol violations - HMGC

Table HMGC.10.3. Important Protocol Violations All Randomized Patients Double-Blind Treatment Period and Taper Phase		BEST AVAILABLE COPY		
Violation Type	Violation Details	Placebo (N=203) n (%)	DLX60QD (N=198) n (%)	Total (N=401) n (%)
Failure to perform safety procedures	Missing supine/standing vital sign	0 (0.0)	1 (0.5)	1 (0.2)
Inclusion/Exclusion	A positive urine drug screen(UDS) for any substances of abuse at Visit 1 (no retest or retest also positive).	4 (2.0)	1 (0.5)	5 (1.2)
	Excl Criteria violated: Pat BMI > 40	1 (0.5)	1 (0.5)	2 (0.5)
	Excl criteria violated: Compliance < 70% to e-Diary between Visit 1 and 2	22 (10.8)	37 (18.7)	59 (14.7)
	Excl criteria violated: Have a history of low back surgery within 12 months	1 (0.5)	0 (0.0)	1 (0.2)
	Incl criteria violated: Onset date is less than 6 months to randomization	1 (0.5)	0 (0.0)	1 (0.2)
	More than episodic use of analgesics	17 (8.4)	7 (3.5)	24 (6.0)
Non-compliance to study drug regimen	Patient has taken the excluded medications	48 (23.6)	34 (17.2)	82 (20.4)
	Significant non-compliance to study drug regimen -> <80% or >120% per visit interval	13 (6.4)	29 (14.6)	42 (10.5)

(Source: Applicant's table from HMGC report, p. 74)

Enrollment/ Subject disposition

Of the 401 randomized patients, four discontinued after randomization but before receiving trial medication, 200 were assigned to the placebo group, and 197 were

assigned to the duloxetine 60 mg group. A total of 146 (74.2%) duloxetine-treated and 156 (76.8%) placebo-treated patients completed the trial. In the double-blind treatment period, duloxetine-treated patients demonstrated a significantly higher rate of discontinuation due to an adverse event compared with placebo (15% vs. 5%) and more placebo-treated patients discontinued due to lack of efficacy compared with duloxetine-treated patients (4% vs. 0.5%).

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Table 39: Subject disposition – HMGC

**Table HMGC.10.1. Reasons for Discontinuation
All Randomized Patients
Double-Blind Treatment Period**

Patient Disposition	PLACEBO (N=203)		DLX60QD (N=198)		Total (N=401)	
	n	(%)	n	(%)	n	(%)
Completed	156	(76.8)	147	(74.2)	303	(75.6)
DC due to ANY reason	47	(23.2)	51	(25.8)	98	(24.4)
Adverse Event	11	(5.4)	30	(15.2)	41	(10.2)
Subject Decision	13	(6.4)	8	(4.0)	21	(5.2)
Protocol Violation	5	(2.5)	6	(3.0)	11	(2.7)
Lack of Efficacy	9	(4.4)	1	(0.5)	10	(2.5)
Physician Decision	3	(1.5)	4	(2.0)	7	(1.7)
Lost to follow up	4	(2.0)	1	(0.5)	5	(1.2)
Entry Criteria Not Met	1	(0.5)	1	(0.5)	2	(0.5)
Sponsor Decision	1	(0.5)	0	(0.0)	1	(0.2)

(Source: Applicant’s table from HMGC report, p. 70)

The duloxetine-treated patients tended to discontinue treatment relatively early, 15% at Week 3, compared to 6% at Week 6, 3% at Week 9, and 3% at Week 12. The early discontinuations were mainly due to adverse events (12% at Week 3).

Extent of exposure

The mean drug exposure was 74 days with 55.1% of patients receiving trial drug for at least 13 weeks, 54.7% for the placebo and 55.6% for the duloxetine-treated patients. Overall, no significant differences were observed between the duloxetine and the placebo treatment groups.

The table below shows the extent of exposure to trial drug for all randomized patients.

Table 40: Study drug exposure for all randomized patients – HMGC

**Table HMGC.12.1. Study Drug Exposure
 All Randomized Patients
 Double-Blind Treatment Period**

Variable Label	PLACEBO (N = 203)	DLX60QD (N = 198)	Total (N = 401)
Duration of Exposure (Days)			
No. of Patients	200	197	397
Mean	76.15	72.01	74.10
SD	20.11	24.69	22.57
Minimum	8.00	2.00	2.00
Median	84.00	84.00	84.00
Maximum	107.00	104.00	107.00
Patient Years	41.70	38.84	80.54
Duration of Exposure - n (%)			
No. of Patients	200	197	397
>0	200 (98.5)	197 (99.5)	397 (99.0)
>=21	194 (95.6)	181 (91.4)	375 (93.5)
>=42	180 (88.7)	165 (83.3)	345 (86.0)
>=63	169 (83.3)	157 (79.3)	326 (81.3)
>=84	111 (54.7)	110 (55.6)	221 (55.1)
>=105	1 (0.5)	0 (0.0)	1 (0.2)

(Source: Applicant’s table form HMGC trial report, p. 164)

Demographics

Overall, the average age of subjects was 54.1 years and was similar between the placebo and duloxetine-treated patients. The majority of patients were female and Caucasian.

There were no significant differences between the duloxetine and placebo groups for age, sex and baseline illness characteristics as illustrated on the following table:

Table 41: Patient Demographic Characteristics and Disease Severity at Baseline – HMGC

**Table HMGC.11.1. Patient Demographic Characteristics at Baseline
 All Randomized Patients
 Double-Blind Treatment Period**

Variable	PLACEBO (N=203)	DLX60QD (N=198)	Total (N=401)
Age (years)			
No. of Patients	203	198	401
Mean	53.43	54.87	54.14
Standard Deviation	14.17	13.27	13.73
Minimum	18.66	19.37	18.66
Median	54.56	56.59	55.54
Maximum	89.30	79.63	89.30
Height (cm)			
No. of Patients	203	198	401
Mean	167.91	168.24	168.07
Standard Deviation	8.82	9.64	9.22
Minimum	144.00	141.00	141.00
Median	168.00	168.00	168.00
Maximum	191.00	201.00	201.00
Weight (kg)			
No. of Patients	203	198	401
Mean	79.35	78.30	78.83
Standard Deviation	14.65	15.83	15.23
Minimum	47.00	43.70	43.70
Median	78.70	77.00	78.40
Maximum	114.40	127.70	127.70
BMI (kg/m²)			
No. of Patients	203	198	401
Mean	28.14	27.56	27.85
Standard Deviation	4.72	4.50	4.62
Minimum	17.26	16.73	16.73
Median	27.66	27.56	27.61
Maximum	41.75	40.20	41.75
Gender; n (%)			
No. of Patients	203	198	401
Female	128 (63.1)	118 (59.6)	246 (61.3)
Male	75 (36.9)	80 (40.4)	155 (38.7)
Race; n (%)			
No. of Patients	203	198	401
African	5 (2.5)	5 (2.5)	10 (2.5)
Caucasian	193 (95.1)	189 (95.5)	382 (95.3)
Hispanic	4 (2.0)	4 (2.0)	8 (2.0)
Native American	1 (0.5)	0 (0.0)	1 (0.2)

(Source: Applicant's table from HMGC trial report, pp. 77-78)

Baseline medical characteristics and concomitant therapy

Medical history and concomitant diseases were similar between the placebo and duloxetine treatment groups. Relative to placebo, the group mean value of baseline Clinical Global Impressions of Severity (CGI-S) was significantly higher in the duloxetine treatment group.

Applicant's efficacy analysis

Overview

On the primary MMRM analysis of the 24-hour BPI average pain score, the applicant found that patients treated with duloxetine 60 mg demonstrated significantly greater pain reduction than placebo-treated patients at Week 12. The LSMean difference at Week 12 between the placebo and DLX 60 mg was -0.68 with $p < 0.001$.

Additional analysis of the primary efficacy variable using BOCF approach where only patients who completed Visit 6 (Week 12) were considered completers, demonstrated statistically significant pain reduction for duloxetine 60 mg compared to placebo (LSMean difference of -0.55, $p=0.004$). When mBOCF approach (baseline value for patients who discontinued early due to adverse events or loss of efficacy) was used, the difference was again statistically significant (LSMean difference of -0.56, $p=0.004$). Similar results were obtained when further mBOCF (baseline value for patients who discontinued early due to adverse events) was used, LSMean difference of -0.55, $p=0.005$.

Analysis of the cumulative distribution of the percent change (100% to 0%, in increments of 10%) of the BPI average pain, using the BOCF approach and the Kolmogorov-Smirnov test showed that there was a significant difference between treatment groups ($p=0.013$) with a higher percentage of duloxetine patients experiencing average pain reduction at each threshold point than placebo patients. It was statistically significant for a 50% response rate and numerically higher for 30% response rate.

The secondary gatekeeper assessments demonstrate significantly greater improvement for PGI-I and numerically higher for physical function (RMDQ-24).

Primary efficacy endpoint and analyses

The primary objective of this study was to assess the efficacy of duloxetine 60 mg QD compared with placebo on the reduction of pain severity as measured by the BPI average pain. The primary efficacy analysis was the MMRM analysis on the BPI average pain.

The applicant found that at each visit (weeks 3, 6, 9, and 12), patients treated with duloxetine 60 mg, reported a significantly greater pain reduction compared to patients treated with placebo. At Week 12 (Visit 6) the LSMean difference between the placebo and duloxetine 60 mg was 0.68 with a $p < 0.001$.

Table 42: BPI average pain score – MMRM analysis (HMGC)

Table HMGC.11.7. Brief Pain Inventory Average Pain Score
 Repeated Measures Analysis
 All Randomized Patients
 Double-Blind Treatment Period

 Variable Analyzed: BPI Average Pain Rating

Visit (Week)	Treatment	N	LS Mean	LS Mean Change	SE	T	DDF	Within Group p-value *a	p-value *b
3 (3)	1) PLACEBO	199	4.81	-0.95	0.12	-7.66	376	<.001	<.001
	2) DLX60QD	195	4.23	-1.53	0.12	-12.30	376	<.001	
4 (6)	1) PLACEBO	180	4.48	-1.28	0.14	-9.31	392	<.001	<.001
	2) DLX60QD	167	3.78	-1.99	0.14	-14.21	389	<.001	
5 (9)	1) PLACEBO	169	4.19	-1.58	0.14	-11.21	372	<.001	.001
	2) DLX60QD	158	3.57	-2.19	0.14	-15.30	367	<.001	
6 (12)	1) PLACEBO	162	3.96	-1.80	0.15	-11.74	367	<.001	.001
	2) DLX60QD	152	3.29	-2.48	0.16	-15.83	363	<.001	

(Source: Applicant's table 11.7 from HMGC trial report, p.97)

In addition to the primary MMRM analysis, the applicant performed additional sensitivity analysis on the primary efficacy variable, including ANCOVA model based on BOCF, mBOCF (baseline value carried forward for patients who discontinued early due to adverse events or loss of efficacy), and further mBOCF (baseline value carried forward only for patients who discontinued early due to adverse events) approach. These sensitivity analyses confirmed the finding from primary analysis. On all the three additional analyses, patients treated with duloxetine 60 mg demonstrated significantly greater pain reduction than placebo-treated patients at Week 12, BOCF ((LSMean difference of -0.55, p=0.004), mBOCF (LSMean difference of -0.56, p=0.004), and m further mBOCF (LSMean difference of -0.55, p=0.005).

The tables below illustrate the difference in pain score reduction between duloxetine 60 mg and placebo for the different analysis.

Table 43: BPI average pain score, mean change from baseline to endpoint, BOCF - HMGC

Table HMGC.11.8. Brief Pain Inventory Average Pain Score
 Mean Change from Baseline to Endpoint
 Baseline Observation Carried Forward Approach
 All Randomized Patients
 Double-Blind Treatment Period

 Variable Analyzed: BPI Average Pain Rating

Treatment	n	Baseline					Change					Endpoint				
		Mean	SD	Min	Median	Max	Mean	SD	Min	Median	Max	Mean	SD	Min	Median	Max
PLACEBO	203	5.75	1.37	4.00	6.00	10.00	-1.46	1.86	-8.00	-1.00	3.00	4.29	2.28	0.00	4.00	10.00
DLX60QD	198	5.84	1.43	4.00	6.00	10.00	-2.03	2.15	-8.00	-2.00	2.00	3.81	2.28	0.00	4.00	9.00

Interaction (Type II SS)*b
 Treatment-by-Investigator F = 1.04 Raw Data df = 26,346 p = .416

Main Effects (Type III SS)*a
 Treatment F = 8.45 Raw Data df = 1,372 p = .004
 Investigator F = 2.54 df = 26,372 p = <.001

Least Squares Means for Change from Baseline*a
 1) PLACEBO -1.37 (SE=0.15)
 2) DLX60QD -1.92 (SE=0.15)

Pairwise Comparison of LS Means*a
 DLX60QD-PLACEBO diff = -0.55 Two-sided 95% CI: (-0.93,-0.18) t = -2.91 p = .004

(Source: Applicant's table 11.8 from HMGC trial report, p.99)

Table 44: BPI average pain score, mean change from baseline to endpoint, mBOCF - HMGC

Table HMGC.14.9. Brief Pain Inventory Average Pain Score
 Mean Change from Baseline to Endpoint
 Modified Baseline Observation Carried Forward Approach
 All Randomized Patients
 Double-Blind Treatment Period

 Variable Analyzed: BPI Average Pain Rating

Treatment	n	Baseline					Change					Endpoint				
		Mean	SD	Min	Median	Max	Mean	SD	Min	Median	Max	Mean	SD	Min	Median	Max
PLACEBO	200	5.73	1.35	4.00	6.00	10.00	-1.66	1.94	-8.00	-1.50	3.00	4.07	2.18	0.00	4.00	10.00
DLX60QD	196	5.84	1.43	4.00	6.00	10.00	-2.24	2.11	-8.00	-2.00	2.00	3.60	2.25	0.00	4.00	9.00

Interaction (Type II SS)*b
 Treatment-by-Investigator F = 0.74 Raw Data df = 26,341 p = .819

Main Effects (Type III SS)*a
 Treatment F = 8.44 Raw Data df = 1,367 p = .004
 Investigator F = 2.27 df = 26,367 p = <.001

Least Squares Means for Change from Baseline*a
 1) PLACEBO -1.58 (SE=0.15)
 2) DLX60QD -2.14 (SE=0.15)

Pairwise Comparison of LS Means*a
 DLX60QD-PLACEBO diff = -0.56 Two-sided 95% CI: (-0.94,-0.18) t = -2.91 p = .004

(Source: Applicant's table 11.8 from HMGC trial report, p.429)

Table 45: BPI average pain score, mean change from baseline to endpoint, further mBOCF - HMGC

Table HMGC.14.10. Brief Pain Inventory Average Pain Score
 Mean Change from Baseline to Endpoint
 Further Modified Baseline Observation Carried Forward Approach
 All Randomized Patients
 Double-Blind Treatment Period

Variable Analyzed: BPI Average Pain Rating																	
Treatment	Baseline						Change					Endpoint					
	n	Mean	SD	Min	Median	Max	Mean	SD	Min	Median	Max	Mean	SD	Min	Median	Max	
PLACEBO	199	5.73	1.35	4.00	6.00	10.00	-1.69	1.94	-8.00	-2.00	3.00	4.04	2.18	0.00	4.00	10.00	
DLX60QD	195	5.85	1.43	4.00	6.00	10.00	-2.26	2.11	-8.00	-2.00	2.00	3.58	2.26	0.00	4.00	9.00	
Interaction (Type II SS)*b			P = 0.78			Raw Data			df = 26,339			p = .771					
Main Effects (Type III SS)*a			P = 7.99			Raw Data			df = 1,365			p = .005					
Treatment			P = 2.31			df = 26,365			p = <.001								
Investigator																	
Least Squares Means for Change from Baseline*a																	
1) PLACEBO -1.60 (SE=0.15)																	
2) DLX60QD -2.15 (SE=0.15)																	
Pairwise Comparison of LS Means*a																	
DLX60QD-PLACEBO diff = -0.55 Two-sided 95% CI: (-0.93,-0.17) t = -2.83 p = .005																	

(Source: Applicant's table 11.8 from HMGC trial report, p.430)

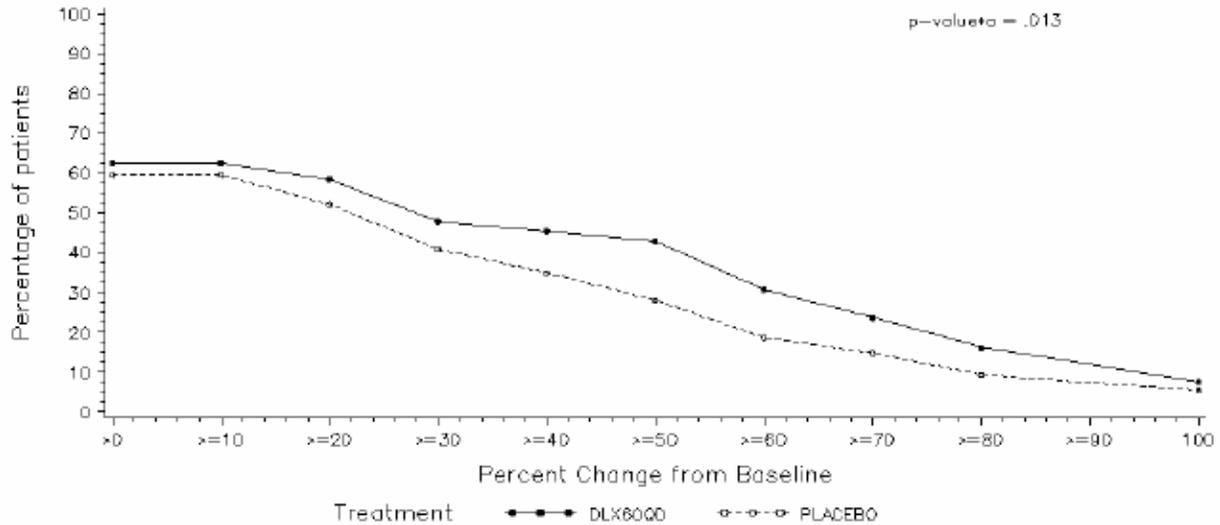
Analysis of the cumulative distribution of the percent change of the BPI average pain, depicting the number of patients whose percentage change from baseline to BOCF endpoint was less than or equal to a given threshold, using the Kolmogorov-Smirnov test showed that there was a significant difference between treatment groups (p=0.013) with a higher percentage of duloxetine patients experiencing average pain reduction at each threshold point than placebo patients.

Figure 11: Cumulative distribution of the percent change from Baseline (BOCF) – HMGC

Clinical Review
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 {Insert Application Type and Number}
 {Insert Product Trade and Generic Name}

PRODUCTION DATA – PRODUCTION MODE
 BPI Average Pain Rating
 Cumulative distribution of the percent change from baseline to endpoint (BOCF)
 All Randomized Patients
 F1J–MC–HMGC: Acute Therapy Phase

14:09 Aug 7, 2009



Abbreviations: BOCF = baseline observation carried forward; BPI = brief pain inventory; DLX = duloxetine; N = number of randomized patients with non-missing baseline; n = number of patients in the specified category; QD = once daily.

(Source: Applicant’s figure 14.1 from HMGC trial report, p.431)

Table 46: BPI average pain score, Cumulative distribution of the percent change from Baseline (BOCF) – HMGC

**Table HMGC.14.11. Brief Pain Inventory Average Pain Score
 Cumulative Distribution of the Percent Change from Baseline
 Baseline Observation Carried Forward Approach
 All Randomized Patients
 Double-Blind Treatment Period**

Pain Score	PLACEBO (N=203)	DLX600D (N=198)
Any Increase	15 (7.4)	12 (6.1)
No Change	67 (33.0)	62 (31.3)
>0% decrease	121 (59.6)	124 (62.6)
>=10% decrease	121 (59.6)	124 (62.6)
>=20% decrease	106 (52.2)	116 (58.6)
>=30% decrease	83 (40.9)	95 (48.0)
>=40% decrease	71 (35.0)	90 (45.5)
>=50% decrease	57 (28.1)	85 (42.9)
>=60% decrease	38 (18.7)	61 (30.8)
>=70% decrease	30 (14.8)	47 (23.7)
>=80% decrease	19 (9.4)	32 (16.2)
100% decrease	11 (5.4)	15 (7.6)

The p-value* α = .013

(Source: Applicant’s table 14.11 from HMGC trial report, p.432)

The 50% response rate at endpoint in BPI average pain using BOCF approach was statistically significant, 28.1% for placebo and 42.9% for DLX 60 mg, $p=0.002$. The 30%

response rate was numerically higher, 40.9% for placebo and 48% for DLX 60 mg, however not statistically significant (p=0.161).

Table 47: BPI average pain score, 30% response rate at endpoint - HMGC

Table HMGC.14.18. Brief Pain Inventory Average Pain Score
 30 Percent Response Rate at Endpoint
 Baseline Observation Carried Forward Approach
 All Randomized Patients
 Double-Blind Treatment Period

 Variable Analyzed : BPI Average Pain Rating: 30% Response at BOCF Endpoint

Treatment	N	Responders n (%)	p-value*a
PLACEBO	203	83 (40.9)	.161
DLX60QD	198	95 (48.0)	

(Source: Applicant’s table 14.18 from HMGC trial report, p.442)

Table 48: BPI average pain score, 50% response rate at endpoint - HMGC

Table HMGC.14.19. Brief Pain Inventory Average Pain Score
 50 Percent Response Rate at Endpoint
 Baseline Observation Carried Forward Approach
 All Randomized Patients
 Double-Blind Treatment Period

 Variable Analyzed : BPI Average Pain Rating: 50% Response at BOCF Endpoint

Treatment	N	Responders n (%)	p-value*a
PLACEBO	203	57 (28.1)	.002
DLX60QD	198	85 (42.9)	

(Source: Applicant’s table 14.19 from HMGC trial report, p.443)

Secondary efficacy endpoints

Because there were no adjustments for the multiple secondary analyses, any p-values associated with secondary efficacy variables should be interpreted as descriptive statistics only.

- Patient’s Global Impressions of improvement (PGI - Improvement) and CLBP and its interference with activities of daily living (RMDQ-24)

The applicant employed a gatekeeper strategy, using LOCF imputation, for sequentially testing the following:

- The comparison of duloxetine 60 mg QD versus placebo on patients’ perceived improvement as measured by PGI-Improvement

- The comparison of duloxetine 60 mg QD versus placebo on the improvement of functioning as measured by the RMDQ-24, a questionnaire addressing CLBP and its interference with activities of daily living

When comparing patient ratings at endpoint on the PGI-I using the LOCF approach, the duloxetine treatment group had a significantly greater improvement compared with the placebo treatment group, LSMean difference of -0.31, $p=0.011$. This result was confirmed by additional sensitivity analyses, BOCF ($p=0.003$), mBOCF ($p<0.001$), and further mBOCF ($p<0.001$).

For the mean change from baseline to endpoint of the RMDQ-24 total score, there was no significant treatment group difference, LSMean difference of -0.47, $p=0.255$ (LOCF).

- The applicant found that duloxetine 60 mg treatment resulted in significant reduction of the BPI worst pain score with LOCF (LSMean difference -0.68, $p=0.002$).
- For SF-36 (LOCF), there was a significantly greater increase (improvement) in the duloxetine 60 mg treatment group compared with the placebo treatment group for the Mental Component Summary score (MCS) and the following domain scores: Bodily Pain, Mental Health, Social Functioning, and Vitality. There was no significant difference between treatment groups in Physical Component Summary (PCS) and the other five MCS domains.

5.3.5 Protocol HMEO

HMEO was a Phase 3, parallel-group, double-blind, fixed-dose, placebo-controlled trial in patients with CLBP. Three dose levels of duloxetine were studied: 20mg/day, 60 mg/day and 120 mg/day. The trial included 287 duloxetine-treated and 117 placebo-treated patients.

The primary objective was to assess the efficacy of duloxetine 60 mg QD compared with placebo on the reduction of pain severity as measured by the weekly mean of the 24-hour average pain scores in patients with CLBP during the 13-week, double-blind treatment period using an 11-point Likert scale patient diary.

This trial failed to show evidence of efficacy of duloxetine in CLBP at any dose on all of the efficacy analyses including MMRM, LOCF, BOCF, and mBOCF.

The safety profile of the drug in this trial was similar to what was seen in the other chronic pain trials.

6 Review of Efficacy

Efficacy Summary

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

All five trials can be considered adequate and well-controlled based on the trial design. All were multicenter, randomized, double-blind, placebo-controlled with duration of the double-blind treatment of at least 12 weeks. Two of the trials, HMEO and HMGC, were of fixed-dose design. In HMEO, duloxetine doses of 20 mg, 60 mg, and 120 mg QD were evaluated, and in HMGC, duloxetine 60 mg QD dose only was evaluated. Three trials, HMEN, HMEP, and HMFG, were of flexible-dose design. In these three trials, patients were originally assigned to 60 mg duloxetine dose or placebo. For HMEP trial, at Week 7, the duloxetine 60 mg QD patient group was forcedly re-randomized to either 60 mg QD duloxetine or 120 mg QD duloxetine for the remaining six weeks of the treatment period. For HMEN and HMFG, at Week 7, only non-responders to duloxetine 60 mg QD were up-titrated to 120 mg QD dose for the remaining six weeks of the treatment period. The blind was preserved both at randomization and re-randomization.

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

The primary efficacy endpoint chosen by the applicant for all OA and CLBP trials was the change from baseline to Week 13 (Week 12 for HMGC) in pain severity. Pain severity was measured by the BPI 24-hour average pain item on an 11-point Likert scale and was expressed as either a weekly mean from patient diaries (HMEP and HMEO) or as a single day report (HMEN, HMFG, and HMGC). The primary analysis for the flexible-dose trials (HMFG, HMEP, and HMEN) was based on the combined 60/120 mg QD duloxetine arm versus placebo. In all five trials, MMRM was the pre-specified analysis for the primary efficacy measure. ANCOVA with LOCF and BOCF imputation

strategies were used as sensitivity analyses. All three statistical methods (MMRM, ANCOVA/LOCF and ANCOVA/BOCF) were also applied to the pre-specified gatekeeper secondary measures. Secondary outcome measures included Patient's Global Impressions of Improvement (PGI-Improvement) and disease-specific physical function scales (WOMAC physical function subscale for OA pain and RMDQ-24 for CLBP).

Based on the pre-specified MMRM analysis the applicant found that the combined 60 mg to 120 mg duloxetine dose demonstrated a greater reduction in 24-hour average pain compared with placebo in three flexible-dose trials (HMEN, HMEP, and HMFG). The MMRM analysis of the fixed-dose trials demonstrated superiority of the duloxetine 60 mg QD dose in one of the trials (HMGC). Results from the applicant's ANCOVA/BOCF sensitivity analysis of the primary outcome measure confirmed significantly greater reduction in 24-hour average pain compared with placebo in three trials, HMEN, HMFG, and HMCG. It is of note that for the ANCOVA/BOCF analysis the applicant used the ITT population but did not include subjects who had no post-baseline pain score recorded. Also for the flexible-dose trials, the ANCOVA/BOCF analysis was based on the combined 60/120 mg QD duloxetine dose versus placebo. Upon further request, the applicant performed an additional ANCOVA/BOCF analysis for the flexible-dose trials, focusing on the 60 mg duloxetine dose only. In this analysis, the applicant treated non-responders (less than 30% improvement) at Week 7 from both the placebo and duloxetine treatment groups as loss of efficacy dropouts. The results from this analysis showed that duloxetine 60 mg QD had statistically significantly greater pain reduction over the 13-week period compared to placebo in two trials, HMEN and HMFG.

When the Division evaluated the applicant's efficacy analyses and findings, several key points were identified as problematic. The MMRM strategy was found unacceptable for the primary analysis because it assumes that data are missing at random and gives a partial credit to data before early discontinuation from the trial due to an adverse event or lack of efficacy. In analgesic trials, early discontinuations must be treated as failures and therefore the pain reduction before a dropout must not be credited in the analysis. In addition, discontinuations are generally not random and are related to treatment assignment. There are proportionately more early discontinuations due to lack of efficacy in the placebo arm and more discontinuations due to adverse events in the active treatment arm. Therefore, non-random dropouts that are treatment related are considered informative when assessing efficacy of the drug.

The Division's approach when evaluating effect in pain trials is to use an imputation method that does not impute a favorable score for patients who have adverse outcomes. One of these methods is baseline-observation-carried-forward (BOCF). BOCF imputes the baseline pain score for missing data due to discontinuation for any reason. Using this approach, assignment of a good pain score to subjects who discontinue early due to adverse event would be avoided. On the other hand assigning baseline pain scores to patients who discontinued due to reasons unrelated to treatment

(for example, inconvenience, schedule conflicts), and who may have benefited if they had stayed in the trial, is punitive. Therefore, combined LOCF/BOCF analysis where BOCF is imputed for early discontinuations due to adverse events and lack of efficacy and LOCF is imputed for all other reasons, is an acceptable alternative. In terms of the population used for the analysis of the 60 mg duloxetine dose only in the flexible-dose trials, the applicant treated non-responders from any treatment group at Week 7 as lack of efficacy dropouts (LOE). However, because placebo patients are expected to have disproportionately more non-responders, treating them as LOE dropouts is unduly penalizing the placebo group. A continuous responder analysis was also performed by the applicant. This analysis generates cumulative distribution function curves using multiple definition of response. Statistical inference comparing those curves typically use Kolmogorov-Smirnov test or van der Waerden test. This analysis provides useful information for comparison of the treatment effect between treatment groups.

The statistical reviewer for this application, Dr. Yongman Kim, reanalyzed the efficacy data for the pivotal trials using the Division's preferred analysis methods. Based on these methods, the combined 60 mg to 120 mg duloxetine dose was found superior to placebo for reducing pain intensity at Week 13 using ANCOVA/BOCF analysis in two trials, HMEN (CLBP population) and HMFG (OA population). When the 60 mg duloxetine dose only was compared to placebo using ANCOVA/BOCF analysis and treating only non-responders to duloxetine 60 mg at Week 7 as loss of efficacy dropouts, no superiority to placebo was demonstrated in either trial (HMEN $p=0.178$, HMFG $p=0.475$). Continuous responder curves for HMEN and HMFG, generated using van der Waerden test, showed statistically significant separation from placebo for the duloxetine 60 to 120 mg dose group (HMEN $p=0.018$, HMFG $p=0.016$), but no sizable separation from placebo for the duloxetine 60 mg only dose group (HMEN $p=0.196$, HMFG $p=0.443$).

Analyses focused on the duloxetine 60 mg dose only, demonstrated superiority to placebo for reducing pain intensity at Week 12 in one fixed-dose trial (HMGC, $p=0.004$) and at Week 7 in two flexible-dose trials (HMEN $p=0.003$ and HMFG $p<0.001$). For HMGC, a continuous responder analysis showed a statistically significant separation between the placebo and duloxetine 60 mg curves ($p=0.024$).

In two trials HMEN and HMFG, a mean plot analyses (BOCF) of the BPI score comparing the three treatments, placebo, duloxetine 60 mg and duloxetine 120 mg (60 mg for seven weeks followed by 120 mg for six weeks), showed that the duloxetine 120 mg dose group presented similar to the placebo group. Those subjects who showed no response to duloxetine 60 mg dose during the first seven weeks of treatment (no separation from placebo) continued not to respond to duloxetine despite dose increase to 120 mg at Week 7.

In summary, based on the Division's preferred analysis methods, the following trials provided evidence for efficacy of duloxetine as a treatment of inflammatory, joint-related

chronic pain presented in the OA population and non-inflammatory, non-neuropathic chronic pain presented in the CLBP population:

- Two positive trials according to the primary endpoint analysis, one in OA and one in CLBP, for the combined 60 to 120 mg duloxetine dose at Week 13
 - Continuous responder analysis with statistically significant separation between the placebo and the combined 60 to 120 mg duloxetine dose curves at Week 13
- One positive trial in CLBP for the 60 mg duloxetine dose at Week 12
 - Continuous responder analysis with statistically significant separation between the placebo and duloxetine 60 mg curves
- Two positive trials, one in OA and one in CLBP, for the 60 mg duloxetine dose at Week 7
- No evidence that duloxetine 120 mg QD dose confers benefit over duloxetine 60 mg QD dose for patients who do not respond to duloxetine 60 mg QD

6.1 Indication

For this application, the applicant seeks approval of duloxetine for the treatment of chronic pain.

6.1.1 Methods

New efficacy data contained in this submission were generated from the following placebo-controlled OA and CLBP trials: HMEN, HMEP, HMFG and HMEO (n=641 DLX, n=486 PBO). With the 120-day safety update, the applicant submitted an additional fixed-dose trial, HMGC (n= 198 DLX 60 mg, n=203 placebo), designed to evaluate the efficacy of DLX 60 mg versus placebo. All trials followed the guidelines for Good Clinical Practice. Analysis of the primary and secondary efficacy endpoints were conducted for all the placebo-controlled trials. Trials HMEN, HMFG and HMGC were presented as having positive results and therefore intended to provide the primary basis of efficacy.

To support the chronic pain indication, the applicant also submitted a summary of efficacy findings for the already approved DPNP and fibromyalgia indication.

The following table provides brief description of all five primary chronic pain trials. For detailed description of trial designs, see Section 5.3.

Table 49: Primary chronic pain trials

Trial ID	Design	Number of Subjects by Arm Entered/ Completed	Duration	Primary Endpoint(s)

Clinical Review
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 {Insert Application Type and Number}
 {Insert Product Trade and Generic Name}

HMFG (OA)	Parallel, double-blind, placebo-controlled	Randomized/Completed: 128/93 DLX 60/120 mg 128/111 placebo	13 weeks	Reduction in 24h average pain item of the BPI
HMEP (OA)	Parallel, double-blind, placebo-controlled	Randomized/Completed: 111/77 - DLX 60/120 mg 120/96 - placebo	13 weeks	Reduction in weekly mean of 24h average pain ratings from patient diaries
HMEN (CLBP)	Parallel, double-blind, placebo-controlled	Randomized/Completed: 115/84 - DLX 60 to 120 mg 121/98 - placebo	13 weeks	Reduction in 24h average pain item of the BPI
HMEO (CLBP)	Parallel, double-blind, placebo-controlled, fixed-dose	Randomized/Completed: 59/43 - DLX 20 mg 116/80 - DLX 60 mg 112/62 - DLX 120 mg 117/82 - placebo	13 weeks	Reduction in weekly mean of 24h average pain ratings from patient diaries
HMGC (CLBP)	Parallel, double-blind, placebo-controlled, fixed-dose	Randomized/Completed: 198/146 - DLX 60 mg QD 203/156 - placebo	12 weeks	Reduction in 24h average pain item of the BPI

(Source: Adapted from applicant's table 2.5.4.1 from clinical overview of efficacy, p. 22)

Table 50: DPNP and FM trials

Indication	Study	Total Daily Dose	Duration of Placebo-Controlled Phase	Status in the United States
DPNP	HMAW	20 mg, 60 mg, 120 mg	12 weeks	Indication approved (NDA 21-733) ^a
	HMAVa HMAVb	60 mg, 120 mg 60 mg, 120 mg	12 weeks 12 weeks	
Fibromyalgia	HMBO	120 mg	12 weeks	Indication approved (NDA 22-148)
	HMCA	60 mg, 120 mg	12 weeks	
	HMCJ	20 mg, 60 mg, 120 mg	12 weeks/ 24 weeks	
	HMEF	60 mg-120 mg	24 weeks	

(Source: Adapted from applicant's table 2.7.3.2 from CSE, p. 16)

6.1.2 Demographics

Based on patient demographics and baseline disease characteristics, the patients enrolled in the different chronic pain trials had mean baseline BPI scores of approximately 6 points, indicating moderate pain.

Duloxetine and placebo treatment groups were generally well balanced within trials, with no significant treatment group differences in patients' gender, age, race, and baseline severity of illness. For more details refer to Section 7.2.1 of this review.

6.1.3 Subject Disposition

Primary chronic pain trials

A total of 641 patients were randomized to duloxetine (20mg, 60 mg, or 120 mg QD) and 486 patients were randomized to placebo in the primary placebo-controlled trials (HMEP, HMEN, HMFG and HMEO). The HMGC trial, submitted with the 120-day safety update, is discussed separately and is not included in the pooled analyses.

In the primary placebo-controlled analyses set, significantly more duloxetine-treated patients (17.2%) discontinued due to any AE compared with placebo-treated patients (6.4%). The table below presents a disposition analysis performed by the applicant after re-categorization based on the review of comments on the case report forms (CRFs) for patients noted as discontinued because of "Physician Decision", "Subject Decision", and "Sponsor Decision".

Table 51: Pooled disposition analysis data for the primary chronic pain trails (HMEN, HMEP, HMFG and HMEO) – any duloxetine dose

Table 2.7.4.8. Reason for Study Discontinuation Following Revision of Comments on Case Report Forms All Randomized Patients Primary Placebo-Controlled Analyses Set

Primary Reason For Discontinuation	PLACEBO (N=486) n (%)	DULOXETINE (N=641) n (%)	TOTAL (N=1127) n (%)
Completed	387 (79.6)	439 (68.5)	826 (73.3)
DC due to any reason	99 (20.4)	202 (31.5)	301 (26.7)
Adverse event	31 (6.4)	110 (17.2)	141 (12.5)
Subject decision	28 (5.8)	32 (5.0)	60 (5.3)
Lack of efficacy	22 (4.5)	20 (3.1)	42 (3.7)
Protocol violation	9 (1.9)	15 (2.3)	24 (2.1)
Lost to follow up	3 (0.6)	18 (2.8)	21 (1.9)

(Source: Applicant's table 2.7.4.8 from SCS, p. 27)

As illustrated on the tables that follow, during the first 7 weeks of treatment, more patients taking duloxetine 60 mg discontinued overall and due to an AE compared with placebo-treated patients and duloxetine 120 mg treated patients. The most frequent reason for discontinuation for the three treatment groups was an adverse event (placebo 3%, DLX 60 mg 12%, and DLX 120 mg 7%).

For the second 6 weeks of treatment, a higher percentage of patients taking duloxetine 120 mg discontinued overall and due to an AE compared with patients taking placebo and duloxetine 60 mg. A similar frequency of discontinuation was observed between patients taking duloxetine 60 mg and those taking placebo. It is to note that the 120 mg duloxetine group during the last 6 weeks includes patients who had a dose increase from their previous 60 mg dose (first 7 weeks) to 120 mg dose.

Table 52: Reason for discontinuation from the trial, first 7 weeks – primary chronic pain trials (pooled analysis)

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**Table 2.1. Reason for Study Discontinuation
 All Randomized Patients
 Pooled Data – Study HMEN, Study HMFG, and Study HMEP (First 7 weeks)**

Primary Reason For Discontinuation	Placebo (N=369) n (%)	DLX60mgQD (N=354) n (%)	Total (N=723) n (%)
Completed first 7 weeks	329 (89.2)	282 (79.7)	611 (84.5)
DC due to any reason	40 (10.8)	72 (20.3)	112 (15.5)
Adverse event	12 (3.3)	41 (11.6)	53 (7.3)
Subject decision	10 (2.7)	16 (4.5)	26 (3.6)
Protocol violation	5 (1.4)	5 (1.4)	10 (1.4)
Lack of efficacy	9 (2.4)	5 (1.4)	14 (1.9)
Lost to follow up	0 (0.0)	4 (1.1)	4 (0.6)
Physician decision	1 (0.3)	1 (0.3)	2 (0.3)
Entry criteria exclusion	2 (0.5)	0 (0.0)	2 (0.3)
Sponsor decision	1 (0.3)	0 (0.0)	1 (0.1)

(Source: Applicant's table 2.2 from 8/14/09 response to information request, page 13)

Table 53: Reason for discontinuation from the trial, last 6 weeks – primary chronic pain trials (pooled analysis)

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Table 2.2. Reason for Study Discontinuation
 All Randomized Patients
 Pooled Data – Study HMEN, Study HMFG, and Study HMEP (Second 6 weeks)

Primary Reason For Discontinuation	Placebo (N=329) n (%)	DLX60mgQD (N=179) n (%)	DLI120mgQD (N=103) n (%)	Total (N=611) n (%)
Completed	305 (92.7)	164 (91.6)	90 (87.4)	559 (91.5)
DC due to any reason	24 (7.3)	15 (8.4)	13 (12.6)	52 (8.5)
Adverse event	9 (2.7)	6 (3.4)	8 (7.8)	23 (3.8)
Subject decision	6 (1.8)	3 (1.7)	1 (1.0)	10 (1.6)
Physician decision	2 (0.6)	3 (1.7)	1 (1.0)	6 (1.0)
Protocol violation	1 (0.3)	2 (1.1)	1 (1.0)	4 (0.7)
Lost to follow up	1 (0.3)	1 (0.6)	1 (1.0)	3 (0.5)
Lack of efficacy	5 (1.5)	0 (0.0)	1 (1.0)	6 (1.0)

(Source: Applicant's table 2.2 from 8/14/09 response to information request, page 14)

A total of 800 patients were randomized to duloxetine in the three DPNP placebo-controlled trials (HMAW, HMAVb, and HMAVa), and 876 patients were randomized to duloxetine in the four fibromyalgia trials (HMBO, HMCA, HMCJ, and HMEF). For both indications, a significantly higher percentage of duloxetine-treated patients discontinued due to adverse events as compared with placebo-treated patients and the rates were comparable to what was observed in OA pain and CLBP trials.

6.1.4 Analysis of Primary Endpoint(s)

Primary Efficacy Measure and Endpoints

The Division's current policy regarding trials evaluating the efficacy of products intended to treat chronic pain, is that the efficacy must be supported by multiple-dose trials of at least 12 weeks duration, with efficacy evaluated at the end of the trial period, to assess the durability of effect over time. The primary efficacy measure must assess pain intensity. The primary efficacy endpoint can be a comparison across treatment groups of the average pain at study end, or the change in pain from baseline to study end. The Division also recommends calculation of response rates in analgesic trials, considering the proportion of treatment responders at the end of treatment. A comparison of response across all levels of response [i.e. a cumulative (continuous) responder analysis] is encouraged, with patients who dropout for any reason counted as non-responders. With regard to the strategy for imputation of missing data, in analgesic trials a method that does not impute a favorable score for patients who stopped taking the drug due to adverse event should be implemented. Patients, who can not tolerate

the drug for the duration of the treatment period, respectively the intended chronic duration of use, should be deemed treatment failures.

To support the claim for the treatment of chronic pain indication, the applicant relays on positive results from HMEN, HMFG, and HMGC primary chronic pain trials in OA and low back pain populations and the approved indications for FM and DPNP pain. The design of the primary chronic pain trials was different but the primary endpoint was similar for all five trials. Three of the trials were designed to study the efficacy of the combined DLX 60 mg and DLX 120 mg dose (HMEN, HMEP, and HMFG). Two trials were of fixed dose design (HMEO and HMGC).

The applicant's choice for the primary efficacy variable was the change in 24 hour average pain score from Baseline to endpoint (last non-missing observation during the 12-week Treatment Phase).

The primary efficacy measure was the BPI 24-hour average pain item on the 11-point Likert scale expressed as either the weekly mean from patient diaries (HMEP and HMEO) or the single day report (HMEN, HMFG, and HMGC).

An MMRM analysis was pre-specified as the primary analysis in all primary chronic pain trials. In addition, the following methods were also utilized as sensitivity analyses: ANCOVA/BOCF, ANCOVA/mBOCF, and ANCOVA/LOCF. In the mBOCF approach, LOCF endpoint was used for patients who discontinued due to non-treatment related reasons and BOCF endpoint was used for patients who discontinued due to treatment-related reasons (adverse events or lack of efficacy).

The MMRM strategy was found unacceptable for the primary analysis because it assumes data are missing at random. This was conveyed to the sponsor during the pre-NDA meeting. In analgesic trials, discontinuations are generally not random. The majority of patient dropout is related to treatment assignment. There are more early discontinuations due to adverse events in the active arm, while patients on placebo tend to discontinue due to lack of efficacy. Therefore, this non-random dropout that is treatment related is considered informative when assessing efficacy of the drug.

As outlined above, the Division's approach when evaluating effect in pain trials is to use an imputation method that does not impute a favorable pain scores for patients who have adverse outcomes. One of these methods is baseline-observation-carried-forward (BOCF). BOCF would impute the baseline pain score for missing data due to discontinuation for any reason. Using this approach assignment of a good pain score to subjects who discontinue early due to adverse event would be avoided. On the other hand assigning baseline score to patients who discontinued due to reasons unrelated to treatment (for example, inconvenience, schedule conflicts), and who may have benefited if they had stayed in the trial, is punishing. Therefore, combined LOCF/BOCF

analysis where BOCF is imputed for early discontinuations due to adverse events and lack of efficacy and LOCF is imputed for all other reasons, is an acceptable alternative.

Therefore, the statistical reviewer for this application recalculated response rates for the pivotal trials using the Division's preferred methods.

Trial Design

The primary chronic pain trials in OA and CLBP used different designs and dosing strategies.

Elements of the trial designs that were common across most of the chronic pain trials were as follows:

- Double-blind, randomized, placebo-controlled trial design
- Evaluated duloxetine doses were of 60 mg to 120 mg daily
- Treatment period duration was of at least 12 weeks
- Baseline pain score of four or greater on an 11-point Likert scale was required for enrollment
- Chronic pain for at least three months prior to entry was a requirement for enrollment
- Primary outcomes included measurements of pain severity, Brief Pain Inventory (BPI) 24-hour average pain item

The completed duloxetine clinical programs for DPNP and fibromyalgia consist of six fixed-dose and one flexible-dose, placebo-controlled trials. From the new primary chronic pain trials in OA and CLBP, only two (HMEO and HMGC in CLBP) are of fixed-dose design. The other three trials had all patients originally assigned to 60 mg duloxetine dose, re-randomized at Week 7 to either 60 mg duloxetine or 120 mg duloxetine for the remaining six weeks of the treatment period (HMEP) or to have only non-responders up-titrated to 120 mg duloxetine dose for the remaining six weeks of the treatment period (HMEN and HMFG). The blind for HMEP, HMEN, and HMFG was preserved both at randomization and re-randomization.

Specific characteristics of the five primary chronic pain trial designs were as follows:

- **HMEP trial** was a Phase 3, parallel-group, double-blind, placebo-controlled trial in male and female patients ≥ 40 years with OA of the knee. The trial included three periods: Screening (1 week), Double-blind Treatment (13 weeks), and Taper (2 weeks). The duration of the double-blind Treatment Period was 13 weeks with randomized treatment assignment in 1:1 ratio to either placebo or duloxetine 60 mg QD. Patients assigned to duloxetine 60 mg began the trial taking duloxetine 30mg QD for one week and then were up-titrated to 60 mg QD dose. Patients who were originally randomized to take duloxetine 60 mg QD were re-randomized at Week 7 to take either duloxetine 60 mg QD or 120 mg QD for the remainder of the study (additional 6 weeks). The primary objective was to assess the efficacy of combined duloxetine 60 to 120 mg once daily (QD) compared with placebo on the reduction of pain severity as measured by the weekly mean of the 24-hour average pain scores

in patients with OA knee pain during the 13-week, double-blind treatment period, using an 11-point Likert scale patient diary.

- **HMEN trial** was a Phase 3, parallel-group, double-blind, placebo-controlled trial in male and female patients ≥ 18 years of age with CLBP as their primary painful condition. Patients were required to have a clinical diagnosis of CLBP, with pain present on most days for at least six months. Pain was to have been either restricted to the lower back or associated with radiation to the proximal portion of the lower limb only (corresponding with Class 1 and Class 2 per Quebec Task Force on Spinal Disorders). Treatment periods and their duration were similar to the one described above for Study HMEP with the difference that at Week 7, non-responders to duloxetine 60 mg QD (less than 30% average pain reduction from baseline) were titrated up to 120 mg QD. This study also includes a 9-month dose-blinded (duloxetine 60 mg QD to 120 mg QD) extension phase. The primary objective was the efficacy of combined duloxetine 60 mg QD to 120 mg QD compared with placebo on the reduction of pain severity as measured by the BPI 24-hour average pain scores in patients with CLBP during the 13-week, double-blind acute treatment period.
- **HMFG trial** had similar design to the HMEN trial but in OA population.
- **HMEO trial** was a Phase 3, parallel-group, double-blind, fixed-dose, placebo-controlled trial in male and female patients ≥ 18 years of age with CLBP as their primary painful condition. This trial evaluated duloxetine at doses of 20 mg QD, 60 mg QD, and 120 mg QD. The primary objective was to assess the efficacy of duloxetine 60 mg QD compared with placebo on the reduction of pain severity as measured by the weekly mean of the 24-hour average pain scores in patients with CLBP during the 13-week, double-blind treatment period using an 11-point Likert scale patient diary.
- **HMGC trial** was a Phase 3, parallel-group, double-blind, fixed-dose, placebo-controlled trial in male and female patients ≥ 18 years of age with CLBP as their primary painful condition. This trial evaluated duloxetine 60 mg QD dose only dose. The primary objective was to assess the efficacy of duloxetine 60 mg QD compared with placebo on the reduction of pain severity as measured by the BPI 24-hour average pain rating in patients with CLBP during 12-week, double-blind treatment period.

Applicant's Efficacy Results

HMEP trial

(Refer to Section 5.3.1 for a detailed description of the trial design, amendments, statistical analysis, and applicant's efficacy results.)

Title: “Duloxetine 60 to 120 mg versus placebo in the treatment of patients with osteoarthritis knee pain.”

Subjects Disposition

Of the 231 randomized patients, 120 were assigned to the placebo group, and 111 were assigned to the duloxetine group.

A total of 89 (80%) of the 111 patients originally assigned to the duloxetine 60 mg a day group, completed seven weeks of treatment and were re-randomized at Week 7, 46 to the 60 mg QD group and 43 to the duloxetine 120 mg QD group. At Week 7, 103 (85.8%) from the placebo group remained to continue the trial.

A total of 173 (74.9%) patients completed the study: 96 (80.0%) in the placebo group and 77 (69.4%) in the duloxetine group.

One hundred and three (85.8%) of the placebo and 89 (80.2%) of the 60 mg duloxetine-treated subjects completed the first seven weeks of treatment. The 89 subjects assigned to the active treatment were re-randomized at Week 7 in a 1:1 ratio to 60 mg or 120 mg duloxetine. Of the re-randomized subjects, 39 (84.8%) of the duloxetine 60 mg QD group and 38 (88.4%) of the duloxetine 120 mg QD group completed the last six weeks of the treatment period.

The disposition for the placebo and 60 mg DLX patients prior to re-randomization is presented on the following table:

(Source: Applicant’s Table 26 from 9/11/08 response to information request submission, p. 172)

More patients in the duloxetine 60 mg treatment group (8.1%) discontinued during the first seven weeks of treatment due to adverse event compared to placebo (4.2%). For the same period, discontinuations due to lack of efficacy were similar between the two groups.

The reason for discontinuation, before and after the re-randomization at Week 7, is presented on the table that follows.

Table 54: Reason for discontinuation by dose – HMEP

Table 2.7.4.21. Reason for Study Discontinuation by Dose Comparison of Data during the First 7 Weeks and the Second 6 Weeks of the Dose-Escalation Studies All Randomized Patients All Primary Chronic Pain Studies – HMEP, HMFG, HMEN, and HMEO

	First 7 weeks of Study		Second 6 weeks of Study		
	Placebo n (%)	DLX60 n (%)	Placebo n (%)	DLX60 n (%)	DLX120 ^b n (%)
Study HMEP ^a	N= 120	N= 111	N= 103	N= 46	N= 43
Any Reason	17 (14.2)	22 (19.8)	7 (6.8)	7 (15.2)	5 (11.6)
Adverse Event	5 (4.2)	9 (8.1)	2 (1.9)	2 (4.3)	4 (9.3)
Subject/Physician Decision	8 (6.6)	7 (6.3)	3 (2.9)	4 (8.7)	0 (0)
Lack of Efficacy	2 (1.7)	2 (1.8)	1 (1.0)	0 (0)	0 (0)

(Source: Applicant's table 2.7.4.21 from SCS, p. 68)

After re-randomization, most patients who discontinued due to adverse events were from the 120 mg QD duloxetine group (9.3%) compared to the 60 mg QD dose group (4.3%) and placebo (1.9%). One subject (1%) discontinued due to lack of efficacy from the placebo group, and no subjects discontinued for this reason from the duloxetine 60 mg and 120 mg treatment groups.

Extent of exposure

The mean drug exposure was 79.6 days with 61.0% of patients receiving study drug for at least 13 weeks, 62.5% for the placebo and 59.3% for the duloxetine-treated patients.

The mean study drug exposure for patients who were re-randomized at Visit 4 (Week 7) to duloxetine 60 mg QD or 120 mg QD was 39.3 days with 67.0% of patients receiving study drug for at least 6 weeks, 65.2% for the DLX 60 mg /day group and 69% for the DLX 120 mg/day group.

Demographics

Overall, the average age of the subjects was 62.3 years and similar between the placebo and duloxetine-treated patients. There were no significant differences between the duloxetine and placebo groups for age, sex and duration of OA since diagnosis, or duration of OA pain since onset. Medical history and concomitant diseases were similar between the placebo and duloxetine treatment groups.

Applicant's Efficacy Analysis

a) Primary Efficacy Endpoint

The applicant found with respect to the primary efficacy variable that the MMRM primary analysis demonstrated a statistically significant improvement from baseline to endpoint in the weekly 24-hour average pain score for the duloxetine 60-120 mg group compared

to placebo. The LS Mean at Week 13 difference between the placebo and DLX 60-120 was 0.84 with $p < 0.001$.

Sensitivity analyses on the primary endpoint included ANCOVA, imputing missing data with LOCF, BOCF and mBOCF methods. The LOCF analysis of mean change from baseline to endpoint in 24-hour average pain score was found to demonstrate statistically significant pain reduction for duloxetine compared to placebo (LS Mean difference of 0.70, $p=0.006$). The results from the mBOCF analysis showed that the duloxetine-treated patients had statistically significant greater improvement compared with placebo-treated patients (LS Mean difference of 0.74, $p=0.047$). Using the BOCF approach the difference was not found to be statistically significant (LS Mean difference of 0.45, $p=0.086$).

Analyses performed comparing the LS Mean Change from Baseline to Week 13 in weekly mean of the 24 hour average pain between subjects who received only 60 mg duloxetine dose and patients who received placebo, failed to show efficacy for the 60 mg duloxetine using the MMRM and ANCOVA/LOCF models.

b) Key Secondary Efficacy Endpoints

Analysis for 30% and 50% response rates at endpoint were found to demonstrate statistically greater response rate in the duloxetine group compared with the placebo group with the LOCF imputation strategy but not when BOCF was used ($p=0.364$). The continuous responder curve was generated by the applicant using the Kolmogorov-Smirnov test.

In the analysis of patients re-randomized to duloxetine 60 mg QD or 120 mg QD, the applicant found statistically greater 24-hour average pain reduction based on LOCF mean change analysis of the weekly mean change from patient diaries when compared duloxetine 120 mg QD re-randomized patients with those re-randomized to duloxetine 60 mg QD. No statistically significant differences were observed between duloxetine 60 mg QD and 120 mg QD on the MMRM analysis of the weekly 24-hour average pain score or the 30% and 50% response rates at endpoint.

The secondary gatekeeper assessments for PGI-I and the WOMAC (MMRM, LOCF, BOCF, and mBOCF) physical function subscale (MMRM, LOCF, BOCF, and mBOCF) were found to demonstrate significantly greater improvement for the duloxetine compared to the placebo-treated patients. The p-values were less than 0.05 and passed the pre-specified sequential gatekeepers at 0.05 level.

HMEN trial

(Refer to Section 5.3.2 for a detailed description of the design, protocol amendments, statistical analysis, and applicant's efficacy results.)

Title: “Effect of Duloxetine 60 mg to 120 mg Once Daily in Patients with Chronic Low Back Pain”

Subjects Disposition

Of the 236 randomized patients, 121 were assigned to the placebo group, and 115 were assigned to the duloxetine group. A total of 94 (81.7%) of the 115 patients originally assigned to the duloxetine 60 mg per day group, completed six weeks of treatment. At Week 7, of 94 patients, 27 (28.7%) required up-titration of duloxetine to 120 mg QD because of insufficient response (< 30% pain score reduction compared to baseline). Sixty-seven patients continued on 60 mg QD duloxetine dose for the remainder of the treatment phase.

A total of 180 (76.3%) patients completed the trial: 96 (79.3.0%) in the placebo group and 84 (73%) in the duloxetine group. Across all groups, 22.9% of patients discontinued the trial. The most frequently reported reason for discontinuation was an adverse event, with a significantly higher rate for the duloxetine (13.9%) compared to placebo (5.8%). The discontinuation rate due to lack of efficacy was similar between the placebo and duloxetine-treated patients.

During the first seven weeks of treatment, significantly more patients administered duloxetine 60 mg QD discontinued overall and due to an AE (21% and 11% respectively) compared to patients administered placebo (10% and 3% respectively).

No significant differences were observed during the last six weeks of treatment.

Table 55: Reason for discontinuation by dose – HMEN

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Table 2.7.4.21. Reason for Study Discontinuation by Dose Comparison of Data during the First 7 Weeks and the Second 6 Weeks of the Dose-Escalation Studies All Randomized Patients All Primary Chronic Pain Studies – HMEP, HMFG, HMEN, and HMEO

	First 7 weeks of Study		Second 6 weeks of Study		
	Placebo n (%)	DLX60 n (%)	Placebo n (%)	DLX60 n (%)	DLX120 ^b n (%)
Study HMEN ^a	N= 121	N= 115	N= 109	N= 64	N= 27
Any Reason	12 (9.9)	24 (20.9)	11 (10.1)	5 (7.8)	2 (7.4)
Adverse Event	4 (3.3)	13 (11.3)	3 (2.8)	2 (3.1)	1 (3.7)
Subject/Physician Decision	3 (2.5)	6 (5.2)	4 (3.7)	2 (3.1)	0 (0)
Lack of Efficacy	2 (1.7)	3 (2.6)	3 (2.8)	0 (0)	0 (0)

(Source: Applicant’s table 2.7.4.21 from SCS, p. 68)

The duloxetine-treated patients tended to discontinue treatment relatively early during the double-blind treatment phase (15.7% at Week 4 compared to 5.2% at Week 7 and 6.1% at Week 13). The early discontinuations were mainly due to adverse events (9.6% at Week 4).

Extent of exposure

The mean study drug exposure was 80 days with 58.5% of patients receiving study drug for at least 13 weeks, 62.0% for the placebo and 54.8% for the duloxetine-treated patients.

Demographics

Overall, the average age of subjects was 51.5 years and similar between the placebo and duloxetine-treated patients. The majority of patients were female and Caucasian.

There were no significant differences between the duloxetine and placebo groups for age, sex baseline illness characteristics, and concomitant diseases.

Applicant's Efficacy Analysis

a) Primary Efficacy Endpoint

Using the primary MMRM analysis of the 24-hour average pain score as recorded on the BPI instrument at clinic visits, the applicant found that patients treated with duloxetine 60 mg to 120 mg for 13 weeks demonstrated significantly greater improvement than placebo-treated patients. The LSMean at Week 13 difference between the placebo and DLX 60-120 was -0.82 with $p < 0.004$.

The additional LOCF analysis of mean change from baseline to endpoint in 24-hour average pain score was found by the applicant to demonstrate statistically significant pain reduction for duloxetine compared to placebo (LSMean difference of -0.64, $p=0.019$). Using the BOCF and mBOCF approach the difference was also found to be statistically significant (LSMean difference of -0.61, $p= 0.019$ for BOCF and LSMean difference of -0.55, $p= 0.041$ for mBOCF).

For this trial, the applicant performed an additional analysis, focusing on the duloxetine 60 mg dose only versus placebo at Week 13. In this analysis, all randomized patients who did not meet protocol specified response criteria (at least a 30% reduction on BPI average pain rating) at the end of the first seven weeks of treatment and had the potential to be up titrated, were treated as discontinued due to lack of efficacy at Week 7 visit, irrespective of their original assigned treatment to duloxetine 60 mg or placebo. The applicant's rationale for this approach was that including all placebo patient data while excluding data of duloxetine-treated patients who titrated up to duloxetine 120 mg QD after seven weeks of treatment could pose a potential bias against the duloxetine 60 mg QD. The reason was that if non-responders to duloxetine 60 mg were allowed to stay on the same treatment for additional six weeks they would have had the potential for additional improvement. Data were analyzed using the BOCF approach, assigning

the baseline average pain rating as the endpoint value for patients who were non-responders at Visit 4 or patients who did not complete the 13-week acute treatment phase. The results showed that duloxetine 60 mg QD had statistically significantly greater pain reduction over the 13-week period compared to placebo (p=0.006).

b) Key Secondary Efficacy Endpoints

Analysis for 30% and 50% response rate at endpoint using the LOCF imputation strategy demonstrated no significant difference between treatment groups. When BOCF approach was used, a statistically greater 50% response rate was demonstrated for the duloxetine group compared with the placebo group (p=0.018). The continuous responder curve was generated by the applicant using the Kolmogorov-Smirnov test.

In the analysis of patients re-randomized to duloxetine 60 mg QD or 120 mg QD at Visit 4 (Week 7), the applicant found statistically greater 24-hour average pain reduction based on LOCF mean change analysis of the weekly mean change from patient diaries when compared duloxetine 120 mg QD re-randomized patients with those re-randomized to duloxetine 60 mg QD. No statistically significant differences were observed between duloxetine 60 mg QD and 120 mg QD on the MMRM analysis of the weekly 24-hour average pain score or the 30% and 50% response rates at endpoint.

The secondary gatekeeper assessments for PGI-I and the RMDQ-24 hour (MMRM, LOCF, BOCF, and mBOCF) physical function subscale (MMRM, LOCF, BOCF, and mBOCF) were found to demonstrate significantly greater improvement for the duloxetine compared to the placebo-treated patients. The p-values were less than 0.05 and passed the pre-specified sequential gatekeepers at 0.05 level.

HMFG trial

(Refer to Section 5.3.3 for a detailed description of the trial design, amendments, statistical analysis, and applicant's efficacy results.)

Title: "Duloxetine 60 to 120 mg versus placebo in the treatment of patients with osteoarthritis knee pain."

Subjects Disposition

Total of 256 subjects (128 per treatment group) were randomized. At Visit 4 (Week 7), 102 (80%) DLX 60 mg-treated patients and 117 (91%) placebo-treated patients continued on with the trial. At Week 7, of the 102 DLX-treated patients, 33 (32%) were considered non-responders and had their dose increased to 120 mg QD and 69 (68%) continued on 60 mg QD DLX dose for the remainder of the treatment phase. Of the 69 subjects who continued on 60 mg DLX, 3 (4.3%) discontinued treatment during the second six weeks of the trial and 6 (18.2%) of the 33 subjects who had their DLX dose increased to 120 mg QD discontinued treatment during the second six weeks of the trial.

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A total of 204 (79.7%) patients completed the treatment phase: 111 (86.7%) from the placebo group and 93 (72.7%) from the duloxetine 60/120 QD group.

Of the 256 randomized subjects, 22.9% across all groups discontinued the trial. The most frequently reported reason for discontinuation was an adverse event, with a significantly higher rate for the duloxetine-treated patients (18.8% for DLX versus 5.5% for placebo). The discontinuation rate due to lack of efficacy was higher for the placebo compared to duloxetine-treated patients (3.9% versus 0.8%, respectively).

The disposition by treatment group and DLX dose for the first 7 weeks and the last 6 weeks of the treatment period is presented on the table that follows.

Table 56: Reason for discontinuation by dose – HMFG

Table 2.7.4.21. Reason for Study Discontinuation by Dose Comparison of Data during the First 7 Weeks and the Second 6 Weeks of the Dose-Escalation Studies All Randomized Patients All Primary Chronic Pain Studies – HMEP, HMFG, HMEN, and HMEO

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	First 7 weeks of Study		Second 6 weeks of Study		
	Placebo n (%)	DLX60 n (%)	Placebo n (%)	DLX60 n (%)	DLX120 ^b n (%)
Study HMFG ^a	N= 128	N= 128	N = 117	N= 69	N= 33
Any Reason	11 (8.6)	26 (20.3)	6 (5.1)	3 (4.3)	6 (18.2)
Adverse Event	3 (2.3)	19 (14.8)	4 (3.4)	2 (2.9)	3 (9.1)
Subject/Physician Decision	0 (0)	4 (3.1)	1 (0.9)	0 (0)	2 (6.0)
Lack of Efficacy	5 (3.9)	0 (0)	1 (0.9)	0 (0)	1 (3.0)

(Source: Applicant's table 2.7.4.21 from SCS, p. 68)

Significantly more patients administered duloxetine 60 mg QD discontinued overall (20% vs. 9%) and due to an AE (15% vs. 2%) during the first seven weeks of treatment compared to patients administered placebo.

The discontinuation due to an AE was lower during the second six weeks of the acute treatment compared with the first seven weeks. However, patients who had their DLX dose increased to 120 mg QD at Week 7, discontinued the trial due to an AE more frequently than patients who continued on duloxetine 60 mg QD (9% versus 3%, respectively).

Extent of exposure

The mean study drug exposure was 81 days with 54.9% of patients receiving study drug for at least 13 weeks, 55.9% for the placebo and 53.9% for the duloxetine-treated patients.

Demographics

Overall, the average age of subjects was 62.5 years and similar between the placebo and duloxetine-treated patients. The placebo group had a significantly higher percentage of female patients (83.6%) compared with the duloxetine group (69.5%). There were no other significant treatment group differences.

Medical history and concomitant diseases were similar between the placebo and DLX treatment groups.

Applicant's Efficacy Analysis

a) Primary Efficacy Endpoint

On the primary MMRM analysis of the 24-hour average pain score as recorded on the BPI instrument at clinic visits, the applicant found that patients treated with duloxetine 60 mg to 120 mg for 13 weeks demonstrated significantly greater improvement than placebo-treated patients. The LSMean at Week 13 difference between the placebo and DLX 60-120 was -0.84 with $p < 0.001$.

The additional sensitivity analyses of the mean change from baseline to endpoint in the BPI average pain score performed by the applicant included ANCOVA with LOCF and BOCF imputation strategies. The LOCF analysis was found to demonstrate statistically significant pain reduction for duloxetine 60-120 mg compared to placebo (LSMean difference of -0.78, $p < 0.001$). Using the BOCF approach the difference was also statistically significant (LSMean difference of -0.59, $p = 0.013$).

An additional analysis focusing on the 60 mg duloxetine dose only versus placebo at Week 13 using ANCOVA/BOCF approach was performed by the applicant. In this analysis, non-responders (less than 30% improvement) at Week 7 from both the placebo and duloxetine treatment groups were treated as loss of efficacy dropouts. The results showed that duloxetine 60 mg QD had statistically significantly greater pain reduction over the 13-week period compared to placebo ($p = 0.007$).

b) Key Secondary Efficacy Endpoints

The secondary gatekeeper assessments for PGI-I and WOMAC physical function using BOCF, did not demonstrate significantly greater improvement for the duloxetine compared to the placebo-treated patients. Only the LOCF analysis of the WOMAC physical functioning subscale showed a statistically significant improvement in the duloxetine-treated patients compared with the placebo-treated patients.

In the response rate analyses at endpoint using the LOCF and BOCF imputation strategies, statistically greater 30% response rate, but not 50% response rate, was demonstrated for the duloxetine group compared with the placebo group. The continuous responder curve was generated using the Kolmogorov-Smirnov test.

At Week 7, 33 (31.1%) of the 106 patients on DLX 60 mg QD required up titration to 120 mg QD because of insufficient response. Of this group, 27.3% met the 30% response criteria ($\geq 30\%$ reduction in BPI average pain rating from baseline to endpoint).

HMGC trial

(This trial was submitted with the 120-day safety update. Refer to Section 5.3.4 for a detailed description of the trial design, amendments, statistical analysis, and applicant's efficacy results.)

Title: "Efficacy of duloxetine 60 mg once daily versus placebo in patients with low back pain."

Subjects Disposition

Of the 401 randomized patients, four discontinued after randomization but before receiving trial medication, 200 were assigned to the placebo group, and 197 were assigned to the duloxetine 60 mg group. A total of 146 (74.2%) duloxetine-treated and 156 (76.8%) placebo-treated patients completed the trial. In the double-blind treatment period, duloxetine-treated patients demonstrated a significantly higher rate of discontinuation due to an adverse event compared with placebo (15% vs. 5%) and more placebo-treated patients discontinued due to lack of efficacy compared with duloxetine-treated patients (4% vs. 0.5%).

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Table 57: Subject disposition – HMGC

Table HMGC.10.1. Reasons for Discontinuation
 All Randomized Patients
 Double-Blind Treatment Period

Patient Disposition	PLACEBO (N=203)		DLX60QD (N=198)		Total (N=401)	
	n	(%)	n	(%)	n	(%)
Completed	156	(76.8)	147	(74.2)	303	(75.6)
DC due to ANY reason	47	(23.2)	51	(25.8)	98	(24.4)
Adverse Event	11	(5.4)	30	(15.2)	41	(10.2)
Subject Decision	13	(6.4)	8	(4.0)	21	(5.2)
Protocol Violation	5	(2.5)	6	(3.0)	11	(2.7)
Lack of Efficacy	9	(4.4)	1	(0.5)	10	(2.5)
Physician Decision	3	(1.5)	4	(2.0)	7	(1.7)
Lost to follow up	4	(2.0)	1	(0.5)	5	(1.2)
Entry Criteria Not Met	1	(0.5)	1	(0.5)	2	(0.5)
Sponsor Decision	1	(0.5)	0	(0.0)	1	(0.2)

(Source: Applicant's table from HMGC report, p. 70)

The duloxetine-treated patients tended to discontinue treatment relatively early, 15% at Week 3, compared to 6% at Week 6, 3% at Week 9, and 3% at Week 12. The early discontinuations were mainly due to adverse events (12% at Week 3).

Extent of exposure

The mean drug exposure was 74 days with 55.1% of patients receiving trial drug for at least 13 weeks, 54.7% for the placebo and 55.6% for the duloxetine-treated patients.

Demographics

The average age of subjects was 54.1 years and similar between the placebo and duloxetine-treated patients. The majority of patients were female and Caucasian.

There were no significant differences between the duloxetine and placebo groups for age, sex, concomitant medical conditions, and baseline illness characteristics.

Applicant's Efficacy Analysis

On the primary MMRM analysis of the 24-hour BPI average pain score, the applicant found that patients treated with duloxetine 60 mg demonstrated significantly greater pain reduction than placebo-treated patients at Week 12. The LSMean difference at Week 12 between the placebo and DLX 60 mg was -0.68 with $p < 0.001$.

Additional analysis of the primary efficacy variable using BOCF approach where only patients who completed Visit 6 (Week 12) were considered completers, demonstrated statistically significant pain reduction for duloxetine 60 mg compared to placebo (LSMean difference of -0.55, $p=0.004$). When the mBOCF approach (baseline value for patients who discontinued early due to adverse events or loss of efficacy) was used, the difference was again statistically significant (LSMean difference of -0.56, $p=0.004$). Similar results were obtained when further mBOCF (baseline value for patients who discontinued early due to adverse events) was used, LSMean difference of -0.55, $p=0.005$.

Analysis of the cumulative distribution of the percent change (100% to 0%, in increments of 10%) of the BPI average pain, using the BOCF approach and the Kolmogorov-Smirnov test showed that there was a significant difference between treatment groups ($p=0.013$) with a higher percentage of duloxetine patients experiencing average pain reduction at each threshold point than placebo patients. It was statistically significant for a 50% response rate and numerically higher for 30% response rate.

The secondary gatekeeper assessments demonstrate significantly greater improvement for PGI-I and numerically higher for physical function (RMDQ-24).

HMEO trial

HMEO was a Phase 3, parallel-group, double-blind, fixed-dose, placebo-controlled trial in patients with CLBP. Three dose levels of duloxetine were studied: 20mg/day, 60 mg/day and 120 mg/day.

The primary objective was to assess the efficacy of duloxetine 60 mg QD compared with placebo on the reduction of pain severity as measured by the weekly mean of the

24-hour average pain scores in patients with CLBP during the 13-week, double-blind treatment period using an 11-point Likert scale patient diary.

This trial had a high drop-out rate, 45% for duloxetine (24% due to AEs) and 30% for placebo (9% due to AEs). In addition, low diary compliance was observed.

This trial failed to show evidence of efficacy of duloxetine in CLBP at any dose on all of the efficacy analysis conducted by the applicant.

Table 58: Primary Endpoint Analyses - HMEO

Weekly 24h Average Pain Score from patient diaries				
Trial	Analysis	Treatment group	LS Mean	P-value
HMEO	MMRM	DLX 20mg	1.74	0.243
		DLX 60 mg	-2.50	0.110
		DLX 120 mg	-2.42	0.236
		PBO	-2.10	
	LOCF	DLX 20mg	-1.59	0.482
		DLX 60 mg	-2.27	0.104
		DLX 120 mg	-2.21	0.167
		PBO	-1.82	
	BOCF	DLX 20mg	-1.37	0.621
		DLX 60 mg	-1.86	0.228
		DLX 120 mg	-1.50	0.893
		PBO	-1.54	
	mBOCF	DLX 20mg	-1.49	0.517
		DLX 60 mg	-2.06	0.200
		DLX 120 mg	-1.80	0.755
		PBO	-1.71	

(Source: Adapted from applicant's table 2.7.3.10 from CSE, p. 58)

Division's Efficacy Analysis and Results

As already described in this section, due to the limitations of the applicant's primary efficacy analysis, the statistical reviewer, Dr. Yongman Kim, conducted additional analyses to evaluate the effect of duloxetine for the treatment of chronic OA and chronic low back pain.

The MMRM, ANCOVA/BOCF and mBOCF analyses were repeated using the ITT population and including subjects who had no post-baseline pain score recorded for both the combined duloxetine 60/120 mg dose group versus placebo (HMEN, HMEP,

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and HMFG) and for the 60 mg duloxetine dose versus placebo (HMGC). The table that follows compares the applicant's and Dr. Kim's analyses results.

Table 59 : Analysis of the primary endpoint

LS Mean Change (SE) from Baseline to Week 13 in BPI	Applicant's Results			Statistical Reviewer's Results		
	Placebo (N=115)	DLX 60/120 (N=109)	p-value	Placebo (N=121)	DLX 60/120 (N=115)	p-value
HMEN trial						
MMRM	-1.5 (0.21)	-2.3 (0.22)	0.004	-1.5 (0.21)	-2.3 (0.21)	0.004
ANCOVA/BOCF	-1.3 (0.20)	-1.9 (0.20)	0.019	-1.2 (0.19)	-1.9 (0.20)	0.009
ANCOVA/mBOCF	-1.4 (0.21)	-1.9 (0.21)	0.041	-1.2 (0.20)	-1.8 (0.20)	0.020
vdW						0.018
HMEP trial						
MMRM	-2.1 (0.16)	-2.9 (0.17)	<0.001	-2.1 (0.15)	-2.9 (0.18)	<0.001
ANCOVA/BOCF	-1.8 (0.19)	-2.2 (0.20)	0.086	-1.8 (0.19)	-2.2 (0.21)	0.162
ANCOVA/mBOCF	-1.9	-2.4	0.047	-1.9 (0.20)	-2.4 (0.21)	0.088
HMFG trial						
MMRM	-1.9 (0.18)	-2.7 (0.20)	<0.001	-1.9 (0.18)	-2.7 (0.20)	<0.001
ANCOVA/BOCF	-1.6 (0.19)	-2.2 (0.20)	0.013	-1.6 (0.19)	-2.2 (0.20)	0.013
ANCOVA/mBOCF	-1.6 (0.19)	-2.3 (0.20)	0.005	-1.6 (0.19)	-2.3 (0.20)	0.005
vdW						0.016
HMGC trial						
	Placebo (N=203)	DLX 60 mg	p-value	Placebo (N=203)	DLX 60 mg	p-value

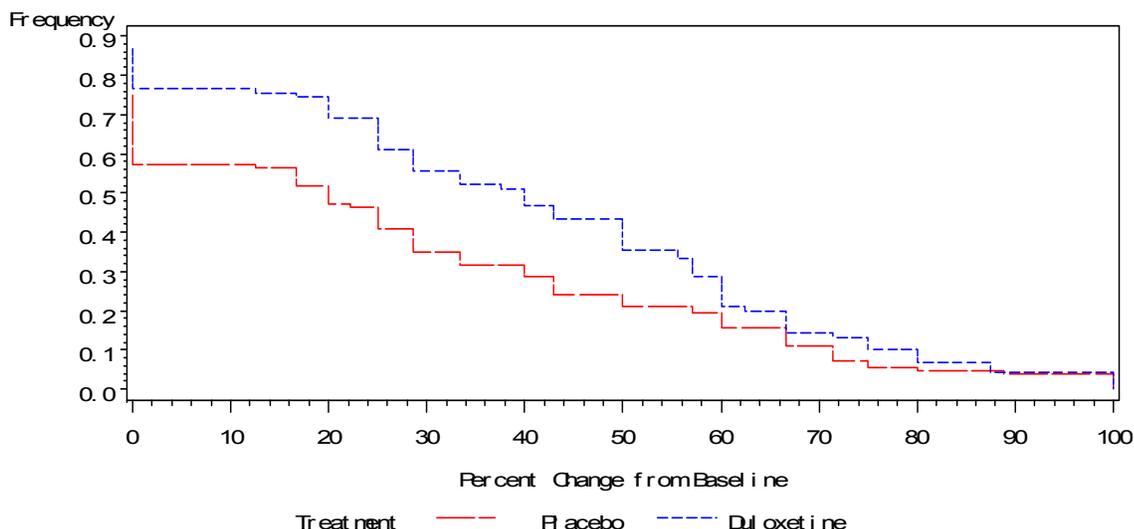
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		(N=198)			(N=198)	
MMRM	-1.9 (0.15)	-2.5 (0.16)	0.001	-1.9 (0.15)	-2.5 (0.16)	0.001
ANCOVA/BOCF	-1.4 (0.15)	-1.9 (0.15)	0.004	-1.5 (0.15)	-2.0 (0.15)	0.004
ANCOVA/mBOCF	-1.6 (0.15)	-2.1 (0.15)	0.004	-1.6 (0.15)	-2.1 (0.15)	0.004
CRA/K-S						0.164
vdW						0.024

(Source: Adapted from a table created by Yongman Kim, statistical reviewer)

As illustrated in the table above, Dr. Kim’s analyses using ANCOVA/BOCF and mBOCF methods confirmed that the combined 60/120 mg dose duloxetine group is statistically superior to placebo in reducing pain intensity in two trials, HMEN (CLBP population) and HMFG (OA population) and that the 60 mg duloxetine dose along is superior to placebo in reducing pain intensity in the fixed dose HMGC trial. Continuous responder curves for HMEN and HMFG, generated using van der Waerden test, showed statistically significant separation from placebo for the duloxetine 60 to 120 mg dose group (HMEN p=0.018, HMFG p=0.016). Continuous responder curve for the fixed-dose 60 mg duloxetine trial, HMGC, also showed a statistically significant separation of the two curves (p=0.024).

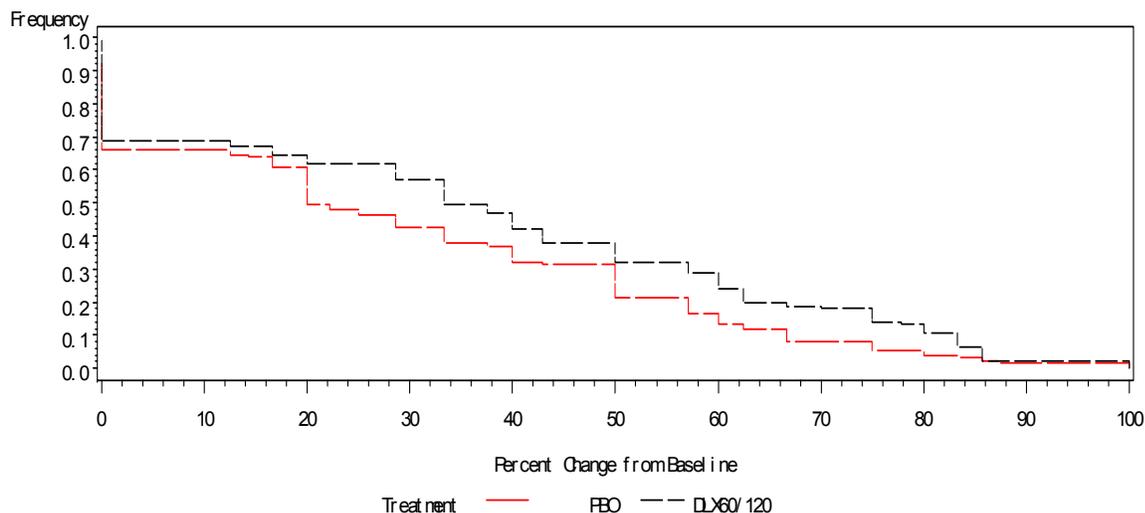
Figure 12: Continuous Responder Analysis – HMEN (DLX 60/120 mg)



*P-value of 0.018 is generated by van der Waerden test to test if BPI Average Pain Score percent change is differed significantly between treatment groups.

(Source: Graph created by Dr. Yongman Kim, statistical reviewer)

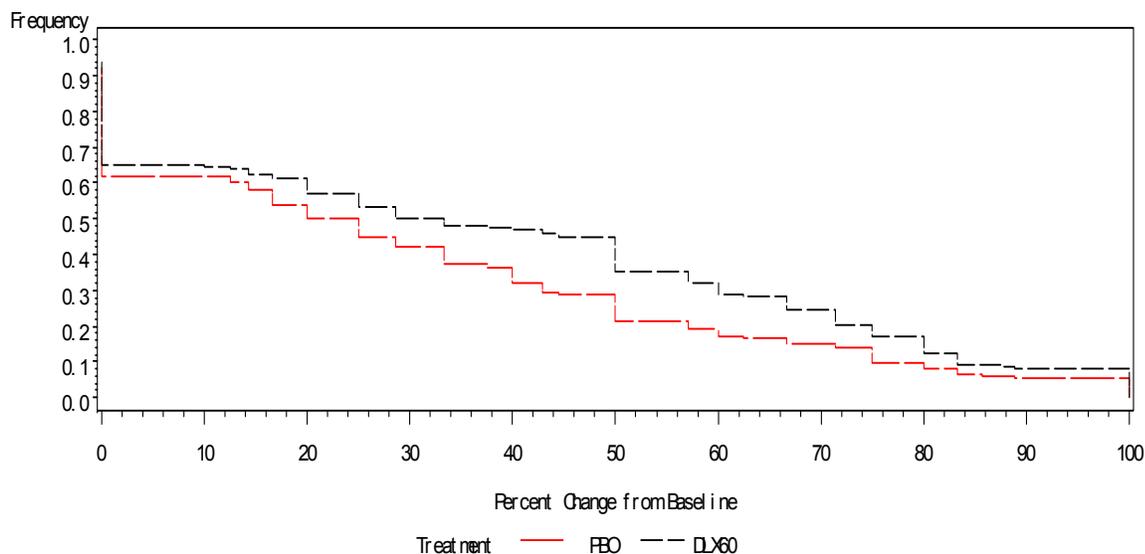
Figure 13: Continuous Responder Analysis – HMFG (DLX 60/120 mg)



*P-value of 0.016 is generated by van der Waerden test to test if BPI Average Pain Score percent change is differed significantly between treatment groups.

(Source: Graph created by Dr. Yongman Kim, statistical reviewer)

Figure 14: Continuous Responder Analysis – HMGC (DLX 60 mg)



*P-value of 0.024 is generated by van der Waerden test to test if BPI Average Pain Score percent change is differed significantly between treatment groups.

(Source: Graph created by Dr. Yongman Kim, statistical reviewer)

Because the safety data for this application showed that duloxetine 120 mg dose is less tolerable and associated with a higher incidence of adverse events, additional efficacy analyses were performed to determine if the duloxetine 60 mg dose alone is effective and if whether a dose increase from 60 mg to 120 mg in patients who did not respond to the 60mg dose confers any additional benefit in terms of efficacy.

As already mentioned, Dr. Kim’s analyses using ANCOVA/BOCF method confirmed that the 60 mg duloxetine dose alone is superior to placebo in reducing pain intensity in the fixed dose HMGC trial. He also performed ANCOVA/BOCF and ANCOVA/mBOCF analyses comparing the efficacy only of the 60 mg duloxetine to placebo for HMEN and HMFG, the two positive trials when the combined 60/120 mg duloxetine dose group was analyzed. In these analyses, subjects who failed to meet the responder definition (30% reduction in pain score) and had their duloxetine dose increased at Week 7 from 60 mg to 120 mg, were treated as failures. As illustrated on the table below, the results of these analyses showed that when the 60 mg duloxetine dose only was analyzed in HMEN and HMFG, no superiority to placebo was demonstrated.

Table 60: Analysis of Efficacy of DLX 60 mg Only versus Placebo (LS Mean Change (SE) from Baseline to Week 13 in 24h average pain) – HMEN and HMFG

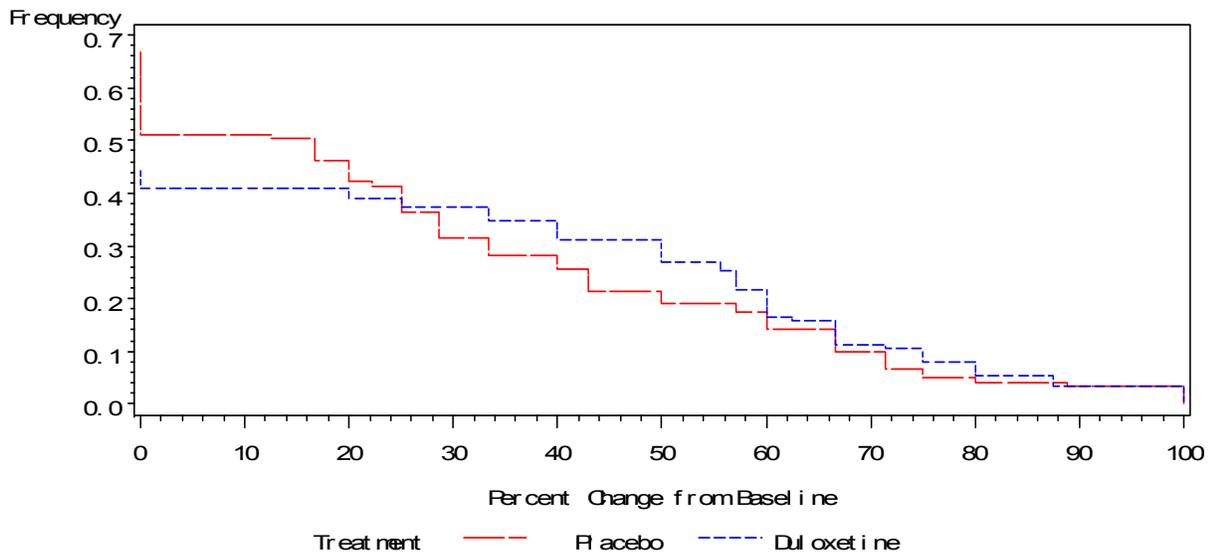
Trial	Placebo (N)	DLX 60 mg (N)	p-value
HMEN			
	Placebo (N=121)	DLX 60 mg (N=115)	p-value
ANCOVA/BOCF	-1.2 (0.19)	-1.5 (0.20)	0.311
ANCOVA/mBOCF	-1.2 (0.20)	-1.5 (0.20)	0.262
CRA/K-S			0.114
vdW			0.196
HMFG			
	Placebo (N=127)	DLX 60 mg (N=121)	p-value
ANCOVA/BOCF	-1.6 (0.19)	-1.8 (0.20)	0.475
ANCOVA/mBOCF	-1.6 (0.19)	-1.9 (0.20)	0.283
CRA/K-S			1.141
vdW			0.443

(Source: Adapted from a table created by Dr. Yongman Kim, statistical reviewer)

Dr. Kim also performed an analysis of the 60 mg duloxetine dose only for the HMEP trial. In this trial, at Week 7, all subjects who were treated with duloxetine 60 mg during the first seven weeks were equally re-randomized to either 60 mg duloxetine or 120 mg duloxetine dose for the remaining six weeks of the double-blind treatment period. These analyses using the MMRM and ANCOVA/BOCF methods found that duloxetine 60 mg is not superior to placebo in reducing pain intensity at Week 13. The continuous responder curves generated for this comparison did not show sizable separation (p=0.753).

A continuous responder curves, treating the 120 mg duloxetine group as failures were generated for HMEN and HMFG using the van der Waerden test. For both trials, no statistically significant separation was demonstrated.

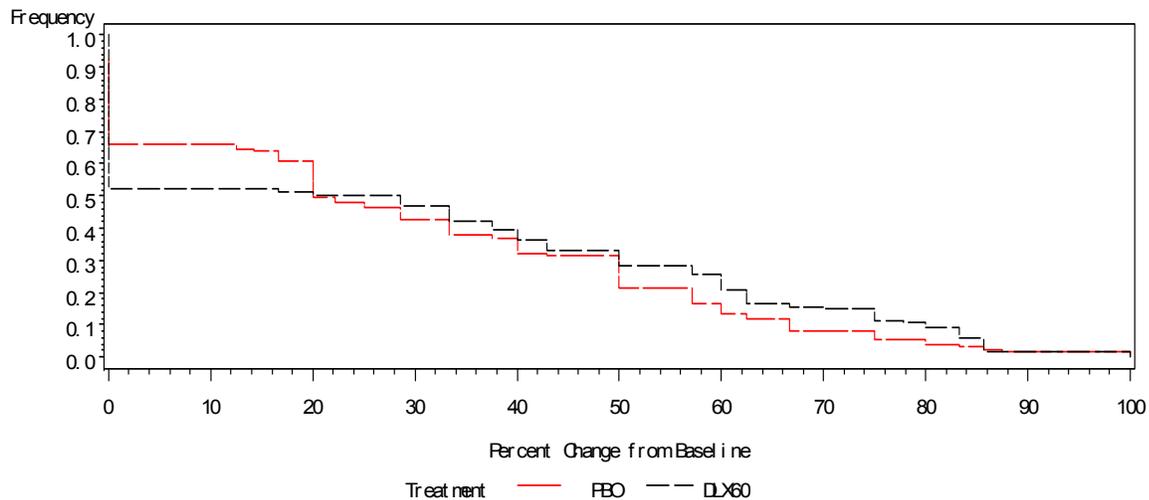
Figure 15: Continuous Responder Analysis Treating DLX 120 mg Group as Failures - HMEN



*P-value of 0.196 is generated by van der Waerden test to test if BPI Average Pain Score percent change is differed significantly between treatment groups.

(Source: Graph created by Dr. Yongman Kim, statistical reviewer)

Figure 16: Continuous Responder Analysis Treating DLX 120 mg Group as failures – HMFG



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*P-value of 0.443 is generated by van der Waerden test to test if BPI Average Pain Score percent change is differed significantly between treatment groups.
 (Source: Graph created by Dr. Yongman Kim, statistical reviewer)

When Dr. Kim analyzed (ANCOVA/BOCF) the duloxetine 60 mg dose only based on data up to Week 7, the duloxetine 60 mg was superior to placebo in reducing pain intensity at Week 7 in both HMEN and HMFG.

Table 61: Duloxetine 60 mg analysis based on data up to Week 7 – HMEN and HMFG

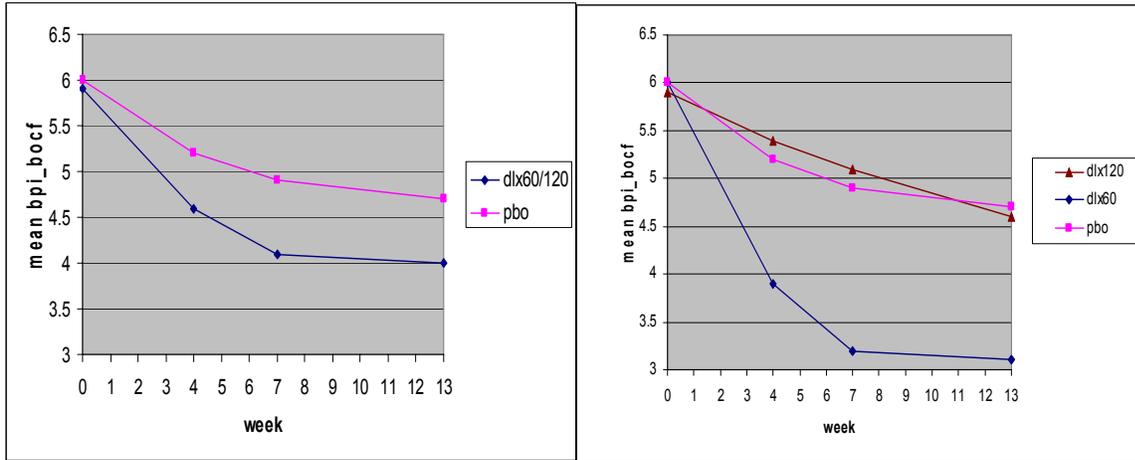
LS Mean Change (SE) from Baseline to Week 7 in BPI	Placebo (N)	DLX60 mg (N)	P-value
HMEN	Placebo (N=121)	DLX60 mg (N=115)	P-value
ANCOVA/BOCF	-1.1 (0.18)	-1.8 (0.19)	0.003
HMFG	Placebo (N=127)	DLX60 mg (N=121)	P-value
ANCOVA/BOCF	-1.3 (0.17)	-2.0 (0.18)	<0.001

(Source: Adapted from a table created by Dr. Yongman Kim, statistical reviewer)

Because the analyses (ANCOVA/BOCF) of the combined 60 to 120 mg duloxetine dose in HMEN and HMFG were able to demonstrate superiority over placebo at Week 13 but failed when the 60 mg duloxetine dose only was analyzed in these trials, Dr. Kim performed additional statistical analyses to investigate if the duloxetine 120 mg dose contributed to the efficacy of the 60 mg dose when the combined 60/120 mg dose was shown to be effective. He performed a mean plot analyses of the BPI score using BOCF. As illustrated on Figure 16 and Figure 18, these analyses showed that duloxetine 120 mg dose group (60 mg for seven weeks followed by 120 mg for six weeks) presented similar to placebo. These subjects showed no response to duloxetine 60 mg dose (no separation from placebo) and continued not to respond to duloxetine despite dose increase to 120 mg at Week 7. This interesting fact can be a basis for future research related to genetics and difference in response rate to a different class of medications.

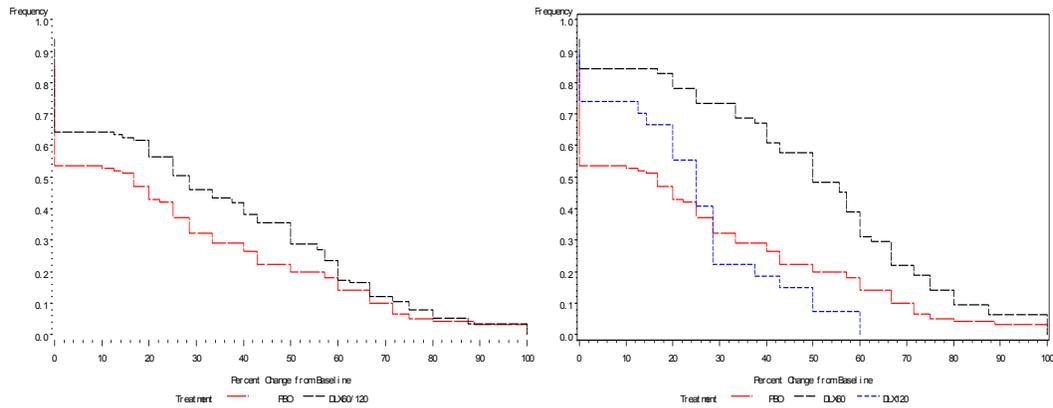
Figure 17: Mean plot for BPI BOCF - HMEN

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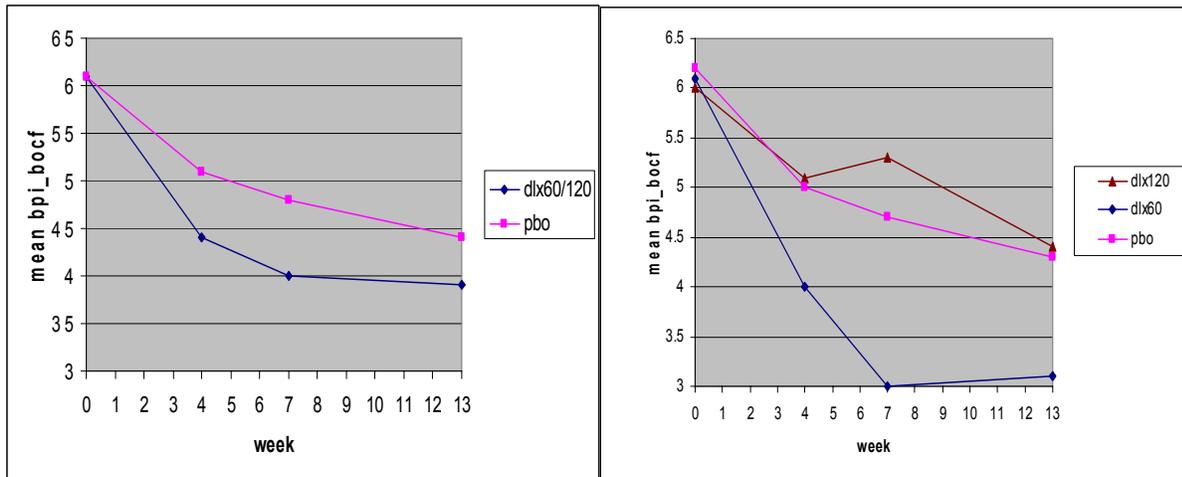
(Source: Graph created by Dr. Yongman Kim, statistical reviewer)

Figure 18: Continuous responder curves - HMEN



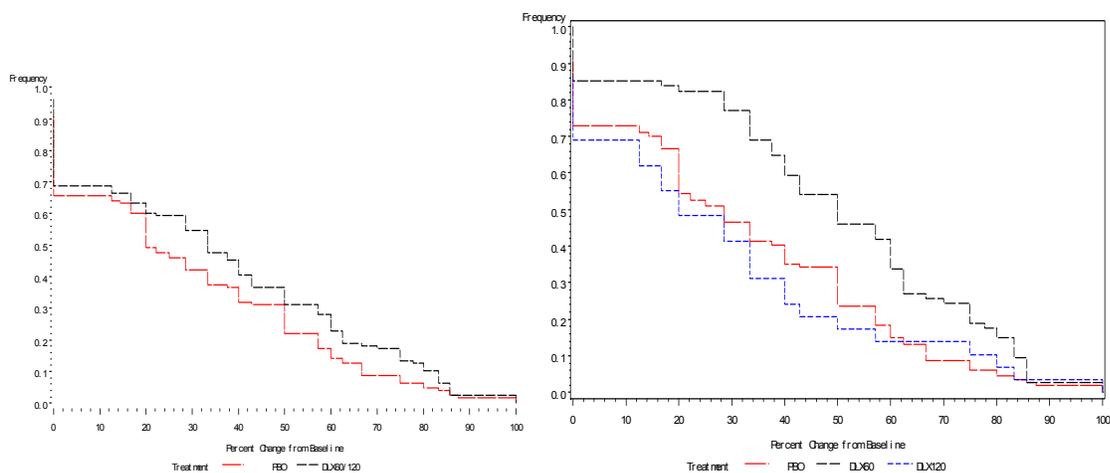
(Source: Graph created by Dr. Yongman Kim, statistical reviewer)

Figure 19: Mean plot for BPI BOCF – HMFG



(Source: Graph created by Dr. Yongman Kim, statistical reviewer)

Figure 20: Continuous responder curves - HMFG



(Source: Graph created by Dr. Yongman Kim, statistical reviewer)

6.1.5 Analysis of Secondary Endpoints(s)

A gatekeeper strategy was used to sequentially test the secondary hypotheses at 0.05 two-sided level of significance until a null hypothesis in the sequence failed to be rejected. The sequential testing was conducted in the following order:

- 1) Comparison between duloxetine 60 mg QD (HMEO, HMGC), duloxetine 60 to 120 mg QD (HMEP, HMEN, and HMFG), and placebo on the endpoint PGI-Improvement
- 2) Comparison between duloxetine 60 to 120 mg QD and placebo on the change from baseline to endpoint on the WOMAC physical function score (HMEP and HMFG), or the comparison between duloxetine 60 mg QD (HMEO and HMGC) or 60 to 120 mg QD (HMEN) and placebo on the change from baseline to endpoint on the RMDQ-24 total score

Similar to the primary efficacy measure, the gatekeeper measures were also analyzed using MMRM, ANCOVA/LOCF, and ANCOVA/BOCF.

The applicant found superiority of duloxetine 60 to 120 mg when compared with placebo for PGI-I (HMEP and HMEN, using BOCF), RMDQ-24 (HMEN, using BOCF) and WOMAC physical function (HMEP, using BOCF).

Table 62: Secondary Gatekeeper assessments of efficacy

**Table 2.7.3.14. Secondary Gatekeeper Assessment of Efficacy
 All Randomized Patients
 13-Week Treatment Phase
 Study F1J-MC-HMFG, Study F1J-MC-HMEP, and Study F1J-MC-HMEN**

Study	Measure	Analysis	Treatment Group ^a	LSMeans (SE)	p-Value
HMFG	PGI-Improvement	LOCF ^b	DLX 60/120 QD	2.93 (0.12)	.164
			Placebo	3.14 (0.12)	
		BOCF ^c	DLX 60/120 QD	2.91 (0.10)	.074
		Placebo	3.12 (0.10)		
		MMRM	DLX 60/120 QD	2.77 (0.11)	.020
			Placebo	3.07 (0.10)	
HMFG	WOMAC physical function subscale score ^h	LOCF ^b	DLX 60/120 QD	-12.69 (1.15)	.016
			Placebo	-9.43 (1.08)	
		BOCF ^c	DLX 60/120 QD	-11.17 (1.17)	.149
		Placebo	-9.20 (1.10)		
		MMRM	DLX 60/120 QD	-14.83 (1.13)	.004
			Placebo	-10.83 (1.05)	
HMEP	PGI-Improvement	LOCF ^b	DLX 60/120 QD	2.38 (0.12)	.001
			Placebo	2.91 (0.12)	
		BOCF ^c	DLX 60/120 QD	2.70 (0.12)	.026
		Placebo	3.04 (0.11)		
		MMRM	DLX 60/120 QD	2.25 (0.12)	<.001
			Placebo	2.88 (0.11)	
HMEP	WOMAC physical function subscale score ^d	LOCF ^b	DLX 60/120 QD	-16.36 (1.18)	.001
			Placebo	-11.18 (1.18)	
		BOCF ^c	DLX 60/120 QD	-13.57 (1.27)	.028
		Placebo	-9.88 (1.22)		
		MMRM	DLX 60/120 QD	-17.96 (1.24)	<.001
			Placebo	-12.05 (1.16)	
HMEN	PGI-Improvement	LOCF ^b	DLX 60/120 QD	2.82 (0.13)	.014
			Placebo	3.23 (0.13)	
		BOCF ^c	DLX 60/120 QD	2.80 (0.12)	.001
		Placebo	3.29 (0.11)		
		MMRM	DLX 60/120 QD	2.59 (0.12)	<.001
			Placebo	3.16 (0.11)	
HMEN	RMDQ-24 total score ^{e,f}	LOCF ^b	DLX 60/120 QD	-3.60 (0.51)	.009
			Placebo	-1.93 (0.50)	
		BOCF ^c	DLX 60/120 QD	-3.24 (0.48)	.042
		Placebo	-2.00 (0.47)		

(Source: Applicant's table 2.7.3.14 from SCE, pp. 69-70)

For the 60 mg duloxetine, fixed-dose trial, HMGC, submitted with the 120-day safety update, superiority to placebo was demonstrated for PGI-I (BOCF, $p=0.003$) but not for RMDQ-24 (BOCF, $p=0.073$).

6.1.6 Other Endpoints

Other secondary endpoints for the primary chronic pain trials included the following:

- Percentage of subjects with 30% and 50% reduction in the 24-hour average pain (11-point Likert)
- Patient's Global Impressions of improvement (PGI - Improvement) assessed at Visits 3, 4, 5, and end of treatment
- Patient's Global Impressions of disease severity (PGI – Severity) assessed at Visit 2
- Clinical Global Impressions of disease severity (CGI – Severity) assessed at Visits 3, 4, 5, and end of treatment
- WOMAC pain, stiffness, physical function subscales assessed at Visits 3, 4, 5, and end of treatment (HMEP and HMFG)
- Severity of pain and the interference of pain on function measured by the Brief Pain Inventory scale (BPI) at Visits 3, 4, 5, and end of treatment visit
- Suicidal risk using the Beck Depression Inventory-II (BDI-II) at each clinic visit
- Anxiety and depression using the Hospital Anxiety and Depression Scale (HADS) assessed at Visits 2, 5, and end of treatment
- Health outcome using Euro-QoL Questionnaire (EQ-5D) assessed at Visits 2, 5, and end of treatment
- Quality of life using Short-Form Health Survey (SF-36) assessed at Visits 2, 5, and end of treatment
- Sleep assessment using The Athens Insomnia Scale (AIS), HMEN trial
- Effect of general health and symptom severity on work productivity and regular activities using Work Productivity and Activity Impairment Instrument (WPAI), HMEN trial

For these secondary endpoints, duloxetine-treated patients on 60 to 120 mg QD showed significantly greater improvement when compared with placebo on most of the BPI items and few of the SF-36.

For the 60 mg fixed-dose duloxetine trial, HMGC, superior efficacy compared to placebo was demonstrated for BPI severity and interference; 50% response rate, based on average pain rating and weekly means of 24-hour average pain; worst pain and night pain ratings; and POMS.

The secondary endpoints were considered acceptable to explore the effect of treatment as based on different analysis of pain, different domains related to pain, and the depression effect on pain.

6.1.7 Subpopulations

Subgroup analysis performed for the primary efficacy variable in HMEN, HMEP, HMFG, HMGC and HMEO included age, gender, ethnic origin, baseline severity of pain, duration of pain, NSAID use, as well as Quebec Task Force Class and History of CLBP surgery (in CLBP trials). No significant treatment-by-subgroup interactions were observed with the exception of the following in HMEP trial:

- In HMEP, duloxetine-treated patients, who were over 65 years of age, had a significantly greater decrease in pain score when compared with placebo-treated patients. Differences between age subgroups were not observed in HMEN or HMEO. This isolated finding is unlikely to effect the interpretation of the efficacy results.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Duloxetine 60 mg QD is the approved dose for the treatment of patients with DPN and FM in the Cymbalta US label. The label further describes that doses greater than 60 mg/day confer no additional benefit and are associated with a higher rate of adverse reactions.

The primary chronic pain trials in OA and CLPB, assessed efficacy of duloxetine 20mg (HMEO trial only), duloxetine 60 mg and duloxetine 120 mg. The findings from these trials also suggest that duloxetine 60 mg QD is the lowest effective dose in patients with OA and CLBP. Although HMFG, HMEP, and HMEN assessed efficacy of a flexible dose of duloxetine 60/120 mg QD, the efficacy of 60 mg QD could still be assessed given that the trials were of fixed-dose design until Week 7 (patients receiving either duloxetine 60 mg QD or placebo). The applicant used ANCOVA model with LOCF imputation for this analysis. The patients sampled, included only those who remained on duloxetine 60 mg QD during the placebo-controlled period (that is, patients who switched to duloxetine 120 mg QD were excluded from the analysis), completed the first seven weeks of trial, and had at least one BPI measure after seven weeks.

Table 63: BPI pain item between and within group change at Week 7 and Week 13

PRIMARY CHRONIC PAIN STUDIES					
Study/Treatment	N	Baseline BPI 24-hour average pain score	Change at Week 7		Change between Week 7 to Week 13
		Mean (SD)	Mean (SD) within-group p-value ⁺	p-val ⁺⁺ (DLX vs PBO)	Mean (SD) within-group p-value ⁺
HMFG					
DLX60QD	68	6.27 (1.43)	-3.38 (1.52); p<.001	<.001	0.04 (1.37); p=.891
PLACEBO	116	6.14 (1.26)	-1.41 (1.75); p<.001		-0.47 (1.30); p<.001
HMEP					
DLX60QD	45	6.18 (1.66)	-2.51 (2.15); p<.001	.022	-0.16 (1.43); p=.569
PLACEBO	102	6.31 (1.60)	-1.65 (2.10); p<.001		-0.24 (1.49); p=.084
HMEN					
DLX60QD	63	5.97 (1.77)	-2.83 (1.83); p<.001	<.001	-0.06 (1.72); p=.562
PLACEBO	102	5.95 (1.66)	-1.14 (2.05); p<.001		-0.33 (1.75); p=.071
HMEO					
DLX60QD	87	5.90 (1.53)	-2.29 (2.06); p<.001	.057	-0.25 (1.33); p=.130
PLACEBO	90	6.22 (1.59)	-1.81 (1.99); p<.001		-0.40 (1.67); p=.020

(Source: Applicant's table 2.7.3.16 from SCE, p. 80)

As described in Section 6.1.4, when Dr. Kim analyzed the duloxetine 60 mg dose only based on data up to Week 7 for HMEN and HMFG trials using ANCOVA/BOCF, the duloxetine 60 mg was superior to placebo in reducing pain intensity at Week 7 (HMEN p=0.003, HMFG p<0.001).

The fixed-dose, 60 mg duloxetine trial (HMGC) found by the applicant, and confirmed by Dr. Yongman Kim to be a positive trial, showed superiority of duloxetine 60 mg to placebo at Week 12 in reducing pain intensity.

A mean plot analyses performed by Dr. Yongman Kim of the BPI score for the three treatment groups (placebo, duloxetine 60 mg, and duloxetine 120 mg) using BOCF, for HMEN and HMFG trials, is also described in Section 6.1.4. These analyses showed that duloxetine 120 mg dose group (60 mg for seven weeks followed by 120 mg for six weeks) presented similar to placebo and is unlikely to have contributed to the efficacy of the 60 mg dose when the combined 60/120 mg dose was shown to be effective.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Maintenance of the duloxetine analgesic effect was evaluated in long-term FM trials (HMEH, HMCJ, and HMEF) and DPNP trials (HMBT and HMEM).

From the primary chronic pain trials, a long-term, dose-blinded (duloxetine 60 mg QD or duloxetine 120 mg QD) extension phase of HMEN (CLBP trial) evaluated the persistency of efficacy over 12 month period. The main objective of the trial was to evaluate the maintenance of effect of duloxetine in patients with CLBP as measured by BPI 24-hour average pain ratings during a 41-week, uncontrolled, double-blind extension treatment phase after 13 weeks of placebo-controlled acute treatment. Detailed description of the trial design and analyses can be found in Section 5.3.2.

The applicant performed an analysis of the mean change from baseline to endpoint for BPI average pain in acute phase duloxetine responders. Acute phase duloxetine responders were defined as patients on 60 mg duloxetine who achieved greater than or equal to a 30% reduction on BPI average pain at the end of the 13-week, double-blind, placebo-controlled acute treatment phase (Visit 5]) and who stayed on duloxetine 60 mg or 120 mg QD during the extension treatment phase.

The applicant found that for acute phase duloxetine responders, the mean change in BPI average pain was -0.97 and the upper bound of the one-sided 97.5% CI was -0.45, which was less than the pre-specified, non-inferiority margin of 1.5 points (p<.001). For acute phase duloxetine 60 mg QD responders, the mean change in BPI average pain was -0.59 and the upper bound of the one-sided 97.5% CI was 0.05, which was less than the pre-specified, non-inferiority margin of 1.5 points (p<.001). The upper limit of the one-sided 97.5% CI was less than zero for acute phase duloxetine responders, representing a reduction in pain for these patients during the extension treatment phase when compared to pain severity at the end of the acute treatment phase.

Table 64: BPI average pain from baseline to endpoint – acute phase duloxetine responders, HMEN extension phase

Table HMEN.11.5. Brief Pain Inventory Average Pain Mean Change from Baseline to Endpoint Acute Phase Duloxetine Responders Extension Treatment Phase

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BPI Average Pain																
Therapy	N	Baseline					Endpoint					Change				
		Mean	SD	Median	Min	Max	Mean	SD	Median	Min	Max	Mean	SD	Median	Min	Max
DLX_DLX60/120	58	2.86	1.71	3.0	0.0	8.0	1.90	1.67	1.0	0.0	6.0	-0.97	1.72	-1.0	-6.0	3.0
1- Sided 97.5% CI : (--, -0.45) t = -10.94 p = <.001																

(Source: Applicant's table HMEN 11.5. from trial report, p. 64)

6.1.10 Additional Efficacy Issues/Analyses

Additional analyses evaluating the efficacy of the duloxetine 60 mg only dose versus placebo at Week 7 and Week 13 as well as a plot analysis of the BPI for the three different dose groups, placebo, DLX 60 mg (DLX 60 mg for 13 weeks), and DLX 120 mg (DLX 60 mg for seven weeks followed by DLX 120 mg for six weeks) are presented in Section 6.1.4. The discussion focuses on whether there is sufficient evidence of efficacy for the duloxetine 60 mg dose and whether dose increase to 120 mg confers any additional benefit.

7 Review of Safety

Safety Summary

The emphasis in the safety review for this application was to determine whether the safety profile of duloxetine in the OA and CLBP population differed from the already-established safety profile in other populations.

The size of the analysis population, shown in the table below, was adequate to assess safety for the intended use of duloxetine to treat chronic pain.

Table 65: Exposure to duloxetine

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

Review of safety data from OA and CLBP trials found no new or unexpected safety signals. There was a difference in the incidence of SAEs observed between treatment groups, 2.3% for duloxetine-treated and 1.2% for placebo-treated patients. While there was a treatment-group difference in the incidence of SAEs, no significant difference between treatment groups was observed for individual SAEs. Significantly more duloxetine-treated patients discontinued due to adverse events compared with placebo-treated patients, 17.0% versus 6.0%. The most common reasons for early discontinuation were gastrointestinal (nausea) and sleep disturbance (somnolence/insomnia) related symptoms. Significantly more duloxetine-treated patients (62.0%) than placebo-treated patients (50.0%) experienced at least one treatment-emergent adverse event (TEAE). Patients in the OA and CLBP trials

experienced the following common adverse events significantly more frequently with duloxetine than placebo treatment: nausea, insomnia, dizziness, dry mouth, somnolence, constipation, and fatigue. Most of these events were dose dependant.

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

In conclusion, no new safety concerns specific to the OA and CLBP patient population were identified during the review of the safety data included in this application. The overall safety profile in OA and CLBP patients resembled the established safety profile for the drug described in the current product label.

7.1 Methods

In support of this New Drug Application, the applicant provided safety data for duloxetine from four new Phase 3 chronic pain trials. Two were conducted in an OA population (HMEP and HMFG) and two were conducted in CLBP population (HMEN and HMEO). These chronic pain trials form the *primary safety analysis set*. In addition, long-term efficacy and safety data for duloxetine treatment of patients with CLBP were obtained from the completed extension phase of HMEN, presented as the *primary long-term analyses set*. Trial design, treatment groups and dosing for the primary chronic pain trials are summarized in Table 1, Section 5.1 of this review.

In addition, the applicant also presented safety information from placebo-controlled trials, all indications, excluding OA and CLBP (all placebo-controlled analysis set) and

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from all trials, all indications duloxetine exposures (all duloxetine exposures analysis set). A list of these trials is included in the following two tables.

Table 66: All placebo-controlled analysis set

Table 3.1. Studies Included in the All Placebo-Controlled Analyses Set

Indication	Study codes
Chronic Pain	F1J-MC-HMEP; F1J-MC-HMEO, F1J-MC-HMEN
Fibromyalgia	F1J-MC-HMCA, F1J-MC-HMBO, F1J-MC-HMEF, F1J-MC-HMCJ
GAD	F1J-MC-HMBR, F1J-MC-HMDT, F1J-MC-HMDU, F1J-MC-HMDW
DPNP	F1J-MC-HMAVa acute, F1J-MC-HMAVb acute, F1J-MC-HMAW acute
MDD	F1J-MC-HMAG, F1J-MC-HMAH, F1J-MC-HMAL, F1J-MC-HMAQa, F1J-MC-HMAQb, F1J-MC-HMATa, F1J-MC-HMATb, F1J-MC-HMAYa, F1J-MC-HMAYb, F1J-MC-HMBHa, F1J-MC-HMBHb, F1J-MC-HMBV, F1J-US-HMCB, F1J-US-HMCR, F1J-MC-HQAC (also referred to as H8I-MC-HQAC), F1J-BI-HMDH
SUI	F1J-MC-SAAW, F1J-MC-SBAB acute, F1J-MC-SBAF acute, F1J-MC-SBAM acute, F1J-MC-SBAT, F1J-MC-SBAV, F1J-MC-SBAX, F1J-MC-SBBA, F1J-EW-SBCC, F1J-MC-SBBR acute, F1J-MC-SBBT, F1J-MC-SBBU, F1J-MC-SAAI, F1J-MC-SAAL, F1J-MC-SBCM
Other LUTD	F1J-MC-SAAA, F1J-MC-SAAB, F1J-MC-SAAH, F1J-MC-SBBL, F1J-MC-SBBO acute

(Source: Applicant’s table from Module 5.3.5.3, Section 3, p.24)

Table 67: All duloxetine exposure analysis set

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Table 4.1. Studies Included in the Overall Duloxetine Exposures Analyses Set

Indication	Study codes
Chronic Pain	F1J-MC-HMEP; F1J-MC-HMEO, F1J-MC-HMEN
Fibromyalgia	F1J-MC-HMCA, F1J-MC-HMBO, F1J-MC-HMEF, F1J-MC-HMCJ, F1J-MC-HMEH
GAD	F1J-MC-HMBR, F1J-MC-HMDT, F1J-MC-HMDU, F1J-MC-HMDW, F1J-MC-HMDV
DPNP	F1J-MC-HMAVa acute, F1J-MC-HMAVb acute, F1J-MC-HMAW acute, F1J-MC-HMAVa extension, F1J-MC-HMAVb extension, F1J-MC-HMAW extension, F1J-MC-HMBT, F1J-MC-HMEM, F1J-MC-HMDY
MDD	F1J-MC-HMAG, F1J-MC-HMAH, F1J-MC-HMAI, F1J-MC-HMAQa, F1J-MC-HMAQb, F1J-MC-HMATa, F1J-MC-HMATb, F1J-MC-HMAYa, F1J-MC-HMAYb, F1J-MC-HMBHa, F1J-MC-HMBHb, F1J-MC-HMBV, F1J-US-HMCB, F1J-US-HMCR, F1J-MC-HQAC (also referred to as H8I-MC-HQAC), F1J-BI-HMDH, F1J-EW-E001, F1J-MC-HMAU, F1J-MC-HMBC, F1J-MC-HMBU, F1J-US-HMBY, F1J-US-HMBZ, F1J-MC-HMCM, F1J-MC-HMCN, F1J-MC-HMCQ, F1J-AA-HMCV, F1J-MC-HMCX, F1J-MC-HMCY, F1J-AY-HMCZ, F1J-MC-HMDD, F1J-MC-HMDG, F1J-MC-HMDG/HMED, F1J-US-HMDR
SUI	F1J-MC-SAAW, F1J-MC-SBAB acute, F1J-MC-SBAF acute, F1J-MC-SBAM acute, F1J-MC-SBAT, F1J-MC-SBAV, F1J-MC-SBAX, F1J-MC-SBBA, F1J-EW-SBCC, F1J-MC-SBBR acute, F1J-MC-SBBT, F1J-MC-SBBU, F1J-MC-SAAI, F1J-MC-SAAL, F1J-MC-SBAB extension, F1J-MC-SBAF extension, F1J-MC-SBAM extension, F1J-MC-SBBR extension, F1J-EW-SBCC extension, F1J-MC-SBAV/SBAW, F1J-MC-SBAT/SBAU, F1J-MC-SBAY, F1J-MC-SBCT, F1J-US-SBCD, F1J-MC-SBCM
Other LUTD	F1J-MC-SAAA, F1J-MC-SAAB, F1J-MC-SAAH, F1J-MC-SBBL, F1J-MC-SBBO acute, F1J-MC-SBBO extension, F1J-MC-SBBX

(Source: Applicant's table from Module 5.3.5.3, Section 4, p.1538)

A Phase 3, fixed-dose trial in CLBP population (HMGc) was submitted with the 120-day safety update and is discussed separately in Section 7.7.1.1 of this review.

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

Refer to Table 1, Section 5.1 and Tables 37 and 38, Section 7.1 of this NDA review.

7.1.2 Categorization of Adverse Events

Adverse events were collected at every visit, captured as actual terms and coded to Medical Dictionary for Regulatory Activities (MedDRA, Version 11.0) terms. Review of the coding of adverse events, comparing the verbatim terms to the preferred terms used by investigators and patients, showed that it was performed correctly.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

Safety data from placebo-controlled clinical trials for OA and CLBP (HMEP, HMEO, HMFG and HMEN) were pooled to form the *primary placebo-controlled analysis set* for this submission. For the *primary long-term analyses set* (HMEN extension phase), two treatment groups were included: PBO_DLX60/120 and DLX_DLX60/120.

Data pools were also formed using data from all placebo-controlled duloxetine trials, excluding the OA and CLBP trials *all placebo-controlled analyses set*. Data from the duloxetine groups were pooled to form the duloxetine group and data from all the placebo groups were pooled to form the placebo group.

Similarly, data from all duloxetine groups from all trials, regardless of indication, were pooled from placebo-controlled, active-comparator controlled trials, open-label trials and all other trials with duloxetine exposures to form the *all duloxetine exposures analyses set*.

The following table summarizes the safety pools analyses sets for this application.

Table 68: Safety pools analyses sets

Table 2.7.4.2. Analyses Sets in the Summary of Clinical Safety

Analyses Set	Content	Treatment Group(s)
Primary placebo-controlled	Placebo-controlled studies of OA and CLBP	Placebo and Duloxetine
Primary long-term treatment	Data from patients who entered extension phase of Study HMEN	Duloxetine: 60 mg or 120 mg
All placebo-controlled	All placebo-controlled studies, indications (FM, DPNP, GAD, LUTD, MDD) completed as of 20 November 2008. This analysis set excludes OA and CLBP study data.	Placebo and Duloxetine
All duloxetine exposures	All completed studies, from controlled and open-label studies in all indications (OA, CLBP, FM, DPNP, GAD, LUTD, MDD) completed as of 20 November 2008	Duloxetine

(Source: Applicant's table 2.7.4.2 from SCS, page 14)

The pooling of safety data from the OA and CLBP trials is acceptable and necessary to support the application. However, data from the duloxetine 60 mg dose group was pooled together with the duloxetine 120 mg dose group to compare the safety of the duloxetine group as a whole to the placebo group. Data presented this way do not allow for comparison of safety between different duloxetine doses.

In order to adequately analyze the safety of duloxetine in comparison to placebo and assess for dose response the applicant was asked to provide pooled analysis for the primary chronic pain trials separately for the first seven weeks and the second six weeks of the double-blind treatment phase; for the first seven-week analysis, to compare safety between patients who were treated with placebo, duloxetine 20mg QD, and duloxetine 60 mg QD; for the second six weeks, to compare safety between patients who received placebo, duloxetine 20mg QD, duloxetine 60 mg QD, and duloxetine 120 mg QD.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

Exposure to drug

Primary Placebo-Controlled Analysis Set

In the primary chronic pain trials (HMEN, HMEP, HMFG and HMEO), 641 patients were exposed to duloxetine doses of 20, 60, and 120 mg once daily for a mean of 74.9 days (76.6 days for the DLX 20mg group, 68.1 days for the DLX 60 mg group, and 53.4 days for the DLX 120 mg dose group) and 486 patients were exposed to placebo for a mean of 82.9 days. Duloxetine-treated patients had a shorter mean duration of exposure than placebo-treated patients.

The overall, trial medication exposure in this analysis set represents 131.5 patient-years of exposure to duloxetine and 110.3 patient-years of exposure to placebo.

Table 69: Trial drug exposure – Primary Chronic Pain Trials

**Table 2.7.4.3. Study Drug Exposure
 All Randomized Patients
 Primary Placebo-Controlled Analyses Set**

Variable	Placebo (N=486)	Duloxetine (N=641)	Total (N=1127)
Duration of Exposure (Days)			
No. Patients	486	641	1127
Mean	82.89	74.92	78.35
STD	22.21	30.76	27.67
Maximum	145.00	160.00	160.00
Median	91.00	91.00	91.00
Minimum	0.00	0.00	0.00
Patient years	110.29	131.47	241.76

(Source: Applicant's table 2.7.4.3 from SCS, page 19)

As illustrated on the table below, the proportion of subjects exposed to duloxetine for more than 90 days was higher for the duloxetine 20mg (50%) and duloxetine 60 mg (40%) compared to duloxetine 120 mg (23%) dose group. This is consistent with the design of three of the four trials where patients did not have the potential to titrate to 120 mg until 60 days after treatment initiation with 60 mg duloxetine.

Table 70: Trial drug exposure by dose received – Primary Chronic Pain Trials

**Table 1.1. Study Drug Exposure by Dose Received
 All Randomized Patients
 Primary Placebo-Controlled Analyses Set - Chronic Pain**

Variable	DLX20mgQD (N=59)	DLX60mgQD (N=470)	DLX120mgQD (N=215)	Any DLX dose (N=641)
Duration of Exposure (Days)				
No. Patients	59	470	215	641
Mean	76.61	68.12	53.42	74.92
STD	30.14	30.42	28.09	30.76
Maximum	137.00	160.00	100.00	160.00
Median	91.00	88.00	42.00	91.00
Minimum	1.00	0.00	0.00	0.00
Patient years	12.38	87.66	31.45	131.48
Duration of Exposure n(%)				
No. Patients	59	470	215	641
0-7	3 (5.1)	32 (6.8)	8 (3.7)	41 (6.4)
8-14	2 (3.4)	11 (2.3)	11 (5.1)	20 (3.1)
15-30	3 (5.1)	24 (5.1)	17 (7.9)	40 (6.2)
31-60	5 (8.5)	129 (27.4)	108 (50.2)	54 (8.4)
61-90	16 (27.1)	81 (17.2)	22 (10.2)	145 (22.6)
91-120	29 (49.2)	190 (40.4)	49 (22.8)	337 (52.6)
>=121	1 (1.7)	3 (0.6)	0 (0)	4 (0.6)

(Source: Applicant's table 1.1 from 8/14/09 response to information request, page 11)

Additionally, another 181 patients from HMEN were exposed to duloxetine (blinded to dose) for up to 41 weeks during the extension phase of the trial. In this analysis set, 83 DLX_DLX60/120-treated patients (patients treated with duloxetine during the acute phase and entered the extension phase at the dose they completed the acute phase) were exposed to duloxetine for a mean of 243.37 days (median: 285), and 55.3 patient-years of exposure. Overall, patients in the long-term exposures analyses set were exposed to duloxetine for approximately six months longer than patients in the primary placebo-controlled analyses set.

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Table 71: Trial drug exposure –HMEN Extension Treatment Phase

Table HMEN.12.1. Study Drug Exposure
 All Randomized Patients
 Extension Treatment Phase

Variable	PLA DLX60/120 (N = 98)	DLX DLX60/120 (N = 83)	Total (N = 181)
Duration of Exposure (Days)			
NO. SUBJECTS	98	83	181
MEAN	224.49	243.37	233.15
STD	94.47	84.82	90.42
MAXIMUM	336.00	369.00	369.00
MEDIAN	281.00	285.00	283.00
MINIMUM	1.00	42.00	1.00
Patient Years	60.23	55.30	115.54

(Source: Applicant’s table 12.1 from HMEN extension phase trial report, page 121)

All Placebo-Controlled Analysis Set

In the all placebo-controlled analysis set (all indications, excluding OA and CLBP trials), 9685 patients were exposed to duloxetine for a mean of 63.6 days (median: 57 days) and 7010 patients were exposed to placebo for a mean of 67.2 days (median: 57 days). Trial medication exposure in this analysis set represents 1687 patient-years.

All Duloxetine Exposures Analysis Set

In the all duloxetine exposures analysis set (all indications), 29,237 patients were exposed to duloxetine for a mean of 177.7 days and a median of 86 days. Trial medication exposure in this analysis set represents 14,223 patient-years.

More than 28,000 patients were exposed to duloxetine in clinical studies/trials across all indications. In addition to clinical trials, more than 13 million patients have been exposed to duloxetine based on postmarketing experience.

In conclusion, the number of subjects exposed to duloxetine to date, the doses and the duration of exposure are adequate to assess safety for the intended use of duloxetine to treat chronic pain.

Demographics

In the primary placebo-controlled analysis set, no significant differences were observed in the demographic characteristics between the placebo and duloxetine treatment groups. The majority of patients were Caucasian (duloxetine: 83.3%, placebo: 84%) and female (duloxetine: 62.1%, placebo: 66.9%). The mean age of duloxetine-treated patients was 56.8 years and placebo-treated patients was 57.5 years.

Table 72: Demographic characteristics for the primary chronic pain trials (HMEN, HMEP, HMFG and HMEO)

**Table 2.7.4.6. Patient Demographics and Baseline Characteristics
 All Randomized Patients
 Primary Placebo-Controlled Analyses Set**

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Variable	PLACEBO (N=486)	DULOXETINE (N=641)	TOTAL (N=1127)
ORIGIN: NO. (%)			
African	25 (5.1%)	35 (5.5%)	60 (5.3%)
Caucasian	408 (84.0%)	534 (83.3%)	942 (83.6%)
East Asian	7 (1.4%)	2 (0.3%)	9 (0.8%)
Hispanic	42 (8.6%)	64 (10.0%)	106 (9.4%)
Native American	3 (0.6%)	3 (0.5%)	6 (0.5%)
West Asian	1 (0.2%)	3 (0.5%)	4 (0.4%)
AGE: YRS			
No. Patients	486	641	1127
Mean	57.46	56.77	57.07
Median	57.73	58.20	57.91
Standard Dev.	12.50	13.56	13.11
Minimum	21.20	19.45	19.45
Maximum	90.94	85.42	90.94
GENDER: NO. (%)			
Female	325 (66.9%)	398 (62.1%)	723 (64.2%)
Male	161 (33.1%)	243 (37.9%)	404 (35.8%)
HEIGHT: CM			
No. Patients	486	641	1127
Mean	166.42	166.87	166.67
Median	165.00	167.00	166.00
Standard Dev.	10.35	10.18	10.25
Minimum	134.00	134.00	134.00
Maximum	197.00	198.00	198.00
WEIGHT: KG			
No. Patients	486	641	1127
Mean	80.98	81.63	81.35
Median	79.55	80.50	80.00
Standard Dev.	15.09	15.82	15.50
Minimum	42.40	45.10	42.40
Maximum	127.60	139.70	139.70

(Source: Applicant's table 2.7.4.6 from CSS, pp. 22-23)

In the primary long-term analyses set, the majority of patients also were Caucasians (DLX_DLX60/120: 78.3%) and females (DLX_DLX60/120: 65.1%). The mean age of DLX_DLX60/120-treated patients was 51.2 years.

The percentage of males in the primary chronic pain trials (acute: 37.9%, long-term: 35.9%) was greater than for all indications combined in the all placebo-controlled analysis set (18.7%) and the all duloxetine analysis set (19.1%). This could be explained by the large number of female patients studied in the stress urinary incontinence (SUI) and fibromyalgia (FM) trials. Additionally, the mean age was higher in the primary placebo-controlled analyses set, which is likely driven by the older patient population in the OA trials (mean: 62.3 years in HMEP; mean: 62.5 years in HMFG). The remaining patient characteristics were consistent between the different analysis sets.

7.2.2 Explorations for Dose Response

Duloxetine 60 mg QD is the approved dose for treatment of patients with DPNP and FM in the Cymbalta US label.

In the DPN and FM trials, the following duloxetine doses were tested: 20 mg, 60 mg, and 120 mg QD. These doses were selected based on trials for other indications. Among the studied doses in the DPNP trials, 60 mg QD was found to be the lowest effective dose. Data from FM trials indicated that 60 mg daily is an effective dose, but the lowest effective dose for this indication may be less than 60 mg daily. A postmarketing commitment protocol for a trial to determine the lowest minimum effective dose in FM patients was submitted to IND 63,615 in March 2009.

Three of the primary chronic pain trials, HMFG, HMEP, and HMEN, were designed and powered to assess efficacy of a flexible dose of duloxetine 60/120 mg QD. Because the trials were fixed-dose until Week 7 (patients received either duloxetine 60 mg QD or placebo), the applicant performed efficacy analysis for the 60 mg QD only dose, Baseline to Week 7 and Week 7 to Week 13. The applicant's findings from these analyses suggest that duloxetine 60 mg QD was the lowest effective dose in patients with OA and CLBP. These findings were confirmed when the analyses were repeated using the Division's preferred statistical methods.

With regard to the 120 mg duloxetine dose, there was no statistically significant difference observed in favor of the 120 mg dose compared with 60 mg dose, across all fixed-dose chronic pain trials (DPNP, FM, and CLBP). Nevertheless, the applicant claims that patients from HMFG and HMEN trials who did not respond to duloxetine 60 mg QD after the initial seven weeks of treatment with duloxetine 60 mg QD and had their dose escalated to 120 mg QD, achieved significant improvement during the subsequent six weeks of treatment. These findings were not confirmed when the analyses were repeated using the Division's preferred statistical methods. For detailed discussion regarding the efficacy analyses and findings refer to Section 6 of this review.

From a safety prospective, in the primary placebo-controlled analysis set, patients administered duloxetine 120 mg experienced the highest frequency of TEAEs than

other treatment groups during the first seven weeks of treatment, 71% for DLX 120 mg, 52% for DLX 60 mg, 59% for DLX 20mg, and 37% for placebo. When comparing the 60 mg and 120 mg duloxetine treatment groups, the following TEAEs were experienced significantly more frequently by duloxetine 120 mg treated patients than duloxetine 60 mg treated patients: insomnia (17% DLX 120 mg vs. 5% for DLX 60 mg), somnolence (12% DLX 120 mg vs. 4% for DLX 60 mg), constipation (11% DLX 120 mg vs. 6% for DLX 60 mg), and headache (8% DLX 120 mg vs. 3% for DLX 60 mg). During the second six weeks no dose relationship for TEAEs was observed.

When comparing the duloxetine 120 mg with 60 mg treatment groups in the all placebo controlled analysis set, patients administered duloxetine 120 mg experienced the following events more frequently than patients administered duloxetine 60 mg: dry mouth, constipation, somnolence, decreased appetite, hyperhydrosis.

For further details refer to Section 7.4.1.

7.2.3 Special Animal and/or In Vitro Testing

No new pre-clinical information was submitted in this sNDA.

7.2.4 Routine Clinical Testing

The safety testing for the OA and CLBP trials was adequate. The primary safety concerns for duloxetine including suicidality and hepatotoxicity were appropriately covered. Safety assessments included vital signs, physical examination, general hematology and chemistry testing (including liver function test), urinalysis, ECGs, questioning about adverse events, and suicidality assessment. Safety was assessed at pre-specified time points during clinic visits with acceptable frequency.

7.2.5 Metabolic, Clearance, and Interaction Workup

No new clinical pharmacology or preclinical information was submitted in this sNDA.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

See Section 2.4 of this review.

7.3 Major Safety Results

7.3.1 Deaths

No deaths were reported during the OA and CLBP trials, including the extension phase of HMEN. One death occurred ten days after HMEO trial discontinuation due to cardiopulmonary arrest.

Subject 001-0105 was an 82-year-old Caucasian female with history of low back pain, osteoarthritis, varicose veins, vitamin B12 deficiency, and incontinence. The patient was taking the following relevant concomitant medications prior to enrolment: vitamin B12, naproxen, and acetylsalicylic acid. She was randomized to duloxetine 120 mg QD for chronic low back pain in HMEO trial and began duloxetine treatment with 30mg QD on 17-Jan-2007. Duloxetine dose was escalated to 120 mg QD in two weeks. The patient was discontinued from the trial based on physician decision and due to adverse events of nausea, constipation, and heartburn. On 24 Feb 2007, the patient took the last dose of duloxetine in the taper phase. The patient was on duloxetine for a total of 39 days. On [REDACTED] (b) (6) the patient experienced 'cardiopulmonary arrest'. Cardiopulmonary resuscitation (CPR) was unsuccessful. No autopsy was performed.

The narrative provided for this patient does not suggest a relationship to trial drug.

In the all placebo controlled analysis set, one death in the duloxetine group and two in the placebo group were reported.

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Table 73: Listing of deaths – all placebo-controlled analysis set

Table 3.19. Listing of Deaths
 All Randomized Patients
 All Placebo-Controlled Analyses Set

Protocol	Indication	Treatment at Randomization	Inv	Patient	Age	Sex	Cause of Death (MedDRA Preferred Term)	Duration of Treatment until Event (Days)
HMAW	DPMP	PLA	104	1617	74	Male	Drowning	3
SBAX	SUI	DLX	905	5006	71	Female	Cerebrovascular accident	52
SBBA	SUI	PLA	106	1614	39	Female	Road traffic accident	215

(Source: Applicant's table 3.19 from CSS, p. 1216)

No patient deaths occurred in any of the fibromyalgia trials.

In the all duloxetine exposures, all indications analysis set 41 deaths were reported. The applicant investigated all deaths individually and determined that many of the deaths were related to the disease state being treated.

The causes of death do not appear to form an obvious pattern suggestive of specific organ toxicity.

Duloxetine carries the antidepressant class black box warning of increased risk for suicide in children and adolescents. There were two deaths by suicide in duloxetine trials for major depressive disorder. One occurred in the placebo group and one in the duloxetine group.

7.3.2 Nonfatal Serious Adverse Events

SAEs in the primary placebo-controlled chronic pain trials (HMEP, HMEN, HMFG and HMEO)

The SAEs for this pooled group were analyzed by treatment group and duloxetine dose received. Analyses were performed separately for the first seven weeks of the acute phase and for the last six weeks. The baseline for the first 7 weeks of treatment is pretreatment only (values obtained before randomization) whereas the baseline for the second 6 weeks of treatment is pre-treatment and the first 7 weeks. Of note, some patients from each treatment arm discontinued after the first 7 weeks of treatment and some patients were taking duloxetine 120 mg after having taken duloxetine 60 mg for 6 weeks. In addition, during the first 7 weeks of treatment, results for the duloxetine 20 mg and 120 mg treatment groups are from Study HMEO only.

As illustrated on the tables below, the frequency of SAEs during the first seven weeks and the last six weeks was similar, 1.3% and 1.2% respectively.

The proportion of patients experiencing an SAE was slightly higher for the duloxetine treatment groups compared to placebo treatment during the first seven weeks (1.7% for DLX 20mg and 60 mg and 1.8% for DLX 120 mg compared to 0.8% for placebo). A similar trend was observed during the last 6 weeks of the treatment period, except that patients who were taking duloxetine 20 mg did not report an SAE.

In the primary long-term analyses set, 5 of 98 (5.1%) PLA_DLX60/120-treated patients and 44 (4.8%) DLX_DLX60/120-treated patients experienced an SAE.

No dose-dependent relationship was observed. No trend for a specific system-organ-class involvement was noted.

My review of the narratives provided by the applicant for each SAE concurs with the conclusions of the investigators regarding the relation of the SAE and study drug administration.

Table 74: SAEs for the first seven weeks of the double-blind treatment phase - HMEP, HMEN, HMFG and HMEO trials

**Table 3.1. Serious Adverse Events by Decreasing Frequency
 MedDRA Preferred Term
 All Randomized Patients
 Primary Placebo-Controlled Analyses Set - Chronic Pain (first 7 weeks)**

MedDRA Preferred Term	PLACEBO	DLX20QD	DLX60QD	DLX120QD	TOTAL
	(N=486) n (%)	(N=59) n (%)	(N=470) n (%)	(N=112) n (%)	(N=1127) n (%)

Patients with >= 1 serious adverse event	4 (0.8)	1 (1.7)	8 (1.7)	2 (1.8)	15 (1.33)
Myocardial infarction	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.9)	2 (0.18)
Osteoarthritis	0 (0.0)	0 (0.0)	2 (0.4)	0 (0.0)	2 (0.18)
Ataxia	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.09)
Atrial fibrillation	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.09)
Dehydration	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.09)
Dizziness	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.09)
Drug intolerance	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.09)
Dyspnoea	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.09)
Gouty arthritis	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.09)
Hypertensive encephalopathy	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.09)
Hypoaesthesia	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	1 (0.09)
Hypoaesthesia oral	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	1 (0.09)
Memory impairment	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.09)
Muscular weakness	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.09)
Non-cardiac chest pain	0 (0.0)	1 (1.7)	0 (0.0)	0 (0.0)	1 (0.09)
Supraventricular tachycardia	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.09)
Transient ischaemic attack	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	1 (0.09)
Vertigo	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.09)

Wrist fracture	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.09)

(Source: Applicant's table 3.1 from 8/14/09 response to information request, pp. 17-18)

Table 75: SAEs for the second six weeks of the double-blind treatment phase - HMEP, HMEN, HMFG and HMEO trials

**Table 3.2. Serious Adverse Events by Decreasing Frequency
 MedDRA Preferred Term
 All Randomized Patients
 Primary Placebo-Controlled Analyses Set - Chronic Pain (Second 6 Weeks)**

MedDRA Preferred Term	PLACEBO	DLX20QD	DLX60QD	DLX120QD	TOTAL
	(N=423) n (%)	(N=45) n (%)	(N=268) n (%)	(N=173) n (%)	(N=909) n (%)

Patients with >= 1 serious adverse event	4 (0.9)	0 (0.0)	5 (1.9)	2 (1.2)	11 (1.21)
Osteoarthritis	0 (0.0)	0 (0.0)	1 (0.4)	1 (0.6)	2 (0.22)
Asthma	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.11)
Bronchitis	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.11)
Diarrhoea	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	1 (0.11)
Myocardial infarction	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.11)
Non-cardiac chest pain	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.11)
Peritonsillar abscess	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.11)
Pyelonephritis acute	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.11)
Rhinitis allergic	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.11)
Supraventricular tachycardia	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.11)
Transient ischaemic attack	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.11)
Wrist fracture	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.11)

(Source: Applicant's table 3.2 from 8/14/09 response to information request, page 19)

Similar to the primary analysis set, in the all placebo-controlled analysis set, the frequency of patients who experienced at least one SAE was similar with duloxetine treatment (142, 1.5%) and placebo treatment (91, 1.3%). Accidental overdose was the most frequently reported SAE for both duloxetine and placebo.

7.3.3 Dropouts and/or Discontinuations

Primary chronic pain trials

As presented in Section 6.1.3, the main reason for premature discontinuation from the primary chronic pain trials was an adverse event. Higher incidence of discontinuations due to adverse events was observed in the duloxetine-treated patients (17.2%) versus the placebo-treated patients (6.4%). The most common AEs leading to discontinuation as illustrated in the table below included nausea, insomnia, somnolence, constipation, anxiety and diarrhea.

Table 76: AEs reported as reason for discontinuation following revision of comments on case report forms – primary chronic pain trials

MedDRA Preferred Term	PLACEBO (N=486) n (%)	DULOXETINE (N=641) n (%)	Total (N=1127) n (%)
Patients Discontinued for any AE	31 (6.4)	110 (17.2)	141 (12.5)
Nausea	3 (0.6)	13 (2.0)	16 (1.4)
Insomnia	2 (0.4)	7 (1.1)	9 (0.8)
Constipation	1 (0.2)	5 (0.8)	6 (0.5)
Somnolence	0 (0.0)	6 (0.9)	6 (0.5)
Anxiety	1 (0.2)	4 (0.6)	5 (0.4)
Diarrhoea	2 (0.4)	3 (0.5)	5 (0.4)

(Source: Applicant's table APP. 2.7.4.17 form SCS, page 196)

For the flexible-dose trials (HMEN, HMFG, and HMEP), during the first 7 weeks, 12% of duloxetine 60 mg versus 3% of the placebo patients discontinued due to adverse event. During the second six weeks of the double-blind treatment, the discontinuation rate due to an AE was similar for the duloxetine 60 mg and placebo (~3%), but higher for the duloxetine 120 mg (8%). Duloxetine 120 mg group had the highest discontinuation rate, both due to any reason and due to adverse event.

In the primary placebo-controlled analysis set, during the first seven weeks of treatment, patients administered placebo had the lowest rate of premature discontinuation from the trial due to an AE (4%), duloxetine 20 mg and 60 mg had a similar rate (14% and 12%, respectively), and duloxetine 120 mg had the highest rate (21%).

Table 77: Discontinuations due to AEs, first 7 weeks – primary chronic pain trials

**Table 3.9. Discontinuation Due to Adverse Events by Decreasing Frequency
 MedDRA Preferred Term
 All Randomized Patients
 Primary Placebo-Controlled Analyses Set – Chronic Pain (First 7 Weeks)**

MedDRA Preferred Term	PLACEBO	DLX20QD	DLX60QD	DLX120QD	TOTAL
	(N=486) n (%)	(N=59) n (%)	(N=470) n (%)	(N=112) n (%)	(N=1127) n (%)

Patients Discontinued for any AE	19 (3.9)	8 (13.6)	56 (11.9)	23 (20.5)	106 (9.41)
Nausea	2 (0.4)	1 (1.7)	8 (1.7)	0 (0.0)	11 (0.98)
Insomnia	1 (0.2)	1 (1.7)	2 (0.4)	2 (1.8)	6 (0.53)
Diarrhoea	2 (0.4)	0 (0.0)	3 (0.6)	0 (0.0)	5 (0.44)
Somnolence	0 (0.0)	1 (1.7)	3 (0.6)	1 (0.9)	5 (0.44)
Anxiety	0 (0.0)	0 (0.0)	2 (0.4)	2 (1.8)	4 (0.35)
Dyspepsia	2 (0.4)	0 (0.0)	2 (0.4)	0 (0.0)	4 (0.35)
Erectile dysfunction	0 (0.0)	0 (0.0)	4 (0.9)	0 (0.0)	4 (0.35)
Vomiting	0 (0.0)	1 (1.7)	2 (0.4)	1 (0.9)	4 (0.35)
Asthenia	0 (0.0)	0 (0.0)	3 (0.6)	0 (0.0)	3 (0.27)
Dizziness	1 (0.2)	0 (0.0)	1 (0.2)	1 (0.9)	3 (0.27)
Fatigue	0 (0.0)	0 (0.0)	2 (0.4)	1 (0.9)	3 (0.27)
Back pain	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)	2 (0.18)
Confusional state	0 (0.0)	1 (1.7)	1 (0.2)	0 (0.0)	2 (0.18)
Constipation	0 (0.0)	1 (1.7)	1 (0.2)	0 (0.0)	2 (0.18)
Ejaculation disorder	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.9)	2 (0.18)
Hot flush	0 (0.0)	0 (0.0)	2 (0.4)	0 (0.0)	2 (0.18)
Lethargy	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.9)	2 (0.18)
Migraine	0 (0.0)	0 (0.0)	2 (0.4)	0 (0.0)	2 (0.18)
Palpitations	0 (0.0)	0 (0.0)	2 (0.4)	0 (0.0)	2 (0.18)
Abdominal distension	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.09)
Abdominal pain	0 (0.0)	1 (1.7)	0 (0.0)	0 (0.0)	1 (0.09)
Abdominal pain upper	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	1 (0.09)
Abnormal dreams	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.09)
Apathy	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	1 (0.09)
Arthralgia	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.09)
Ataxia	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.09)
Atrial fibrillation	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.09)
Blood creatine phosphokinase increased	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.09)
Bursitis	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	1 (0.09)
Decreased appetite	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	1 (0.09)
Diabetic neuropathy	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.09)
Disturbance in attention	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.09)
Drug intolerance	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.09)
Dysphoria	0 (0.0)	1 (1.7)	0 (0.0)	0 (0.0)	1 (0.09)
Flatulence	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.09)
Frequent bowel movements	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.09)
Gastroenteritis	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	1 (0.09)

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Glaucoma	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.09)
Haemorrhoids	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.09)
Headache	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.09)
Hepatic enzyme increased	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.09)
Hyperhidrosis	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	1 (0.09)
Hypersensitivity	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.09)
Hypertension	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	1 (0.09)
Hypertensive encephalopathy	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.09)
Intervertebral disc protrusion	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.09)
Loss of libido	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	1 (0.09)
Memory impairment	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.09)
Muscular weakness	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.09)
Myocardial infarction	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	1 (0.09)
Pregnancy	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.09)
Restless legs syndrome	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	1 (0.09)
Sedation	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	1 (0.09)
Serotonin syndrome	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.09)
Sleep disorder	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.09)
Testicular pain	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	1 (0.09)

(Source: Applicant's table 3.9 from 8/14/09 response to information request, pp. 35-37)

During the last six weeks of acute treatment, the frequency of discontinuations for patients administered duloxetine 20 mg and 60 mg decreased to the frequency of patients administered placebo. The duloxetine 120 mg group remained with the highest discontinuation rate, both due to any reason and due to adverse event, but the overall frequency of events decreased from 21% during the first seven weeks of treatment to 7% during the last six weeks of treatment.

Table 78: Discontinuations due to AEs, second 6 weeks – primary chronic pain trials

Table 3.10. Discontinuation Due to Adverse Events by Decreasing Frequency
 MedDRA Preferred Term
 All Randomized Patients
 Primary Placebo-Controlled Analyses Set – Chronic Pain (Second 6 Weeks)

MedDRA Preferred Term	PLACEBO (N=423) n (%)	DLX20QD (N=45) n (%)	DLX60QD (N=268) n (%)	DLX120QD (N=173) n (%)	TOTAL (N=909) n (%)
Patients Discontinued for any AE	12 (2.8)	1 (2.2)	8 (3.0)	12 (6.9)	33 (3.63)
Nausea	1 (0.2)	0 (0.0)	1 (0.4)	3 (1.7)	5 (0.55)
Constipation	1 (0.2)	0 (0.0)	0 (0.0)	2 (1.2)	3 (0.33)
Insomnia	1 (0.2)	0 (0.0)	0 (0.0)	2 (1.2)	3 (0.33)
Rash	0 (0.0)	0 (0.0)	2 (0.7)	0 (0.0)	2 (0.22)
Abdominal pain upper	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.11)
Aggression	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.11)
Anxiety	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.11)
Arthralgia	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	1 (0.11)
Bronchitis	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.11)
Condition aggravated	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	1 (0.11)
Dengue fever	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.11)
Dizziness	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.11)
Dysgeusia	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	1 (0.11)
Headache	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.11)
Hepatic enzyme increased	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	1 (0.11)
Hepatitis	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.11)
Hypercreatininaemia	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	1 (0.11)
Irritability	0 (0.0)	1 (2.2)	0 (0.0)	0 (0.0)	1 (0.11)
Loss of libido	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.11)

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Non-cardiac chest pain	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.11)
Peritonsillar abscess	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.11)
Pyelonephritis acute	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.11)
Somnolence	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.11)
Supraventricular tachycardia	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.11)

(Source: Applicant's table 3.9 from 8/14/09 response to information request, pp. 39-40)

During the extension phase of the HMEN trial, more patients on PLA_DLX 60/120 (13%) compared to DLX_DLX 60/120 (6%) discontinued the trial due to an adverse event.

These results suggest that, duloxetine-treated patients discontinued treatment during the first month of therapy due primarily to intolerance to the gastrointestinal (GI) and central nervous system (CNS) side effects. The higher discontinuation rate for duloxetine 120 mg, compared to duloxetine 60 mg and placebo, during the second six weeks in the flexible-dose trials, suggests a dose-response to the GI and CNS side effects.

All placebo-controlled and all-duloxetine exposure analysis sets

In the all placebo-controlled analysis set, more duloxetine-treated patients discontinued due to an AE (14%) compared to placebo-patients (5%). Somnolence, fatigue, dizziness, and vomiting, were again the leading events.

In the open-label trials analysis set, patients administered duloxetine 60 mg and 120 mg reported similar frequencies of discontinuation as patients in the placebo-controlled analysis set.

7.3.4 Significant Adverse Events

For this application, no adverse events met the definition for a significant adverse event. Events of primary safety concern are described in Section 7.3.5.

7.3.5 Submission Specific Primary Safety Concerns

This section addresses significant AEs observed in the duloxetine OA and CLBP that are already described in the approved duloxetine label. These include: hepatotoxicity, clinical worsening of suicide risk, and severe cutaneous reactions.

Hepatotoxicity

The most recent product label with the approval of duloxetine for the treatment of fibromyalgia was changed to include the following information regarding hepatotoxicity in the WARNINGS and PRECAUTIONS section:

“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.

Cymbalta increased the risk of elevation of serum transaminase levels in development program clinical trials. Liver transaminase elevations resulted in the discontinuation of 0.3% (82/27,229) of Cymbalta-treated patients. In these patients, the median time to detection of the transaminase elevation was about two months. In placebo-controlled trials in any indication, elevation of ALT >3 times the upper limit of normal occurred in 1.1% (85/7,632) of Cymbalta-treated patients compared to 0.2% (13/5,578) of placebo-treated patients. In placebo-controlled studies using a fixed dose design, there was evidence of a dose response relationship for ALT and AST elevation of >3 times the upper limit of normal and >5 times the upper limit of normal, respectively.

Because it is possible that duloxetine and alcohol may interact to cause liver injury or that duloxetine may aggravate pre-existing liver disease, Cymbalta should ordinarily not be prescribed to patients with substantial alcohol use or evidence of chronic liver disease.”

Primary Chronic Pain Trials

Hepatic-related adverse events

In the primary placebo-controlled analysis set (HMEN, HMEP, HMFG and HMEO trials), no patients from the placebo and the 20 mg duloxetine treatment groups were documented to have had hepatic-related adverse events during the first seven weeks of the Treatment Phase. Patients taking duloxetine 60 mg and 120 mg experienced a similar frequency of hepatic-related TEAEs (1.5% and 1.8%, respectively). During the last six weeks of acute treatment where pretreatment and the first seven weeks of treatment were considered as baseline, one subject from the 60 mg duloxetine group (0.4%) experienced an event of increased bilirubin.

Table 79: Hepatic-related TEAE for the first 7 weeks of the Treatment Phase – pooled data from HMEN, HMEP, HMFG and HMEO trials

**Table 5.1. Hepatic-Related Treatment-Emergent Adverse Events
 MedDRA Preferred Term
 All Randomized Patients
 Primary Placebo-Controlled Analyses Set - Chronic Pain (First 7 Weeks)**

MedDRA Preferred Term	PLACEBO	DLX20QD	DLX60QD	DLX120QD	TOTAL
	(N=486) n (%)	(N=59) n (%)	(N=470) n (%)	(N=112) n (%)	(N=1127) n (%)
Patients with >= 1 TEAE	0 (0.0)	0 (0.0)	7 (1.5)	2 (1.8)	9 (0.80)
Hepatic enzyme increased	0 (0.0)	0 (0.0)	2 (0.4)	1 (0.9)	3 (0.27)
Alanine aminotransferase increased	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.9)	2 (0.18)
Aspartate aminotransferase increased	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	1 (0.09)
Blood alkaline phosphatase increased	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.09)
Hepatic steatosis	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.09)
Hepatitis	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.09)
Liver function test abnormal	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.09)

(Source: Applicant's table 5.1 form 8/14/09 response to information request, page 98)

**Table 80: Hepatic-related TEAE for the last 6 weeks of the Treatment Phase –
 pooled data from HMEN, HMEP, HMFG and HMEO trials**

**Table 5.2. Hepatic-Related Treatment-Emergent Adverse Events
 MedDRA Preferred Term
 All Randomized Patients
 Primary Placebo-Controlled Analyses Set - Chronic Pain (Second 6 Weeks)**

MedDRA Preferred Term	PLACEBO	DLX20QD	DLX60QD	DLX120QD	TOTAL
	(N=423) n (%)	(N=45) n (%)	(N=268) n (%)	(N=173) n (%)	(N=909) n (%)
Patients with >= 1 Treatment-Emergent Event	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.11)
Blood bilirubin increased	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.11)

(Source: Applicant's table 5.1 form 8/14/09 response to information request, page 99)

The above analyses included all randomized patients, with normal and abnormal baseline liver function test values. To further understand whether patients with abnormal baseline LFTs could have been more susceptible to develop liver abnormalities, the applicant was asked to conduct a second analysis similar to the one above but including only patients with abnormal baseline LFTs. The results of these analyses showed that of the 470 patients on DLX 60 mg, 94 had abnormal LFTs at randomization. Of these 94, total of 6 (6.4%) experienced a hepatic-related TEAE during the first seven weeks. When these numbers are compared to the numbers for all of the randomized subjects, it shows that from the seven subjects randomized to 60 mg duloxetine who reported hepatic-related TEAE, six had baseline LFTs abnormalities. Of the 112 patients on DLX 120 mg, 12 had abnormal LFTs at the time of randomization. Of these 12 subjects, 1 (8.3%) experienced a hepatic-related TEAE during the first seven weeks. Again when compared to the numbers for all of the randomized subjects, from the two randomized to 120 mg duloxetine subjects who reported hepatic-related TEAE, one had baseline LFTs abnormalities. During the second six weeks, the one subject who reported hepatic-related TEAE (bilirubin increased) had an abnormal baseline LFTs.

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These findings suggest that most of the patients that reported a hepatic-related TEAE had some baseline liver dysfunction presenting as abnormal LFTs.

Table 81: Hepatic-related TEAE, all patients with abnormally high LFTs – primary chronic pain trials – first 7 weeks

Table 4.1. Hepatic-Related Treatment-Emergent Adverse Events
 MedDRA Preferred Term
 All Randomized Patients with Abnormally High Baseline Hepatic Laboratory Values
 Primary Placebo-Controlled Analyses Set - Chronic Pain (first 7 weeks)

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MedDRA Preferred Term	PLACEBO (N=109) n (%)	DLX20QD (N=9) n (%)	DLX60QD (N=94) n (%)	DLX120QD (N=12) n (%)	TOTAL (N=224) n (%)	p-Value Fisher's Exact
Patients with >= 1 TEAE	0 (0.0)	0 (0.0)	6 (6.4)	1 (8.3)	7 (3.13)	.009
Alanine aminotransferase increased	0 (0.0)	0 (0.0)	1 (1.1)	1 (8.3)	2 (0.89)	.463
Hepatic enzyme increased	0 (0.0)	0 (0.0)	2 (2.1)	0 (0.0)	2 (0.89)	.213
Aspartate aminotransferase increased	0 (0.0)	0 (0.0)	0 (0.0)	1 (8.3)	1 (0.45)	
Blood alkaline phosphatase increased	0 (0.0)	0 (0.0)	1 (1.1)	0 (0.0)	1 (0.45)	.463
Hepatic steatosis	0 (0.0)	0 (0.0)	1 (1.1)	0 (0.0)	1 (0.45)	.463
Liver function test abnormal	0 (0.0)	0 (0.0)	1 (1.1)	0 (0.0)	1 (0.45)	.463

(Source: Applicant's table 4.1 from 10/7/09 response to information request, p.10)

Table 82: Hepatic-related TEAE, all patients with abnormally high LFTs – primary chronic pain trials – last 6 weeks

Table 4.2. Hepatic-Related Treatment-Emergent Adverse Events
 MedDRA Preferred Term
 All Randomized Patients with Abnormally High Baseline Hepatic Laboratory Values
 Primary Placebo-Controlled Analyses Set - Chronic Pain (second 6 weeks)

MedDRA Preferred Term	PLACEBO (N=129) n (%)	DLX20QD (N=9) n (%)	DLX60QD (N=83) n (%)	DLX120QD (N=46) n (%)	TOTAL (N=267) n (%)
Patients with >= 1 Treatment-Emergent Event	0 (0.0)	0 (0.0)	1 (1.2)	0 (0.0)	1 (0.37)
Blood bilirubin increased	0 (0.0)	0 (0.0)	1 (1.2)	0 (0.0)	1 (0.37)

(Source: Applicant's table 4.2 from 10/7/09 response to information request, p.11)

After three months of blinded therapy with placebo or duloxetine 60 mg or 120 mg, HMEN trial continued with an extension phase during which patients received duloxetine only, 60 mg or 120 mg, for additional nine months. Analysis of hepatic-related AEs by dose at the time of the event was performed by the applicant and is presented on the table that follows. The results from this analysis show that the majority of the reported events were from the 120 mg dose group. Nevertheless, the numbers were overall small and all reported AEs were for abnormal liver function tests.

Table 83: Hepatic-related AEs – HMEN extension phase

Table 1. Treatment-Emergent Hepatic Adverse Events by Decreasing Frequency, MedDRA Preferred Terms Visit-wise Analysis; All Randomized Patients who Entered Extension Phase F1J-MC-HMEN, Extension Phase

VISIT	Event Preferred Term	---DLX60QD---		---DLX120QD---		---Total---	
		N	n(%)	N	n(%)	N	n(%)
7.00	Patients with >=1 TEAEs	149	0(0.0%)	25	1(4.0%)	174	1(0.6%)
	Hepatic enzyme increased	149	0(0.0%)	25	1(4.0%)	174	1(0.6%)
8.00	Patients with >=1 TEAEs	103	1(1.0%)	55	0(0.0%)	158	1(0.6%)
	Gamma-glutamyltransferase increased	103	1(1.0%)	55	0(0.0%)	158	1(0.6%)
11.00	Patients with >=1 TEAEs	72	0(0.0%)	54	1(1.9%)	126	1(0.8%)
	Alanine aminotransferase increased	72	0(0.0%)	54	1(1.9%)	126	1(0.8%)
	Aspartate aminotransferase increased	72	0(0.0%)	54	1(1.9%)	126	1(0.8%)
	Blood alkaline phosphatase increased	72	0(0.0%)	54	1(1.9%)	126	1(0.8%)
	Gamma-glutamyltransferase increased	72	0(0.0%)	54	1(1.9%)	126	1(0.8%)

(Source: Applicant's table 1, from 10/19/09 response to information request, p. 7)

Abnormal hepatic laboratory values

For treatment-emergent abnormal hepatic laboratory values at endpoint in patients with normal baseline hepatic lab values, abnormally high ALT and AST values were observed more frequently with duloxetine compared to placebo during the first seven weeks of the treatment period. This trend was not observed during the second 6 weeks of treatment. The increases in ALT and AST were not associated with bilirubin elevations.

Table 84: Treatment-emergent abnormal hepatic laboratory analytes – Primary Chronic Pain Trials (first 7 weeks)

Table 5.5. Treatment Emergent Abnormal Laboratory Values at Endpoint - Hepatic Laboratory Analytes All Randomized Patients with a Normal Baseline Primary Placebo-Controlled Analyses Set - Chronic Pain (First 7 weeks)

Lab Test	Direction	Placebo			DLX20QD			DLX60QD			DLX120QD			DLX Total		
		N	n	%	N	n	%	N	n	%	N	n	%	N	n	%
ALKALINE PHOSPHATASE	Normal->High	457	5	1.1	56	1	1.8	424	6	1.4	103	1	1.0	583	8	1.4
	Normal->Low	457	1	0.2	56	0	0	424	0	0	103	0	0	583	0	0
ALT/SGPT	Normal->High	411	15	3.6	53	1	1.9	398	19	4.8	100	7	7.0	551	27	4.9
	Normal->Low	411	2	0.5	53	0	0	398	1	0.3	100	0	0	551	1	0.2
AST/SGOT	Normal->High	438	10	2.3	56	3	5.4	417	21	5.0	103	8	7.8	576	32	5.6
	Normal->Low	438	1	0.2	56	0	0	417	0	0	103	1	1.0	576	1	0.2
BILIRUBIN, TOTAL	Normal->High	445	5	1.1	58	0	0	423	2	0.5	103	0	0	584	2	0.3
	Normal->Low	445	7	1.6	58	1	1.7	423	9	2.1	103	2	1.9	584	12	2.1
GAMMA GLUTAMYLTRANSFERASE (GGT)	Normal->High	418	12	2.9	53	3	5.7	400	12	3.0	99	2	2.0	552	17	3.1
	Normal->Low	418	0	0	53	0	0	400	2	0.5	99	1	1.0	552	3	0.5

(Source: Applicant's table 5.5 form 8/14/09 response to information request, page 105)

Table 85: Treatment-emergent abnormal hepatic laboratory analytes – Primary Chronic Pain Trials (last 6 weeks)

Table 5.6. Treatment Emergent Abnormal Laboratory Values at Endpoint - Hepatic Laboratory Analytes All Randomized Patients with a Normal Baseline Primary Placebo-Controlled Analyses Set - Chronic Pain (Second 6 weeks)

Lab Test	Direction	Placebo			DLX20QD			DLX60QD			DLX120QD			DLX Total		
		N	n	%	N	n	%	N	n	%	N	n	%	N	n	%
ALKALINE PHOSPHATASE	Normal->High	381	1	0.3	41	1	2.4	229	4	1.7	161	2	1.2	431	7	1.6
	Normal->Low	381	3	0.8	41	0	0	229	0	0	161	0	0	431	0	0
ALT/SGPT	Normal->High	328	13	4.0	41	1	2.4	203	11	5.4	144	7	4.9	388	19	4.9
	Normal->Low	328	0	0	41	0	0	203	0	0	144	0	0	388	0	0
AST/SGOT	Normal->High	353	7	2.0	40	1	2.5	219	12	5.5	146	4	2.7	405	17	4.2
	Normal->Low	353	1	0.3	40	0	0	219	0	0	146	0	0	405	0	0
BILIRUBIN, TOTAL	Normal->High	361	3	0.8	43	0	0	230	1	0.4	154	0	0	427	1	0.2
	Normal->Low	361	8	2.2	43	2	4.7	230	4	1.7	154	3	1.9	427	9	2.1
GAMMA GLUTAMYLTRANSFERASE (GGT)	Normal->High	343	10	2.9	38	0	0	210	4	1.9	144	3	2.1	392	7	1.8
	Normal->Low	343	2	0.6	38	1	2.6	210	0	0	144	0	0	392	1	0.3

(Source: Applicant's table 5.5 form 8/14/09 response to information request, page 106)

Shift tables were also created for patients with abnormally high LFTs at baseline. This analysis showed that the majority of the patients from all treatment groups, who had abnormal baseline ALT/AST at baseline, had either normal or high but not higher readings at endpoint. This trend of changes was observed both during the first seven weeks and the second six weeks of the treatment period. (Refer to Section 7.4.2.2.)

The shifts in hepatic laboratory analyte values at anytime and by dose at each visit for all randomized patients who entered the extension phase of HMEN are also discussed in Section 7.4.2.2. More patients on duloxetine 60 mg developed elevations in gamma glutamyl transferase and more patients on duloxetine 120 mg developed elevations in AST levels and bilirubin.

Markedly abnormal transaminase levels

Clinically significant increases in ALT and AST levels were infrequent in the primary chronic pain trials. When such elevations did occur, ALT and AST levels either normalized or were trending back towards normal values at subsequent visits. Because of the small numbers it is difficult to evaluate for dose response. Nevertheless, no such a trend was observed in the primary chronic pain trials.

The overall number of patients who experienced abnormally high ALT elevation in the primary chronic pain trials was small. During the first seven weeks of treatment, more patients taking duloxetine 60 mg (9, 2%) experienced ALT elevation >3 times the upper limit of normal (3X ULN) compared to placebo (3, 0.6%) and duloxetine 120 mg (1, 1%). Three of the patients taking duloxetine 60 mg experienced an elevation >5X ULN and one experienced an elevation >10X ULN. During the second six weeks of treatment, there was no difference between the placebo and duloxetine 60 mg treatment groups in the frequency of ALT elevation >3X ULN. No patients from the duloxetine 120 mg dose group reported ALT elevation >3X ULN during the second six weeks.

Table 86: Marked outliers for ALT, all randomized patients - Primary Chronic Pain Trials

Parameter	Maximum Post-Baseline		
	>3xULN	>5xULN	>10xULN
First 7 wks			
ALT			
Placebo	3 (0.6%)	0	0
DLX 20mg	0	0	0
DLX 60 mg	9 (2.0%)	3 (0.7%)	1 (0.3%)
DLX 120 mg	1 (1%)	0	0
Second 6 wks			
ALT			
Placebo	1 (0.4%)	0	0
DLX 20mg	0	0	0
DLX 60 mg	2 (0.5%)	1 (0.2%)	0
DLX 120 mg	0	0	0

(Source: Adapted from applicant's tables 5.7 and 5.8 from 8/14/09 response to information request and tables 4.11 and 4.12 from 10/7/09 response to information request)

With respect to AST levels, three patients assigned to duloxetine 60 mg experienced an AST elevation >3X ULN, with one of the patients experiencing an increase >5X ULN during the first 7 weeks of treatment. No AST increases >3X ULN were reported during the second 6 weeks of treatment.

Table 87: Marked outliers for AST, all randomized patients - Primary Chronic Pain Trials

Parameter	Maximum Post-Baseline		
	>3xULN	>5xULN	>10xULN
First 7 wks			
AST			

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Placebo	1 (0.2%)	0	0
DLX 20mg	0	0	0
DLX 60 mg	4 (0.9%)	1 (0.2%)	0
DLX 120 mg	0	0	0
Second 6 wks	No elevations > 3x ULN DLX 60 mg >3xULN 1 (0.4%)		

(Source: Adapted from applicant's tables 5.9 and 5.10 from 8/14/09 response to information request and tables 4.13 and 4.14 from 10/7/09 response to information request)

During the extension phase of HMEN, one patient (2.4%) from the 120 mg duloxetine group who had a normal baseline ALT value reported an ALT increase > 3xULN and one patient (5.9%), also from the 120 mg duloxetine group, who had an abnormal baseline ALT value, reported an ALT increase > 3xULN.

Reversibility of elevated liver function analytes over time

In order to assess reversibility of abnormal liver function over time, the applicant was asked to provide available laboratory values over time for subjects with abnormal ALT/AST and bilirubin values for the primary chronic pain analysis set. All patients who experienced a clinically significant increase in ALT, AST, or bilirubin levels (>3X ULN for ALT and AST and >2X ULN for total and direct bilirubin) and who had normal (≤1X ULN) baseline values were included in this analysis. The results revealed that five duloxetine-treated patients experienced a total of eight clinically significant events. None was rated as serious. For four out of the five patients, the LFT values returned to normal during subsequent visits. The one patient with an abnormal ALT and AST level at endpoint (HMFG-1315) experienced consistently decreasing values following the elevations such that the ALT value at the last visit was 52 U/L (normal: 34 U/L) and the AST value at the last visit was 36 U/L (normal: 34 U/L). No duloxetine-treated patients with normal baseline values experienced a clinically significant increase in total bilirubin or direct bilirubin levels.

Of the five duloxetine-treated patients reporting a clinically significant increase in ALT or AST levels, three patients (HMEO-3431, HMEO-2206 and HMEO-2007) discontinued due to a hepatic-related adverse event. Patient HMEO-3431 experienced a clinically significant increase in both ALT and AST levels and discontinued due to the adverse event of "hepatitis". Patient HMEO-2007 experienced a clinically significant increase in ALT levels and discontinued due to the adverse event of "hepatic enzyme increased". For both of these patients, their ALT and/or AST levels returned to normal values by

their last visit. Subject HMEO-2206 had a baseline LFT elevation and experienced worsening of the liver enzyme elevation during the treatment phase. The elevated liver enzymes were ongoing at the time of discontinuation.

My review of the narratives (summary provided below) revealed that all three events were most likely related to duloxetine treatment.

Subject 020-2007 in Study HMEO was a 48-year-old female of East Asian descent assigned to 120 mg duloxetine group who discontinued the study due to elevated liver enzymes. The patient experienced an elevation in ALT to 107 U/L which was greater than 3 times the ULN (normal reference range: 6-34 U/L.) and GGT 52 days after starting duloxetine. Bilirubin remained within reference ranges. Hepatic serologies and INR were not performed. There was no history of liver disease or alcohol use. The patient was taking the following concomitant medications prior to study entry: Salonpas medicated bandage, ibuprofen and paracetamol. Nine days after the last dose of duloxetine, the patient's LFTs returned to normal.

Subject 022-2206 in Study HMEO was a 30-year-old male of East Asian descent assigned to 60 mg duloxetine dose that discontinued the study due to the worsening of the secondary condition of 'elevated liver enzymes' from mild to moderate severity. The patient had a history of liver enzyme elevation in 2004. No concomitant medications use prior to study entry was reported. Patient's baseline laboratory values were as follows: ALT 64 U/L (normal reference range: 6-43 U/L) and GGT 252 U/L (normal reference range: 10-61 U/L). Twenty-eight days after starting duloxetine, the patient experienced the worsening of the secondary condition of 'elevated liver enzymes' from mild to moderate severity: ALT 147 U/L, AST 60 U/L (normal reference range: 11-36 U/L), alkaline phosphatase 152 U/L (normal reference range: 31-129 U/L) and GGT 332 U/L. The patient was not treated for the event. The 'elevated liver enzymes' were ongoing at the time of discontinuation.

Subject 034-3431 in Study HMEO was a 52 year-old female of Hispanic descent assigned to 60 mg duloxetine dose that discontinued the trial after 49 days of treatment with duloxetine due to drug induced hepatitis. The patient also experienced an elevation in ALT to 356 U/L which was greater than 10 times the ULN (reference range: 6-34 U/L). Her past medical history was significant for pulmonary and genital tuberculosis (1975). Concomitant medication prior to study entry included: ibuprofen and diclofenac. Social alcohol consumption was reported. Eleven days after starting duloxetine, the patient experienced the adverse event of 'pharyngitis' for which she was treated with amoxicillin. Forty days after starting duloxetine, the patient experienced the adverse event of 'acute gastroenterocolitis' with symptoms of abdominal pain in the right upper quadrant, diarrhea and yellow feces that resolved in three days. The patient was not treated for the event. Forty nine days after starting duloxetine, the patient experienced the adverse event of 'drug induced hepatitis. Increase in ALT to 258 U/L and AST to 165 U/L was documented. The patient was not treated for the event. The

patient was on duloxetine for a total of 54 days. Two days after stopping duloxetine, the patient had an increase in ALT to 356 U/L, a decrease in AST to 156 U/L. Hepatic serology was negative. Twenty three days after stopping duloxetine patient's hepatic enzymes were within normal range.

One patient (HMEN-2118), whose ALT elevation occurred during the extension phase (visit 10), discontinued because of pregnancy and had normal ALT levels at the last visit.

All placebo-controlled trials

In the all placebo-controlled analysis set, patients administered duloxetine experienced a higher incidence (0.4%) of hepatic-related TEAE compared to patients administered placebo (0.2%).

Table 88: Hepatic-related TEAE - All Placebo-Controlled Analysis Set

Event	PLACEBO (N=7010) n(%)	DULOXETINE (N=9685) n(%)

PATIENTS WITH ≥1 TEAE	33 (0.2%)	93 (0.4%)
Alanine aminotransferase increased	7 (0.1%)	26 (0.3%)
Hepatic enzyme increased	7 (0.1%)	24 (0.2%)
Aspartate aminotransferase increased	5 (0.1%)	15 (0.2%)
Gamma-glutamyltransferase increased	5 (0.1%)	10 (0.1%)
Liver function test abnormal	5 (0.1%)	10 (0.1%)
Blood alkaline phosphatase increased	3 (0.0%)	5 (0.1%)
Blood bilirubin increased	4 (0.1%)	4 (0.0%)
Hepatic cyst	2 (0.0%)	1 (0.0%)
Hepatic steatosis	0 (0.0%)	2 (0.0%)
Liver disorder	1 (0.0%)	1 (0.0%)
Hepatic enzyme abnormal	0 (0.0%)	1 (0.0%)
Hepatic function abnormal	0 (0.0%)	1 (0.0%)
Hepatic neoplasm malignant	1 (0.0%)	0 (0.0%)
Hepatitis toxic	0 (0.0%)	1 (0.0%)
Spider naevus	0 (0.0%)	1 (0.0%)

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(Source: Applicant's table 8.19 from SCS, page 4010)

A similar profile of hepatic-related events was observed in the all duloxetine exposure analysis set.

Multitrial analysis for dose relationship of liver enzyme elevations

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To further explore the dose relationship for LFT elevations among all duloxetine doses, the applicant performed an additional analysis for patients with hepatic ALT elevations of >3X, >5X, or >10X ULN, including all fixed- and flexible-dose trials. This analysis is based on the visit wise dose information, to determine the number of patients with ALT elevation at each dose group. The actual dose the patient received at the time (visit) of the first occurrence of an ALT elevation was considered as the dose group to which the patient belonged. However, for the total number of patients in each dose group with or without an ALT elevation, all possible doses each patient may have taken were considered as the dose group. On the table that follows, the determination of the “n” (the number of patients in each dose group) is unique. For the determination of “N”, patients were double counted (included in both dose groups) if they started duloxetine treatment with one dose and later were titrated up or down to another dose group.

Table 89: Treatment-emergent high ALT values at anytime – all randomized patients with normal baseline values – all duloxetine exposure integrated set

**Treatment-Emergent Abnormally High ALT Values at Anytime
 All Randomized Patients with Normal Baseline Value
 (≤1X (b) (4) ULN)
 Overall Duloxetine Exposure Integrated Analyses Set**

Analyte	Reference Limits	Therapy	N	n	Percent
ALT	> 3X (b) (4) ULN	DLX dose unknown	74	0	(0)
		DLX ≤20mg	1060	5	(0.47)
		DLX 30mg	786	1	(0.13)
		DLX 40mg	595	7	(1.18)
		DLX 60mg	5908	38	(0.64)
		DLX 80mg	9993	128	(1.28)
		DLX 90mg	1302	10	(0.77)
		DLX 120mg	4317	61	(1.41)
		DLX Overall	20163	250	(1.24)
ALT	> 5X (b) (4) ULN	DLX dose unknown	74	0	(0)
		DLX ≤20mg	1060	3	(0.28)
		DLX 30mg	786	0	(0)
		DLX 40mg	595	3	(0.50)
		DLX 60mg	5908	12	(0.20)
		DLX 80mg	9993	61	(0.61)
		DLX 90mg	1302	4	(0.31)
		DLX 120mg	4317	31	(0.72)
		DLX Overall	20163	114	(0.57)

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ALT	>10X (b) (4) ULN	DLX dose unknown	74	0	(0)
		DLX <=20mg	1060	0	(0)
		DLX 30mg	786	0	(0)
		DLX 40mg	595	0	(0)
		DLX 60mg	5908	8	(0.14)
		DLX 80mg	9993	16	(0.16)
		DLX 90mg	1302	2	(0.15)
		DLX 120mg	4317	12	(0.28)
		DLX Overall	20163	38	(0.19)

(Source: Applicant's table 8.22 from ISS, pp. 4017-4019)

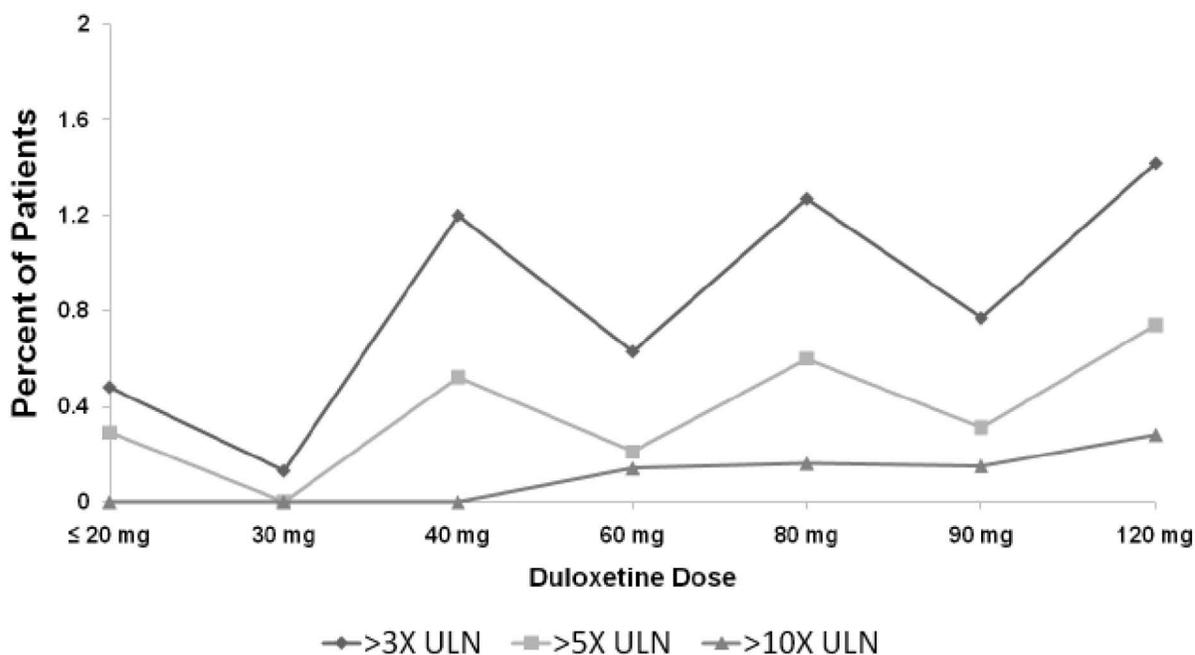


Figure 8.1. Treatment-Emergent Abnormally High ALT Values at Anytime: Overall Duloxetine (DLX) Exposure Integrated Safety Database

(Source: Applicant's figure 8.1 from ISS, page 4020)

As illustrated on the table and figure above, overall the duloxetine 120 mg dose group experienced numerically higher frequency of LFT elevations (>3, >5, and >10 x ULN) compared to the other duloxetine dose groups.

Depression and Suicide

Duloxetine carries the antidepressant class Box Warning of increased "risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and

young adults in short-term studies of major depressive disorder (MDD) and other psychiatric disorders.”

Most suicide attempts and suicidal ideation with duloxetine treatment occurred in patients with underlying psychiatric diagnoses. In studies of duloxetine for non-psychiatric diagnoses, there were no cases of completed suicides in either duloxetine or placebo arms.

In the fibromyalgia placebo-controlled trials, among patients with depression at baseline, more placebo-treated patients than duloxetine-treated patients reported the emergence or worsening of any suicidal ideation. Suicidal ideation was the SAE reported most frequently in the fibromyalgia placebo-controlled and open-label studies (5 patients; 0.4%). One of these patients attempted suicide but recovered without any permanent disabilities. There were no completed suicides in any of the fibromyalgia studies.

The Agency requested that the applicant perform a Standard MedDRA Query (SMQ) for depression and self-injury in the primary chronic pain patient population (Pre-NDA Meeting, 18 October 2007). The results of these analyses were submitted with the NDA 22-333, Cymbalta for chronic pain, March 2008. No significant differences with any SMQ were observed between treatment groups (duloxetine (13, 2.5%) and placebo (7, 2.0%). No patients reported a TEAE related to suicide/self-injury SMQ.

There were no cases of suicide ideation or suicide behavior in the primary chronic pain patient population. With regards to signs and symptoms of depression, no dose-dependent relationship was observed. During the first 7 weeks of treatment, no significant differences in TEAEs related to depression, suicide or self-injury were observed between patients taking duloxetine 60 mg compared with patients taking placebo. The frequency of these TEAEs decreased overall during the second 6 weeks of acute treatment, with patients taking duloxetine 120 mg and placebo experiencing events with a similar frequency and patients taking duloxetine 20 mg or 60 mg experiencing no events.

Table 90: Depression and Suicide – Primary Chronic Pain Trials, first 7 weeks

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**Table 3.3. Depression and Suicide/Self-Injury (SMQ code 20000035 20000037)
 Treatment-Emergent Adverse Events
 MedDRA Preferred Term
 All Randomized Patients
 Primary Placebo-Controlled Analyses Set - Chronic Pain (first 7 weeks)**

MedDRA Preferred Term	PLACEBO	DLX20QD	DLX60QD	DLX120QD	TOTAL
	(N=486) n (%)	(N=59) n (%)	(N=470) n (%)	(N=112) n (%)	(N=1127) n (%)
Patients with >= 1 Treatment-Emergent Event	6 (1.2)	1 (1.7)	11 (2.3)	3 (2.7)	21 (1.86)
Disturbance in attention	1 (0.2)	0 (0.0)	2 (0.4)	0 (0.0)	3 (0.27)
Hypersomnia	0 (0.0)	1 (1.7)	1 (0.2)	1 (0.9)	3 (0.27)
Apathy	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.9)	2 (0.18)
Depressed mood	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)	2 (0.18)
Early morning awakening	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)	2 (0.18)
Memory impairment	0 (0.0)	0 (0.0)	2 (0.4)	0 (0.0)	2 (0.18)
Middle insomnia	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.9)	2 (0.18)
Poor quality sleep	0 (0.0)	0 (0.0)	2 (0.4)	0 (0.0)	2 (0.18)
Depression	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.09)
Initial insomnia	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.09)
Mood altered	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.09)
Tearfulness	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.09)

(Source: Applicant's table 3.3 form 8/14/09 response to information request, page 21)

Table 91: Depression and Suicide – Primary Chronic Pain Trials, last 6 weeks

**Table 3.4. Depression and Suicide/Self-Injury (SMQ code 20000035 20000037)
 Treatment-Emergent Adverse Events
 MedDRA Preferred Term
 All Randomized Patients
 Primary Placebo-Controlled Analyses Set - Chronic Pain (Second 6 Weeks)**

MedDRA Preferred Term	PLACEBO	DLX20QD	DLX60QD	DLX120QD	TOTAL
	(N=423) n (%)	(N=45) n (%)	(N=268) n (%)	(N=173) n (%)	(N=909) n (%)
Patients with >= 1 Treatment-Emergent Event	3 (0.7)	0 (0.0)	0 (0.0)	1 (0.6)	4 (0.44)
Depression	2 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.22)
Disturbance in attention	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	1 (0.11)
Memory impairment	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	1 (0.11)
Middle insomnia	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.11)

(Source: Applicant's table 3.3 form 8/14/09 response to information request, page 22)

In the all placebo-controlled trials (all indications), greater incidence of suicide behavior or ideation was observed in duloxetine-treated patients compared with placebo-treated patients in the 18 to <25 year subgroup. The majority of events were related to suicidal ideation (37 [0.36%] of 10,245 duloxetine-treated patients and 24 [0.32%] of 7436 placebo-treated patients). All completed suicides and suicide attempts occurred in patients enrolled in MDD and GAD trials. In all pain trials, which excluded patients with comorbid depression, no suicidal ideation or behaviors were observed in duloxetine-treated patients, and suicidal ideation was observed in 2 placebo-treated patients.

Severe Cutaneous Reactions

Although no severe cutaneous reactions have been reported in clinical trials of duloxetine, in postmarketing experience there have been reports of rash, angioneurotic edema, Steven-Johnson Syndrome, and urticaria associated with duloxetine use. This information is included in the current Cymbalta label.

In the primary placebo-controlled trials (OA and CLBP) three events (stomatitis, mouth ulceration, and conjunctivitis) were experienced by six patients. No dose relationship was observed. In total, there were two patients from the 60 mg duloxetine group (1.2%) who discontinued due to cutaneous adverse events of rash. All adverse events resolved without sequelae.

During the first 7 weeks of treatment, two patients (one taking placebo and one taking duloxetine 60 mg) experienced stomatitis and one patient (duloxetine 120 mg) experienced mouth ulceration. Three patients (one taking placebo and two taking duloxetine 20 mg) experienced conjunctivitis during the second 6 weeks of treatment.

Table 92: Severe Cutaneous TEAEs – Primary Chronic pain trials – first 7 weeks

Table 3.5. Severe Cutaneous Adverse Reaction Treatment-Emergent Adverse Events MedDRA Preferred Term All Randomized Patients Primary Placebo-Controlled Analyses Set - Chronic Pain (first 7 weeks)

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MedDRA Preferred Term	PLACEBO (N=486) n (%)	DLX20QD (N=59) n (%)	DLX60QD (N=470) n (%)	DLX120QD (N=112) n (%)	TOTAL (N=1127) n (%)
Patients with >= 1 TEAE	1 (0.2)	0 (0.0)	1 (0.2)	1 (0.9)	3 (0.27)
Stomatitis	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)	2 (0.18)
Mouth ulceration	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	1 (0.09)

(Source: Applicant's table 3.5 form 8/14/09 response to information request, page 24)

Table 93: Severe Cutaneous TEAEs – Primary Chronic pain trials – last 6 weeks

Table 3.6. Severe Cutaneous Adverse Reaction Treatment-Emergent Adverse Events MedDRA Preferred Term All Randomized Patients Primary Placebo-Controlled Analyses Set - Chronic Pain (Second 6 Weeks)

MedDRA Preferred Term	PLACEBO (N=423) n (%)	DLX20QD (N=45) n (%)	DLX60QD (N=268) n (%)	DLX120QD (N=173) n (%)	TOTAL (N=909) n (%)
Patients with >= 1 Treatment-Emergent Event	1 (0.2)	2 (4.4)	0 (0.0)	0 (0.0)	3 (0.33)
Conjunctivitis	1 (0.2)	2 (4.4)	0 (0.0)	0 (0.0)	3 (0.33)

(Source: Applicant's table 3.5 form 8/14/09 response to information request, page 25)

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Primary chronic pain trials (HMEN, HMFG, HMEP, and HMEO)

In the primary placebo-controlled analysis set, patients administered duloxetine 120 mg experienced the highest frequency of treatment-emergent adverse events (TEAEs) compared to treatment groups during the first seven weeks of treatment, 71% for DLX 120 mg, 53% for DLX 60 mg, 59% for DLX 20mg, and 37% for placebo (Complete table of TEAEs is located in the Appendix 9.5).

The most frequently reported adverse events were: insomnia, nausea, dry mouth, constipation, headache, somnolence, fatigue and dizziness. When comparing the 60 mg and 120 mg duloxetine treatment groups, the following TEAEs were experienced more frequently by duloxetine 120 mg treated patients than duloxetine 60 mg treated patients: insomnia (17% DLX 120 mg vs. 5% for DLX 60 mg), somnolence (12% DLX 120 mg vs. 4% for DLX 60 mg), constipation (11% DLX 120 mg vs. 6% for DLX 60 mg), and headache (8% DLX 120 mg vs. 3% for DLX 60 mg). It is to note that the 20mg duloxetine group experienced the highest incidence of nausea (15.3%) among all treatment groups (placebo-2.1%, DLX 60 mg-11.5%, and DLX 120 mg-10.7%).

Table 94: TEAEs greater or equal to 1% for the first 7 weeks of treatment – Primary Placebo-Controlled Analysis Set

**Table 3.7. Treatment-Emergent Adverse Event ≥1% in Any Treatment Group
 By Decreased Frequency and by Randomized Dose
 MedDRA Preferred Term
 All Randomized Patients
 Primary Placebo-Controlled Analyses Set - Chronic Pain (First 7 Weeks)**

MedDRA Preferred Term	PLACEBO	DLX20QD	DLX60QD	DLX120QD	TOTAL
	(N=486) n (%)	(N=59) n (%)	(N=470) n (%)	(N=112) n (%)	(N=1127) n (%)

Patients with >= 1 TEAE	181 (37.2)	35 (59.3)	247 (52.6)	80 (71.4)	543 (48.18)
Nausea	10 (2.1)	9 (15.3)	54 (11.5)	12 (10.7)	85 (7.54)
Insomnia	7 (1.4)	5 (8.5)	21 (4.5)	19 (17.0)	52 (4.61)
Diarrhoea	14 (2.9)	2 (3.4)	27 (5.7)	6 (5.4)	49 (4.35)
Dry mouth	5 (1.0)	3 (5.1)	29 (6.2)	11 (9.8)	48 (4.26)
Constipation	3 (0.6)	2 (3.4)	28 (6.0)	12 (10.7)	45 (3.99)
Headache	18 (3.7)	1 (1.7)	16 (3.4)	9 (8.0)	44 (3.90)
Somnolence	4 (0.8)	2 (3.4)	19 (4.0)	13 (11.6)	38 (3.37)
Fatigue	2 (0.4)	0 (0.0)	24 (5.1)	10 (8.9)	36 (3.19)
Dizziness	7 (1.4)	3 (5.1)	16 (3.4)	7 (6.3)	33 (2.93)
Hyperhidrosis	3 (0.6)	0 (0.0)	14 (3.0)	5 (4.5)	22 (1.95)
Influenza	6 (1.2)	3 (5.1)	8 (1.7)	2 (1.8)	19 (1.69)
Arthralgia	7 (1.4)	2 (3.4)	9 (1.9)	0 (0.0)	18 (1.60)
Decreased appetite	1 (0.2)	0 (0.0)	10 (2.1)	5 (4.5)	16 (1.42)
Nasopharyngitis	7 (1.4)	1 (1.7)	7 (1.5)	1 (0.9)	16 (1.42)
Abdominal pain upper	3 (0.6)	0 (0.0)	9 (1.9)	2 (1.8)	14 (1.24)
Erectile dysfunction	0 (0.0)	1 (1.7)	10 (2.1)	3 (2.7)	14 (1.24)
Dyspepsia	4 (0.8)	1 (1.7)	5 (1.1)	3 (2.7)	13 (1.15)

(Source: Applicant's Table 3.7 from 8/14/00, response to information request, p. 27)

During the second six weeks no dose relationship for TEAEs was observed.

**Table 95: TEAEs greater or equal to 1% for the last 6 weeks of treatment –
 Primary Placebo-Controlled Analysis Set**

**Table 3.8. Treatment-Emergent Adverse Event $\geq 1\%$ in Any Treatment Group
 By Decreased Frequency by Randomized Dose
 MedDRA Preferred Term
 All Randomized Patients
 Primary Placebo-Controlled Analyses Set - Chronic Pain (Second 6 Weeks)**

MedDRA Preferred Term	PLACEBO (N=423) n (%)	DLX20QD (N=45) n (%)	DLX60QD (N=268) n (%)	DLX120QD (N=173) n (%)	TOTAL (N=909) n (%)
Patients with ≥ 1 Treatment-Emergent Event	87 (20.6)	12 (26.7)	68 (25.4)	45 (26.0)	212 (23.32)
Dizziness	2 (0.5)	0 (0.0)	7 (2.6)	5 (2.9)	14 (1.54)
Headache	4 (0.9)	1 (2.2)	6 (2.2)	3 (1.7)	14 (1.54)
Insomnia	6 (1.4)	0 (0.0)	2 (0.7)	4 (2.3)	12 (1.32)
Influenza	3 (0.7)	0 (0.0)	4 (1.5)	4 (2.3)	11 (1.21)
Arthralgia	6 (1.4)	0 (0.0)	3 (1.1)	1 (0.6)	10 (1.10)
Nausea	3 (0.7)	2 (4.4)	2 (0.7)	3 (1.7)	10 (1.10)
Diarrhoea	3 (0.7)	0 (0.0)	1 (0.4)	4 (2.3)	8 (0.88)
Somnolence	1 (0.2)	1 (2.2)	3 (1.1)	1 (0.6)	6 (0.66)
Constipation	1 (0.2)	0 (0.0)	1 (0.4)	3 (1.7)	5 (0.55)
Pain in extremity	1 (0.2)	0 (0.0)	2 (0.7)	2 (1.2)	5 (0.55)
Gastroenteritis	0 (0.0)	1 (2.2)	3 (1.1)	0 (0.0)	4 (0.44)
Conjunctivitis	1 (0.2)	2 (4.4)	0 (0.0)	0 (0.0)	3 (0.33)
Neck pain	0 (0.0)	0 (0.0)	3 (1.1)	0 (0.0)	3 (0.33)
Non-cardiac chest pain	2 (0.5)	1 (2.2)	0 (0.0)	0 (0.0)	3 (0.33)
Pharyngitis	0 (0.0)	2 (4.4)	0 (0.0)	1 (0.6)	3 (0.33)
Pruritus	0 (0.0)	0 (0.0)	1 (0.4)	2 (1.2)	3 (0.33)
Sinusitis	1 (0.2)	1 (2.2)	1 (0.4)	0 (0.0)	3 (0.33)
Anorexia	0 (0.0)	1 (2.2)	1 (0.4)	0 (0.0)	2 (0.22)

(Source: Applicant's Table from 8/14/09, response to information request, p. 32)

In general, the most common TEAEs reported by duloxetine-treated patients occurred early in treatment (first week). For a majority of duloxetine-treated patients, these events resolved between 15 and 30 days after onset.

The majority of adverse events in the primary placebo-controlled analysis set were recorded as mild or moderate in severity. Nevertheless, more duloxetine-treated patients (11.7%) reported their adverse events as "severe" compared with placebo-treated patients (5.3%) and for individual common events, patients reported nausea and fatigue as "severe" significantly more frequently with duloxetine (1.7% and 1.4%, respectively) than placebo (0.2% and 0%).

All placebo-controlled analysis set

In the all placebo-controlled analysis set and all duloxetine exposure analysis set, the data are difficult to interpret for the different duloxetine dose groups since the majority of the pooled trials were not fixed-dose and of different design. Similar to the primary chronic pain trials, the duloxetine-treated patients experienced the following common adverse events significantly more frequently than placebo: nausea, headache, dry mouth, somnolence, insomnia, constipation, and fatigue.

Table 96: TEAEs – All Placebo-Controlled Analysis Set

**Table 3.6. Treatment-Emergent Adverse Events by Decreasing Frequency
 MedDRA Preferred Term
 All Randomized Patients
 All Placebo-Controlled Analyses Set**

MedDRA Preferred Term	PLACEBO (N=7010) n (%)	DULOXETINE (N=9685) n (%)	TOTAL (N=16695) n (%)
Patients with >= 1 Treatment-Emergent Adverse Event	4069 (58.0)	7095 (73.3)	11164 (66.9)
Nausea	528 (7.5)	2340 (24.2)	2868 (17.2)
Headache	682 (9.7)	1202 (12.4)	1884 (11.3)
Dry mouth	280 (4.0)	1254 (12.9)	1534 (9.2)
Constipation	231 (3.3)	997 (10.3)	1228 (7.4)
Dizziness	289 (4.1)	927 (9.6)	1216 (7.3)
Fatigue	273 (3.9)	901 (9.3)	1174 (7.0)
Insomnia	273 (3.9)	835 (8.6)	1108 (6.6)
Diarrhoea	341 (4.9)	732 (7.6)	1073 (6.4)
Somnolence	118 (1.7)	675 (7.0)	793 (4.7)

(Source: Applicant's table from ISS, p. 33)

Overall the 60 mg and the 120 mg dose groups had similar incidence of TEAEs (82.7% vs. 80.4%). Nevertheless, patients administered duloxetine 120 mg experienced the following main events more frequently than patients administered duloxetine 60 mg: somnolence, fatigue, insomnia, dry mouth, constipation, and tremor.

Table 97: TEAEs for 60 mg and 120 mg dose groups – All Placebo-Controlled fixed dose trials

Table 3.23. Treatment-Emergent Adverse Events by Decreasing Frequency and By Dose All Randomized Patients in Fixed Dose Studies All Placebo-Controlled Analyses Set

MedDRA Preferred Term	DLX60MG/Day (N=913) n (%)	DLX120MG/Day (N=904) n (%)	TOTAL (N=1817) n (%)	CMH p-Value (a)
PATIENTS WITH >=1 TEAE	734 (80.4)	748 (82.7)	1482 (81.6)	.179
Nausea	268 (29.4)	274 (30.3)	542 (29.8)	.671
Headache	136 (14.9)	136 (15.0)	272 (15.0)	.927
*Somnolence	103 (11.3)	152 (16.8)	255 (14.0)	<.001
*Fatigue	112 (12.3)	133 (14.7)	245 (13.5)	.126
Dry mouth	98 (10.7)	138 (15.3)	236 (13.0)	.004
*Insomnia	98 (10.7)	123 (13.6)	221 (12.2)	.057
Dizziness	97 (10.6)	122 (13.5)	219 (12.1)	.061
Constipation	81 (8.9)	120 (13.3)	201 (11.1)	.002
*Decreased appetite	74 (8.1)	115 (12.7)	189 (10.4)	.001

(Source: Applicant's Table from ISS, p. 1286)

The most commonly observed TEAEs in the all duloxetine exposure analysis set were similar to the one described above for the primary chronic pain trials and all placebo-controlled trials.

7.4.2 Laboratory Findings

In the four chronic pain trials, hematology laboratory tests were only collected at baseline. Thus, no statistical analysis was conducted for hematology.

Pooled analysis for chemistry and liver function are presented by treatment group and separately for the first seven weeks and then the second six weeks of treatment (Week 8 to Week 13 of the Acute Phase).

All four chronic pain trials (HMEN, HMEP, HMFG and HMEO) incorporate duloxetine 60-mg treatment group during the first seven weeks of treatment. The results for the duloxetine 20 mg and 120 mg treatment groups during the first seven weeks of treatment come from Study HMEO only. The baseline for the first seven weeks of treatment is the pretreatment value whereas the baseline for the second six weeks of treatment is based on pre-treatment values and values from the first seven weeks of treatment. Additionally, the patient population is different between the treatment periods. Some patients, for example, will have been on 120 mg only after being on duloxetine 60 for six weeks (HMEP, HMEN and HMFG) whereas the remaining patients were on duloxetine 120 mg for the entire trial (HMEO). Also, some patients from each treatment arm discontinued after the first seven weeks of treatment.

Because only one scheduled visit (Visit 5) fell into the interval of last six weeks, the results of mean change from baseline to endpoint and mean change from baseline to maximum are identical for the last six weeks.

7.4.2.1 Chemistry Analyses

Analysis focused on measures of central tendency

For the primary chronic pain analysis set, during the first seven weeks of the treatment period, greater decreases in calcium, chloride, sodium, and total protein were observed for patients administered duloxetine 60 mg compared with patients administered placebo. Greater decreases in these analytes were also observed for patients taking duloxetine 120 mg when compared with those taking duloxetine 60 mg. Additionally, a difference was observed in alkaline phosphatase (ALKPH) where the levels in patients taking placebo decreased and levels in patients taking duloxetine 60 mg increased. Overall, the absolute numbers were small.

During the second 6 weeks of treatment, no consistent trends were observed compared with the first 7 weeks of treatment.

Calcium, chloride, and total protein changes were not observed consistently within the all-placebo-controlled analysis set and are not described in the current label.

Table 98: Biochemistry Parameters – Mean change from baseline – First 7 weeks of Treatment Period – Primary Chronic Pain Trials

Table 4.2. Laboratory Values - Chemistry Analytes
 Change from Baseline to Endpoint
 All Randomized Patients
 Primary Placebo-Controlled Analyses Set - Chronic Pain (first 7 weeks)

Lab Test	Lab Unit	Therapy	N	Baseline		Change to Endpoint	
				Mean	SD	Mean	SD
ALBUMIN	g/L	Placebo	461	41.49	2.85	-0.59	2.45
		DLX60QD	432	41.63	2.93	-0.84	2.42
		DLX20QD	57	41.93	2.78	-1.74	2.91
		DLX120QD	104	41.59	3.12	-1.20	2.98
ALKALINE PHOSPHATASE	U/L	Placebo	462	75.40	20.75	-0.55	10.72
		DLX60QD	436	78.30	22.67	0.92	11.15
		DLX20QD	58	85.07	21.05	-0.26	9.88
		DLX120QD	104	76.10	25.70	1.08	11.46
ALT/SGPT	U/L	Placebo	459	24.14	13.49	-1.02	10.36
		DLX60QD	430	23.03	12.87	1.43	27.14
		DLX20QD	56	24.05	15.21	-1.75	8.95
		DLX120QD	104	20.63	10.07	2.64	11.91
AST/SGOT	U/L	Placebo	456	23.04	8.19	-0.53	7.01
		DLX60QD	423	22.32	7.07	1.30	13.77
		DLX20QD	56	22.27	7.73	-1.07	7.65
		DLX120QD	103	21.54	7.32	1.79	7.43
BICARBONATE, HCO ₃	mmol/L	Placebo	460	24.46	2.79	0.19	3.02
		DLX60QD	431	24.60	2.52	0.22	2.79
BICARBONATE, HCO ₃		DLX20QD	57	23.57	2.79	1.02	3.24
		DLX120QD	104	23.60	2.51	1.97	2.76
BILIRUBIN, DIRECT	umol/L	Placebo	444	1.96	0.95	0.03	0.79
		DLX60QD	417	1.93	0.92	0.00	0.78
		DLX20QD	56	1.91	0.86	-0.20	0.84
		DLX120QD	102	1.86	0.80	-0.05	0.79
BILIRUBIN, TOTAL	umol/L	Placebo	461	8.44	4.56	0.29	3.12
		DLX60QD	431	8.17	4.19	0.03	3.02
		DLX20QD	57	8.28	3.37	-0.96	2.84
		DLX120QD	104	7.77	3.80	-0.49	3.01
CALCIUM	mmol/L	Placebo	463	2.42	0.11	-0.01	0.09
		DLX60QD	437	2.42	0.09	-0.03	0.09
		DLX20QD	58	2.44	0.08	-0.04	0.11
		DLX120QD	104	2.46	0.10	-0.05	0.10
CHLORIDE	mmol/L	Placebo	463	103.97	2.48	-0.35	2.42
		DLX60QD	437	103.87	2.39	-0.72	2.59
		DLX20QD	58	103.31	2.61	-0.10	1.99
		DLX120QD	104	103.43	2.58	-0.97	2.47
GLUCOSE, NON-FASTING OR RANDOM		DLX20QD	56	5.35	0.84	0.33	1.17
		DLX120QD	104	5.57	1.55	0.07	1.51
INORGANIC PHOSPHORUS	mmol/L	Placebo	460	1.16	0.17	-0.01	0.17
		DLX60QD	434	1.15	0.16	-0.01	0.18
		DLX20QD	57	1.16	0.20	-0.02	0.18
		DLX120QD	104	1.18	0.15	-0.02	0.18
POTASSIUM	mmol/L	Placebo	459	4.36	0.38	-0.02	0.48
		DLX60QD	433	4.36	0.37	-0.01	0.42
		DLX20QD	56	4.35	0.37	-0.09	0.40
		DLX120QD	104	4.32	0.42	-0.00	0.44
SODIUM	mmol/L	Placebo	463	141.30	2.41	-0.55	2.45
		DLX60QD	437	141.29	2.27	-0.90	2.52
		DLX20QD	58	141.14	2.52	-0.86	2.39
		DLX120QD	104	141.12	2.46	-1.34	2.62
TOTAL PROTEIN	g/L	Placebo	463	72.26	4.35	-1.02	3.70
		DLX60QD	437	72.25	4.38	-1.59	3.49
		DLX20QD	58	73.21	4.78	-2.64	4.24
		DLX120QD	104	72.54	4.54	-2.30	3.90

UREA NITROGEN	mmol/L	Placebo	463	5.86	1.83	-0.02	1.46
		DLX60QD	437	5.87	1.63	-0.07	1.44
		DLX20QD	58	5.89	2.83	-0.46	2.64
		DLX120QD	104	6.00	1.73	-0.14	1.17
URIC ACID	umol/L	Placebo	463	304.56	80.74	4.39	48.25
		DLX60QD	436	308.47	79.67	-12.97	47.93
		DLX20QD	58	321.98	92.58	-13.45	46.08
		DLX120QD	104	310.11	85.66	-21.94	45.47

(Source: Applicant's table 4.2 form 8/14/09 response to information request, pp. 44-48)

Table 99: Biochemistry Parameters – Mean change from baseline – Last 6 weeks of Treatment Period – Primary Chronic Pain Trials

Table 4.3. Laboratory Values - Chemistry Analytes
 Change from Baseline to Endpoint
 All Randomized Patients
 Primary Placebo-Controlled Analyses Set - Chronic Pain (Second 6 Weeks)

Lab Test	Lab Unit	Therapy	N	Baseline		Change to Endpoint	
				Mean	SD	Mean	SD
ALBUMIN	g/L	Placebo	393	40.88	2.63	-0.05	2.40
		DLX60QD	245	40.59	2.85	0.07	2.53
		DLX20QD	44	40.64	3.07	0.20	2.24
		DLX120QD	166	40.93	2.59	-0.16	2.24
ALKALINE PHOSPHATASE	U/L	Placebo	396	74.69	22.57	-1.71	11.30
		DLX60QD	246	80.13	24.20	1.95	12.93
		DLX20QD	44	85.91	22.53	-1.23	9.35
		DLX120QD	167	76.13	24.74	0.18	11.76
ALT/SGPT	U/L	Placebo	393	22.60	14.56	-0.01	11.68
		DLX60QD	245	23.68	20.18	-0.53	19.14
		DLX20QD	44	21.84	10.59	0.48	9.66
		DLX120QD	166	25.43	35.31	-1.48	34.35
AST/SGOT	U/L	Placebo	385	22.29	10.26	0.01	7.76
		DLX60QD	242	23.36	12.59	-0.41	12.01
		DLX20QD	44	20.55	4.85	1.61	6.28
		DLX120QD	163	23.64	15.30	-0.71	14.30
BICARBONATE, HCO3	mmol/L	Placebo	393	24.74	2.42	0.09	2.65
		DLX60QD	245	24.97	2.37	0.29	2.66
		DLX20QD	44	24.90	2.39	0.03	2.53
		DLX120QD	166	25.17	2.69	0.26	2.54
BILIRUBIN, DIRECT	umol/L	Placebo	376	1.99	1.02	-0.05	0.88
		DLX60QD	240	1.93	0.93	-0.09	0.87
		DLX20QD	43	1.70	0.56	-0.14	0.60
		DLX120QD	162	1.93	0.82	-0.12	0.70
BILIRUBIN, TOTAL	umol/L	Placebo	393	8.65	4.44	-0.15	3.24
		DLX60QD	245	8.25	4.07	-0.12	3.43
		DLX20QD	44	7.44	2.89	-0.26	3.06
		DLX120QD	166	8.17	3.57	-0.42	2.76
CALCIUM	mmol/L	Placebo	396	2.40	0.09	-0.01	0.09
		DLX60QD	246	2.39	0.09	0.01	0.09
		DLX20QD	44	2.41	0.11	-0.00	0.10
		DLX120QD	167	2.40	0.09	0.01	0.08
CHLORIDE	mmol/L	Placebo	396	103.62	2.41	0.14	2.31
		DLX60QD	246	103.12	2.50	0.20	2.48
		DLX20QD	44	103.23	1.92	-0.16	2.01
		DLX120QD	167	102.72	2.81	0.10	2.48
CHOLESTEROL	mmol/L	Placebo	396	5.42	1.06	-0.05	0.72
		DLX60QD	246	5.51	1.06	0.04	0.71
		DLX20QD	44	5.50	1.13	0.14	0.70
		DLX120QD	167	5.42	1.05	0.09	0.62

POTASSIUM	mmol/L	Placebo	396	4.36	0.46	-0.00	0.50
		DLX60QD	246	4.34	0.42	0.02	0.47
		DLX20QD	44	4.31	0.39	0.05	0.36
		DLX120QD	167	4.34	0.45	0.06	0.41
SODIUM	mmol/L	Placebo	396	140.79	2.30	-0.14	2.31
		DLX60QD	246	140.32	2.27	0.38	2.40
		DLX20QD	44	140.36	1.79	0.00	2.15
		DLX120QD	167	140.04	2.60	0.19	2.71
TOTAL PROTEIN	g/L	Placebo	396	71.15	3.87	-0.16	3.35
		DLX60QD	246	70.57	3.88	0.33	3.31
		DLX20QD	44	70.75	4.21	0.30	3.28
		DLX120QD	167	70.32	4.00	0.08	3.09
UREA NITROGEN	mmol/L	Placebo	396	5.82	1.75	0.05	1.37
		DLX60QD	246	5.75	1.67	0.11	1.39
		DLX20QD	44	5.57	1.79	0.47	1.29
		DLX120QD	167	5.87	1.76	0.03	1.31
URIC ACID	umol/L	Placebo	396	309.44	83.43	1.15	47.45
		DLX60QD	246	292.60	80.15	7.14	45.10
		DLX20QD	44	301.52	83.28	5.23	40.38
		DLX120QD	167	287.08	83.70	10.36	45.85

(Source: Applicant's table 4.3 form 8/14/09 response to information request, pp. 49-52)

Analyses of mean change from baseline to maximum for the first 7 weeks of treatment and for the second 6 weeks of treatment produced similar results to the analyses from baseline to endpoint.

Results from the primary long-term analysis set (HMEN extension) demonstrate that for the majority of chemistry analytes, levels tended to return to baseline values with continued duloxetine treatment (DLX_DLX60/120-treated patients from HMEN extension compared with acute duloxetine exposure from primary placebo-controlled analyses set). Two notable exceptions are ALT and gamma glutamyl transferase (GGT) analytes, with mean increases observed during both long-term and acute duloxetine exposure.

Analysis focused on outliers or shifts from normal to abnormal

For treatment-emergent abnormal laboratory values at endpoint, during the first seven weeks of treatment, high AST values were experienced by more patients administered duloxetine in a dose dependant manner (DLX 20mg-5.4%, DLX 60 mg-5.0%, and DLX 120 mg-7.8%) compared to patients administered placebo (2.3%). Similarly, more patients on duloxetine 60 mg (4.8%) and duloxetine 120 mg (6.9%) experienced high ALT values during the first seven weeks of treatment compared to duloxetine 20mg (1.9%) and placebo (3.6%). No associated changes in bilirubin were observed. Section 7.4.2.2 provides additional hepatic laboratory analysis.

High bicarbonate level during the first seven weeks of treatment was experienced more frequently by subjects on duloxetine 120 mg (2.8%) compared to duloxetine 60 mg (0.9%) and placebo (0%).

These differences in ALT/AST and bicarbonate levels were not observed or were decreased during the second six weeks of treatment.

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Similar results were noted for treatment-emergent abnormal values at any endpoint.

The current product label informs that duloxetine increases the risk of elevation of serum transaminases levels. Elevation of bicarbonate levels is not included.

Table 100: Shifts from baseline to “high” and “low” values at endpoint for biochemistry parameters – Primary controlled analysis set – First 7 weeks of treatment

Table 4.8. Treatment Emergent Abnormal Laboratory Values at Endpoint - Chemistry Analy
 (b) (4) Reference Ranges
 All Randomized Patients
 Primary Placebo-Controlled Analyses Set - Chronic Pain (first 7 weeks)

Lab Test	Direction	Placebo			DLX20QD			DLX60QD			DLX120QD		
		N	n	%	N	n	%	N	n	%	N	n	%
ALBUMIN	High	462	1	0.2	57	0	0	437	0	0	104	0	0
	Low	466	0	0	58	0	0	440	0	0	106	1	0.9
ALKALINE PHOSPHATASE	High	458	5	1.1	56	1	1.8	425	6	1.4	104	1	1.0
	Low	467	1	0.2	58	0	0	443	0	0	105	0	0
ALT/SGPT	High	412	15	3.6	53	1	1.9	399	19	4.8	101	7	6.9
	Low	466	2	0.4	58	0	0	439	1	0.2	105	0	0
AST/SGOT	High	439	10	2.3	56	3	5.4	418	21	5.0	103	8	7.8
	Low	465	1	0.2	58	0	0	433	0	0	106	1	0.9
BICARBONATE, HCO3	High	462	0	0	58	0	0	439	4	0.9	106	3	2.8
	Low	464	1	0.2	57	0	0	441	4	0.9	105	0	0
BILIRUBIN, DIRECT	High	455	2	0.4	58	0	0	431	0	0	105	0	0
	Low	456	0	0	58	0	0	431	0	0	105	0	0
BILIRUBIN, TOTAL	High	455	5	1.1	58	0	0	433	2	0.5	105	0	0
	Low	458	7	1.5	58	1	1.7	431	9	2.1	104	2	1.9
CALCIUM	High	457	0	0	56	1	1.8	437	2	0.5	101	1	1.0
CALCIUM	Low	467	0	0	58	0	0	445	0	0	106	0	0
CHLORIDE	High	467	0	0	58	0	0	445	0	0	106	0	0
	Low	467	1	0.2	58	0	0	445	0	0	106	1	0.9
CHOLESTEROL	High	456	4	0.9	57	2	3.5	427	7	1.6	102	2	2.0
	Low	379	37	9.8	49	6	12.2	374	32	8.6	76	7	9.2
CREATINE PHOSPHOKINASE	High	396	28	7.1	49	4	8.2	373	32	8.6	89	3	3.4
	Low	467	0	0	58	0	0	441	0	0	106	0	0
CREATININE	High	452	6	1.3	55	2	3.6	429	5	1.2	103	1	1.0
	Low	468	0	0	58	0	0	444	0	0	106	0	0
GAMMA GLUTAMYLTRANSFERASE (GGT)	High	419	12	2.9	53	3	5.7	401	12	3.0	100	2	2.0
	Low	467	0	0	58	0	0	443	2	0.5	105	1	1.0
GLUCOSE, NON-FASTING OR RANDOM	High	359	2	0.6	58	0	0	334	5	1.5	104	1	1.0
	Low	356	8	2.2	56	0	0	336	4	1.2	105	3	2.9

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INORGANIC PHOSPHORUS	High	465	0	0	58	0	0	440	1	0.2	106	0	0
	Low	465	1	0.2	58	0	0	440	2	0.5	106	1	0.9
POTASSIUM	High	460	4	0.9	58	0	0	435	5	1.1	104	0	0
	Low	464	2	0.4	58	0	0	440	5	1.1	106	1	0.9
SODIUM	High	455	6	1.3	56	0	0	433	6	1.4	102	1	1.0
	Low	464	1	0.2	58	0	0	445	1	0.2	106	2	1.9
TOTAL PROTEIN	High	461	4	0.9	57	1	1.8	438	3	0.7	106	0	0
	Low	466	1	0.2	58	1	1.7	445	1	0.2	106	0	0
UREA NITROGEN	High	450	11	2.4	55	1	1.8	431	11	2.6	101	2	2.0
	Low	468	0	0	58	0	0	445	0	0	106	0	0
URIC ACID	High	455	15	3.3	54	1	1.9	429	4	0.9	101	1	1.0
	Low	465	1	0.2	57	0	0	442	5	1.1	106	1	0.9

(Source: Applicant's table 4.8 form 8/14/09 response to information request, pp. 68-70)

Table 101: Shifts from baseline to “high” and “low” values at endpoint for biochemistry parameters – Primary controlled analysis set – Last 6 weeks of treatment

Table 4.9. Treatment Emergent Abnormal Laboratory Values at Endpoint - Chemistry Analytes
 (b) (4) Reference Ranges
 All Randomized Patients with
 Primary Placebo-Controlled Analyses Set - Chronic Pain (Second 6 Weeks)

Lab Test	Direction	Placebo			DLX20QD			DLI60QD			DLI120QD		
		N	n	%	N	n	%	N	n	%	N	n	%
ALBUMIN	High	391	2	0.5	43	0	0	244	1	0.4	165	1	0.6
	Low	394	2	0.5	44	0	0	246	0	0	167	1	0.6
ALKALINE PHOSPHATASE	High	384	1	0.3	41	1	2.4	231	4	1.7	162	2	1.2
	Low	395	3	0.8	44	0	0	245	0	0	167	0	0
ALT/SGPT	High	331	13	3.9	41	1	2.4	204	11	5.4	144	7	4.9
	Low	392	0	0	44	0	0	246	0	0	167	0	0
AST/SGOT	High	355	7	2.0	40	1	2.5	220	12	5.5	147	4	2.7
	Low	385	1	0.3	44	0	0	243	0	0	163	0	0
BICARBONATE, HCO3	High	392	1	0.3	44	1	2.3	243	3	1.2	163	2	1.2
	Low	390	1	0.3	43	0	0	244	1	0.4	167	0	0
BILIRUBIN, DIRECT	High	376	0	0	43	0	0	242	1	0.4	163	0	0
	Low	379	0	0	43	0	0	242	0	0	163	0	0
BILIRUBIN, TOTAL	High	379	3	0.8	44	0	0	241	1	0.4	164	0	0
	Low	377	8	2.1	43	2	4.7	236	4	1.7	157	3	1.9
CALCIUM	High	390	1	0.3	42	0	0	243	1	0.4	161	0	0
	Low	397	1	0.3	44	0	0	247	1	0.4	168	0	0
CHLORIDE	High	397	0	0	44	0	0	247	0	0	168	0	0

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CHLORIDE	Low	396	0	0	44	0	0	247	0	0	167	0	0
CHOLESTEROL	High	382	4	1.0	41	0	0	235	5	2.1	158	4	2.5
	Low	281	19	6.8	34	0	0	184	8	4.3	117	1	0.9
CREATINE PHOSPHOKINASE	High	297	15	5.1	35	4	11.4	182	5	2.7	131	4	3.1
	Low	395	0	0	44	0	0	247	0	0	167	0	0
CREATININE	High	374	8	2.1	39	1	2.6	233	3	1.3	161	2	1.2
	Low	398	0	0	44	0	0	247	1	0.4	168	0	0
GAMMA GLUTAMYLTRANSFERASE(GGT)	High	344	10	2.9	38	0	0	213	4	1.9	145	3	2.1
	Low	397	2	0.5	44	1	2.3	244	0	0	167	0	0
GLUCOSE, NON-FASTING OR RANDOM	High	302	3	1.0	44	0	0	186	2	1.1	138	2	1.4
	Low	292	0	0	40	1	2.5	181	2	1.1	134	2	1.5
INORGANIC PHOSPHORUS	High	396	1	0.3	44	0	0	244	3	1.2	168	0	0
	Low	396	0	0	44	0	0	245	0	0	165	0	0
POTASSIUM	High	388	3	0.8	43	0	0	239	1	0.4	160	2	1.3
	Low	395	2	0.5	44	0	0	245	2	0.8	162	1	0.6
SODIUM	High	375	3	0.8	42	0	0	232	2	0.9	163	3	1.8
	Low	393	2	0.5	44	0	0	245	2	0.8	164	1	0.6
TOTAL PROTEIN	High	391	0	0	43	0	0	243	0	0	165	1	0.6
	Low	395	2	0.5	43	0	0	246	0	0	168	0	0
UREA NITROGEN	High	369	5	1.4	40	2	5.0	233	4	1.7	147	3	2.0
	Low	398	0	0	44	0	0	246	0	0	168	0	0
URIC ACID	High	370	4	1.1	39	0	0	236	0	0	162	2	1.2
	Low	396	4	1.0	43	0	0	243	2	0.8	164	1	0.6

(Source: Applicant's table 4.9 from 8/14/09 response to information request, pp. 71-70)

In the all placebo-controlled analysis set, duloxetine-treated patients experienced high ALT (0.3%) and cholesterol values (1.3%) significantly more frequently than placebo-treated patients (0.1 and 0.9%, respectively).

When comparing the placebo-controlled analysis sets, the analytes with greater changes in duloxetine-treated patients in the primary placebo-controlled analyses (but not in the all placebo-controlled analyses) were mean albumin and mean direct bilirubin decreased at endpoint. However, these changes do not appear clinically meaningful. For other analytes, similar mean changes were observed in both placebo-controlled analyses sets, including mean increases in ALT and AST levels

Dropouts for chemistry abnormalities

Primary chronic pain trials

During the first 7 weeks of the treatment period, one subject from the 60 mg duloxetine group discontinued due to hepatic enzyme increase, and one subject from the placebo group discontinued due to creatine phosphokinase increase.

During the last 6 weeks, one subject from the 120 mg duloxetine group discontinued due to hepatic enzyme increase, and one subject from the 120 mg duloxetine group discontinued due to high creatinine values.

7.4.2.2 Liver Function Laboratory Analyses

The applicant has completed comprehensive reviews of duloxetine effect on the liver for previous applications and the hepatotoxicity associated with the drug is already described in the approved product label. The label states that duloxetine “increases the risk of elevation of serum transaminase levels.” The approved label goes on to describe that transaminase elevations led to discontinuation of 0.3% (82/27229) duloxetine-treated patients and that in these patients, the median time to detection of transaminase elevation was approximately 2 months. Additionally in controlled trials for all indications (other than fibromyalgia), elevations > 3 x ULN were observed in 1.1% (85/7632) of duloxetine-treated patients compared to 0.2% (13/5578) of placebo-treated patients.

Also, the label states that there is evidence of a dose-response effect for ALT and AST elevation of > 3 x ULN and > 5 x ULN.

Further, the label describes that “... 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....”

The analysis of hepatic related AEs and liver enzyme elevation in the OA and CLBP trials were consistent with what is already described in the label. Overall, a small number of subjects experienced hepatic related AEs. Nevertheless, no hepatic-related AEs were reported from subjects who received placebo and 20mg duloxetine treatment. The frequency of hepatic TEAES for the 60 mg and 120 mg duloxetine treatment groups was similar. More duloxetine-treated patients developed elevated AST/ALT but those were not associated with bilirubin elevation. Most of the subjects who developed hepatic-related TEAE had a baseline abnormally high LFTs. Three subjects on active treatment discontinued due to liver-related AEs. Analysis of the cases with elevated liver enzymes overtime showed that the majority returned to baseline after drug discontinuation and some even with continuous treatment with duloxetine. (See section 7.3.5 for details.)

Analysis of liver function tests focused on measure of central tendency

On the tables that follow the mean change from baseline to maximum analysis are presented for the first seven weeks of treatment and for the second six weeks of treatment. Similar results were observed in mean change from baseline to maximum analysis.

During the first seven weeks of treatment, numeric differences between patients administered placebo and those administered duloxetine 60 mg and duloxetine 120 mg were observed where levels of ALT, AST, and alkaline phosphatase increased with duloxetine treatment and decreased with placebo treatment. Mean change to maximum was similar for duloxetine 60 mg and duloxetine 120 mg.

During the second 6 weeks of treatment, a similar trend (that is, an increase) was observed with alkaline phosphatase levels while the opposite trend (that is, a decrease) was observed with ALT, AST, and total bilirubin levels when compared with the first 7 weeks of treatment. Overall, no dose related trends were observed in mean change to maximum between the duloxetine dose groups.

Table 102: Hepatic enzymes – Change from baseline to Maximum (HMEN, HMEP, HMFG, and HMEO – First 7 weeks)

Table 5.3. Hepatic Laboratory Analytes - Change from Baseline to Maximum All Randomized Patients Primary Placebo-Controlled Analyses Set - Chronic Pain (first 7 weeks)

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Analyte	Unit	Therapy	N	Baseline		Change to Maximum	
				Mean	SD	Mean	SD
ALT	U/L	Placebo	459	24.14	13.49	0.80	11.45
		DLI20QD	56	24.05	15.21	-0.39	8.52
		DLI60QD	430	23.03	12.87	3.35	27.57
		DLI120QD	104	20.63	10.07	3.55	11.50
AST	U/L	Placebo	456	23.04	8.19	0.68	7.29
		DLI20QD	56	22.27	7.73	0.25	6.33
		DLI60QD	423	22.32	7.07	2.75	14.95
		DLI120QD	103	21.54	7.32	2.50	7.24
T.BILI	umol/L	Placebo	461	8.44	4.56	0.90	3.06
		DLI20QD	57	8.28	3.37	-0.20	2.71
		DLI60QD	431	8.17	4.19	0.83	3.15
		DLI120QD	104	7.77	3.80	0.41	2.79
ALKPH	U/L	Placebo	462	75.40	20.75	1.54	10.63
		DLI20QD	58	85.07	21.05	1.74	9.90
		DLI60QD	436	78.30	22.67	2.69	11.43
		DLI120QD	104	76.10	25.70	2.57	10.84
GGT	U/L	Placebo	462	28.98	24.61	0.55	12.14
		DLI20QD	58	33.90	43.32	-0.45	13.47
		DLI60QD	436	28.49	24.63	1.27	19.39
		DLI120QD	104	25.46	18.96	0.32	17.24

(Source: Applicant's table 5.3 from 8/14/09 response to information request, pp. 101-102)

Table 103: Hepatic enzymes – Change from baseline to Maximum (HMEN, HMEP, HMFG, and HMEO – Last 6 weeks)

Table 5.4. Hepatic Laboratory Analytes - Change from Baseline to Maximum
 All Randomized Patients
 Primary Placebo-Controlled Analyses Set - Chronic Pain (second 6 weeks)

Analyte	Unit	Therapy	N	Baseline		Change to Maximum	
				Mean	SD	Mean	SD
ALT	U/L	Placebo	393	22.60	14.56	-0.01	11.68
		DLX20QD	44	21.84	10.59	0.48	9.66
		DLX60QD	245	23.68	20.18	-0.53	19.14
		DLX120QD	166	25.43	35.31	-1.48	34.35
AST	U/L	Placebo	385	22.29	10.26	0.01	7.76
		DLX20QD	44	20.55	4.85	1.61	6.28
		DLX60QD	242	23.36	12.59	-0.41	12.01
		DLX120QD	163	23.64	15.30	-0.71	14.30
T. BILI	umol/L	Placebo	393	8.65	4.44	-0.15	3.24
		DLX20QD	44	7.44	2.89	-0.26	3.06
		DLX60QD	245	8.25	4.07	-0.12	3.43
		DLX120QD	166	8.17	3.57	-0.42	2.76
ALP	U/L	Placebo	396	74.69	22.57	-1.71	11.30
		DLX20QD	44	85.91	22.53	-1.23	9.35
		DLX60QD	246	80.13	24.20	1.95	12.93
		DLX120QD	167	76.13	24.74	0.18	11.76
GGT	U/L	Placebo	396	26.97	23.32	0.03	14.64
		DLX20QD	44	31.82	37.97	-1.23	13.64
		DLX60QD	246	25.79	20.75	2.92	14.87
		DLX120QD	167	26.80	26.86	0.23	15.45

(Source: Applicant's table 5.4 from 8/14/09 response to information request, pp. 103-104)

Analysis focused on outliers or shifts from normal to abnormal

For treatment-emergent abnormal hepatic laboratory values, analyses were performed separately for patients who had a normal baseline LFTs values and for patients who had abnormal high baseline LFTs values.

- All randomized patients with normal baseline values
 As illustrated on the tables below, more patients from the duloxetine 60 mg and 120 mg treatment groups with normal baseline values, experienced high ALT and AST values during the first seven weeks of treatment compared to placebo patients [AST: duloxetine 20mg (5.4%), duloxetine 60 mg (5.0%), duloxetine 120 mg (7.8%), and placebo (2.3%); ALT: duloxetine 20mg (1.9%), duloxetine 60 mg (4.8%), duloxetine 120 mg (7.0%), and placebo (3.6%)]. No associated changes in bilirubin were observed.

These differences were not apparent during the second six weeks of the treatment period.

Table 104: Shifts from baseline to “high” and “low” values at endpoint for LFTs- Primary chronic pain trials – First 7 weeks of treatment

Table 5.5. Treatment Emergent Abnormal Laboratory Values at Endpoint - Hepatic Laboratory Analytes All Randomized Patients with a Normal Baseline Primary Placebo-Controlled Analyses Set - Chronic Pain (First 7 weeks)

Lab Test	Direction	Placebo			DLX20QD			DLX60QD			DLX120QD			DLX Total		
		N	n	%	N	n	%	N	n	%	N	n	%	N	n	%
ALKALINE PHOSPHATASE	Normal->High	457	5	1.1	56	1	1.8	424	6	1.4	103	1	1.0	583	8	1.4
	Normal->Low	457	1	0.2	56	0	0	424	0	0	103	0	0	583	0	0
ALT/SGPT	Normal->High	411	15	3.6	53	1	1.9	398	19	4.8	100	7	7.0	551	27	4.9
	Normal->Low	411	2	0.5	53	0	0	398	1	0.3	100	0	0	551	1	0.2
AST/SGOT	Normal->High	438	10	2.3	56	3	5.4	417	21	5.0	103	8	7.8	576	32	5.6
	Normal->Low	438	1	0.2	56	0	0	417	0	0	103	1	1.0	576	1	0.2
BILIRUBIN, TOTAL	Normal->High	445	5	1.1	58	0	0	423	2	0.5	103	0	0	584	2	0.3
	Normal->Low	445	7	1.6	58	1	1.7	423	9	2.1	103	2	1.9	584	12	2.1
GAMMA GLUTAMYLTRANSFERASE (GGT)	Normal->High	418	12	2.9	53	3	5.7	400	12	3.0	99	2	2.0	552	17	3.1
	Normal->Low	418	0	0	53	0	0	400	2	0.5	99	1	1.0	552	3	0.5

(Source: Applicant's table 5.5 from 8/14/09 response to information request, p. 105)

Table 105: Shifts from baseline to “high” and “low” values at endpoint for LFTs– Primary chronic pain trials – Last 6 weeks of treatment

Table 5.6. Treatment Emergent Abnormal Laboratory Values at Endpoint - Hepatic Laboratory Analytes All Randomized Patients with a Normal Baseline Primary Placebo-Controlled Analyses Set - Chronic Pain (Second 6 weeks)

Lab Test	Direction	Placebo			DLX20QD			DLX60QD			DLX120QD			DLX Total		
		N	n	%	N	n	%	N	n	%	N	n	%	N	n	%
ALKALINE PHOSPHATASE	Normal->High	381	1	0.3	41	1	2.4	229	4	1.7	161	2	1.2	431	7	1.6
	Normal->Low	381	3	0.8	41	0	0	229	0	0	161	0	0	431	0	0
ALT/SGPT	Normal->High	328	13	4.0	41	1	2.4	203	11	5.4	144	7	4.9	388	19	4.9
	Normal->Low	328	0	0	41	0	0	203	0	0	144	0	0	388	0	0
AST/SGOT	Normal->High	353	7	2.0	40	1	2.5	219	12	5.5	146	4	2.7	405	17	4.2
	Normal->Low	353	1	0.3	40	0	0	219	0	0	146	0	0	405	0	0
BILIRUBIN, TOTAL	Normal->High	361	3	0.8	43	0	0	230	1	0.4	154	0	0	427	1	0.2
	Normal->Low	361	8	2.2	43	2	4.7	230	4	1.7	154	3	1.9	427	9	2.1
GAMMA GLUTAMYLTRANSFERASE (GGT)	Normal->High	343	10	2.9	38	0	0	210	4	1.9	144	3	2.1	392	7	1.8
	Normal->Low	343	2	0.6	38	1	2.6	210	0	0	144	0	0	392	1	0.3

(Source: Applicant's table 5.6 from 8/14/09 response to information request, p. 106)

- All randomized patients with abnormal baseline values
 This analysis shows that the majority of the patients from all treatment groups, who had abnormal baseline ALT/AST at baseline, had either normal or high but not higher readings at endpoint. This trend of changes was observed both during the first 7 weeks and the second 6 weeks of the treatment period.

Table 106: Shifts from baseline for LFTs in patients with abnormal high baseline LFT values– Primary chronic pain trials – First 7 weeks of treatment

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**Table 4.7. Shift Table for Laboratory Values at Endpoint - Hepatic Laboratory Analytes
 All Randomized Patients with At Least One Abnormally High Value at Baseline
 Primary Placebo-Controlled Analyses Set - Chronic Pain (first 7 weeks)**

Lab Test	Direction	Placebo			DLX20QD			DLX60QD			DLX120QD			DLX Total		
		N	n	%	N	n	%	N	n	%	N	n	%	N	n	%
ALKALINE PHOSPHATASE	High->Low	10	0	0	2	0	0	19	0	0	2	0	0	23	0	0
	High->Normal	10	3	30.0	2	1	50.0	19	5	26.3	2	0	0	23	6	26.1
	High->High	10	2	20.0	2	0	0	19	6	31.6	2	2	100	23	8	34.8
	High->Higher	10	5	50.0	2	1	50.0	19	8	42.1	2	0	0	23	9	39.1
ALT/SGPT	High->Low	55	0	0	5	0	0	41	0	0	5	0	0	51	0	0
	High->Normal	55	22	40.0	5	3	60.0	41	23	56.1	5	2	40.0	51	28	54.9
	High->High	55	13	23.6	5	1	20.0	41	8	19.5	5	1	20.0	51	10	19.6
	High->Higher	55	20	36.4	5	1	20.0	41	10	24.4	5	2	40.0	51	13	25.5
AST/SGOT	High->Low	27	0	0	2	0	0	16	0	0	3	0	0	21	0	0
	High->Normal	27	14	51.9	2	2	100	16	10	62.5	3	1	33.3	21	13	61.9
	High->High	27	6	22.2	2	0	0	16	4	25.0	3	1	33.3	21	5	23.8
	High->Higher	27	7	25.9	2	0	0	16	2	12.5	3	1	33.3	21	3	14.3
BILIRUBIN, TOTAL	High->Low	13	0	0	0	0	0	8	0	0	1	0	0	9	0	0
	High->Normal	13	7	53.8	0	0	0	8	7	87.5	1	1	100	9	8	88.9
	High->High	13	3	23.1	0	0	0	8	0	0	1	0	0	9	0	0
	High->Higher	13	3	23.1	0	0	0	8	1	12.5	1	0	0	9	1	11.1
GAMMA GLUTAMYLTRANSFERASE (GPT)	High->Low	49	0	0	5	0	0	43	0	0	6	0	0	54	0	0
	High->Normal	49	16	32.7	5	1	20.0	43	16	37.2	6	2	33.3	54	19	35.2
GAMMA GLUTAMYLTRANSFERASE (GPT)	High->High	49	25	51.0	5	2	40.0	43	12	27.9	6	2	33.3	54	16	29.6
	High->Higher	49	8	16.3	5	2	40.0	43	15	34.9	6	2	33.3	54	19	35.2

(Source: Applicant's table 4.7 form 10/7/09 response to information request, pp. 21-22)

Table 107: Shifts from baseline for LFTs in patients with abnormal high baseline LFT values– Primary chronic pain trials – Second 6 weeks of treatment

**Table 4.8. Shift Table for Laboratory Values at Endpoint - Hepatic Laboratory Analytes
 All Randomized Patients with At Least One Abnormally High Value at Baseline
 Primary Placebo-Controlled Analyses Set - Chronic Pain (second 6 weeks)**

Lab Test	Direction	Placebo			DLX20QD			DLX60QD			DLX120QD			DLX Total		
		N	n	%	N	n	%	N	n	%	N	n	%	N	n	%
ALKALINE PHOSPHATASE	High->Low	14	0	0	3	0	0	16	0	0	6	0	0	25	0	0
	High->Normal	14	7	50.0	3	3	100	16	6	37.5	6	1	16.7	25	10	40.0
	High->High	14	1	7.1	3	0	0	16	1	6.3	6	3	50.0	25	4	16.0
	High->Higher	14	6	42.9	3	0	0	16	9	56.3	6	2	33.3	25	11	44.0
ALT/SGPT	High->Low	64	0	0	3	0	0	43	0	0	23	0	0	69	0	0
	High->Normal	64	37	57.8	3	1	33.3	43	28	65.1	23	15	65.2	69	44	63.8
	High->High	64	8	12.5	3	1	33.3	43	6	14.0	23	4	17.4	69	11	15.9
	High->Higher	64	19	29.7	3	1	33.3	43	9	20.9	23	4	17.4	69	14	20.3
AST/SGOT	High->Low	32	0	0	4	0	0	24	0	0	17	0	0	45	0	0
	High->Normal	32	22	68.8	4	4	100	24	16	66.7	17	12	70.6	45	32	71.1
	High->High	32	6	18.8	4	0	0	24	3	12.5	17	1	5.9	45	4	8.9
	High->Higher	32	4	12.5	4	0	0	24	5	20.8	17	4	23.5	45	9	20.0
BILIRUBIN, TOTAL	High->Low	16	0	0	0	0	0	6	0	0	3	0	0	9	0	0
	High->Normal	16	11	68.8	0	0	0	6	4	66.7	3	2	66.7	9	6	66.7
	High->High	16	1	6.3	0	0	0	6	1	16.7	3	1	33.3	9	2	22.2
	High->Higher	16	4	25.0	0	0	0	6	1	16.7	3	0	0	9	1	11.1
GAMMA GLUTAMYLTRANSFERASE (GPT)	High->Low	54	0	0	6	0	0	34	0	0	23	0	0	63	0	0
	High->Normal	54	27	50.0	6	1	16.7	34	15	44.1	23	9	39.1	63	25	39.7
	High->High	54	13	24.1	6	1	16.7	34	2	5.9	23	5	21.7	63	8	12.7
GAMMA GLUTAMYLTRANSFERASE (GPT)	High->Higher	54	14	25.9	6	4	66.7	34	17	50.0	23	9	39.1	63	30	47.6

(Source: Applicant's table 4.8 form 10/7/09 response to information request, pp. 23-24)

- All randomized patients who entered HMEN extension phase

The table below presents the shifts in hepatic laboratory analyte values at anytime by dose at each visit of the extension phase for all randomized patients who entered the extension phase of HMEN. In this analyses, the shift from low or normal at baseline to high at post-baseline (L/N→H) was determined by the applicant as the number of patients who had high values at any time during post-baseline (numerator) among all the patients who have normal or low values at all the baseline visits (denominator); the shift from high or normal at baseline to low at post-baseline (H/N→L) was determined as the number of patients who had low values at any time during post-baseline (numerator) among all the patients who have normal or high values at all the baseline visits (denominator). As illustrated on the table below, more patients on duloxetine 60 mg developed elevations in gamma glutamyl transferase and more patients on duloxetine 120 mg developed elevations in AST levels and bilirubin levels.

Table 108: Shifts from baseline at anytime, all randomized patients in HMEN extension phase

Table 3. Treatment-Emergent Abnormal Laboratory Values at Anytime - Hepatic Laboratory Analytes All Randomized Patients who Entered Extension Phase by Dose F1J-MC-HMEN Extension Treatment Phase

Lab Analyte	Visit	Direction	--- DLX60QD ---			--- DLX120QD ---			----- Total -----		
			N	n	(%)	N	n	(%)	N	n	(%)
ALKALINE PHOSPHATASE	6	H/N-->L	11	0	(0)	0	0		11	0	(0)
		L/N-->H	11	0	(0)	0	0		11	0	(0)
	7	H/N-->L	136	0	(0)	24	0	(0)	160	0	(0)
		L/N-->H	131	2	(1.5)	24	0	(0)	155	2	(1.3)
	8	H/N-->L	98	0	(0)	50	0	(0)	148	0	(0)
		L/N-->H	95	2	(2.1)	47	1	(2.1)	142	3	(2.1)
	9	H/N-->L	78	0	(0)	56	0	(0)	134	0	(0)
		L/N-->H	74	0	(0)	52	0	(0)	126	0	(0)
	10	H/N-->L	70	0	(0)	54	0	(0)	124	0	(0)
		L/N-->H	66	1	(1.5)	51	0	(0)	117	1	(0.9)
	11	H/N-->L	67	0	(0)	50	0	(0)	117	0	(0)
L/N-->H		63	1	(1.6)	46	1	(2.2)	109	2	(1.8)	
ALT/SGPT	6	H/N-->L	11	0	(0)	0	0		11	0	(0)
		L/N-->H	6	0	(0)	0	0		6	0	(0)
	7	H/N-->L	136	0	(0)	24	0	(0)	160	0	(0)
		L/N-->H	117	7	(6.0)	22	1	(4.5)	139	8	(5.8)
	8	H/N-->L	94	0	(0)	49	0	(0)	143	0	(0)
		L/N-->H	77	1	(1.3)	43	4	(9.3)	120	5	(4.2)
	9	H/N-->L	76	0	(0)	55	0	(0)	131	0	(0)
		L/N-->H	61	2	(3.3)	42	0	(0)	103	2	(1.9)
	10	H/N-->L	69	0	(0)	53	0	(0)	122	0	(0)

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ALT/SGPT	10	L/N-->H	55	1	(1.8)	42	4	(9.5)	97	5	(5.2)
	11	H/N-->L	67	0	(0)	50	0	(0)	117	0	(0)
		L/N-->H	52	4	(7.7)	33	0	(0)	85	4	(4.7)
AST/SGOT	6	H/N-->L	11	0	(0)	0	0		11	0	(0)
		L/N-->H	8	0	(0)	0	0		8	0	(0)
	7	H/N-->L	133	0	(0)	24	0	(0)	157	0	(0)
		L/N-->H	119	6	(5.0)	21	0	(0)	140	6	(4.3)
	8	H/N-->L	94	0	(0)	48	0	(0)	142	0	(0)
		L/N-->H	78	0	(0)	45	3	(6.7)	123	3	(2.4)
	9	H/N-->L	76	0	(0)	54	0	(0)	130	0	(0)
		L/N-->H	63	0	(0)	45	2	(4.4)	108	2	(1.9)
	10	H/N-->L	68	0	(0)	53	0	(0)	121	0	(0)
		L/N-->H	58	1	(1.7)	42	2	(4.8)	100	3	(3.0)
	11	H/N-->L	67	0	(0)	49	0	(0)	116	0	(0)
	L/N-->H	55	1	(1.8)	35	1	(2.9)	90	2	(2.2)	
BILIRUBIN, TOTAL	6	H/N-->L	11	0	(0)	0	0		11	0	(0)
		L/N-->H	9	0	(0)	0	0		9	0	(0)
	7	H/N-->L	127	2	(1.6)	20	3	(15.0)	147	5	(3.4)
		L/N-->H	127	1	(0.8)	24	0	(0)	151	1	(0.7)
8	H/N-->L	84	2	(2.4)	44	0	(0)	128	2	(1.6)	
BILIRUBIN, TOTAL	8	L/N-->H	89	0	(0)	46	1	(2.2)	135	1	(0.7)
	9	H/N-->L	65	1	(1.5)	52	2	(3.8)	117	3	(2.6)
		L/N-->H	72	0	(0)	52	0	(0)	124	0	(0)
	10	H/N-->L	57	1	(1.8)	47	0	(0)	104	1	(1.0)
		L/N-->H	64	0	(0)	49	0	(0)	113	0	(0)
	11	H/N-->L	55	3	(5.5)	45	1	(2.2)	100	4	(4.0)
	L/N-->H	64	0	(0)	47	0	(0)	111	0	(0)	
GAMMA GLUTAMYLTRANSFERASE (GGT)	6	H/N-->L	11	0	(0)	0	0		11	0	(0)
		L/N-->H	7	1	(14.3)	0	0		7	1	(14.3)
	7	H/N-->L	136	1	(0.7)	24	0	(0)	160	1	(0.6)
		L/N-->H	119	4	(3.4)	19	0	(0)	138	4	(2.9)
	8	H/N-->L	98	1	(1.0)	49	1	(2.0)	147	2	(1.4)
		L/N-->H	82	4	(4.9)	43	1	(2.3)	125	5	(4.0)
	9	H/N-->L	77	0	(0)	54	0	(0)	131	0	(0)
		L/N-->H	62	2	(3.2)	47	3	(6.4)	109	5	(4.6)
	10	H/N-->L	69	0	(0)	52	0	(0)	121	0	(0)
		L/N-->H	57	0	(0)	43	1	(2.3)	100	1	(1.0)
	11	H/N-->L	66	0	(0)	49	0	(0)	115	0	(0)
	L/N-->H	51	0	(0)	37	1	(2.7)	88	1	(1.1)	

(Source: Applicant's table 3, from 10/19/09 response to information request, pp. 10-12)

Marked Outliers and dropouts for LFT abnormalities

- All randomized patients with normal baseline LFTs values

Overall, the number of patients who developed markedly abnormal ALT/AST values was small. For treatment-emergent abnormally high alanine transaminase (ALT) values, three duloxetine-treated patients (three administered 60 mg and one administered 120 mg) experienced ALT elevation more than three times upper limit of normal (>3xULN) during the first seven weeks of treatment. Two of the patients taking duloxetine 60 mg experienced an elevation >5X ULN while the third patient experienced an elevation >10X ULN. During the second 6 weeks of treatment, one patient (assigned to placebo) experienced an ALT elevation >3X ULN.

With respect to AST levels, three patients assigned to duloxetine 60 mg experienced an AST level >3X ULN, with one of the patients experiencing an increase >5X ULN during the first 7 weeks of treatment. No patients reported AST increases >3X ULN during the second 6 weeks of treatment.

Table 109: Markedly abnormal high ALT/AST values in patients with normal baseline values – HMEN, HMEO, HMEP, and HMFG

Parameter/Treatment	Maximum Post-Baseline		
	>3xULN	>5xULN	>10xULN
<i>Fist 7 weeks</i>			
ALT			
Placebo (N=412)	0	0	0
DLX 20mg (N=53)	0	0	0
DLX 60 mg (N=399)	3 (0.8%)	2 (0.5%)	01 (0.3%)
DLX 120 mg (N=101)	1 (1%)	0	0
AST			
Placebo (N=439)	0	0	0
DLX 20mg (N=56)	0	0	0
DLX 60 mg (N=418)	3 (0.7%)	1 (0.2%)	0
DLX 120 mg (N=103)	0	0	0
<i>Last 6 weeks</i>			
ALT			
Placebo (N=331)	1 (0.3%)	0	0
DLX 20mg (N=41)	0	0	0
DLX 60 mg (N=204)	0	0	0
DLX 120 mg (N=144)	0	0	0
AST			
Placebo (N=355)	0	0	0
DLX 20mg (N=40)	0	0	0
DLX 60 mg (N=220)	0	0	0
DLX 120 mg (N=147)	0	0	0

(Source: Derived from Applicant's tables 5.7, 5.8, 5.9 and 5.10 from 8/14/09 response to information request, pp. 109-111)

- All randomized patients with abnormal high baseline LFTs values
 More patients from the 60 mg DLX dose group who had abnormal baseline ALT/AST values developed >3xULN ALT/AST compared to the placebo group (14% versus 6%).
 Of note, no patients from the 20 mg and the 120 mg DLX dose groups with abnormal baseline transaminases developed markedly abnormal values.

Table 110: Markedly abnormal high ALT/AST values in patients with abnormal high baseline values – HMEN, HMEO, HMEP, and HMFG

Parameter/Treatment	Maximum Post-Baseline		
	>3xULN	>5xULN	>10xULN
<i>Fist 7 weeks</i>			

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ALT			
Placebo (N=55)	3 (5.5%)	0	0
DLX 20mg (N=5)	0	0	0
DLX 60 mg (N=41)	6 (14.3%)	1 (2.4%)	0
DLX 120 mg (N=5)	0	0	0
AST			
Placebo (N=27)	1 (3.7%)	0	0
DLX 20mg (N=2)	0	0	0
DLX 60 mg (N=16)	1 (6.3%)	0	0
DLX 120 mg (N=3)	0	0	0
<i>Last 6 weeks</i>			
ALT			
Placebo (N=64)	0	0	0
DLX 20mg (N=3)	0	0	0
DLX 60 mg (N=43)	2 (4.7%)	1 (2.3%)	0
DLX 120 mg (N=23)	0	0	0
AST			
Placebo (N=32)	0	0	0
DLX 20mg (N=4)	0	0	0
DLX 60 mg (N=24)	1 (4.2%)	0	0
DLX 120 mg (N=17)	0	0	0

(Source: Derived from Applicant's tables 4.11, 4.12, 4.13 and 4.14 from 10/7/09 response to information request, pp. 29-32)

- Patients randomized into the HMEN extension phase
 During the extension phase of HMEN, one patient (2.4%) from the 120 mg duloxetine group who had a normal baseline ALT value reported an ALT increase > 3xULN and one patient (5.9%), also from the 120 mg duloxetine group, who had an abnormal baseline ALT value, reported an ALT increase > 3xULN.

Reversibility of abnormal liver function overtime

Analysis of the cases with elevated liver enzymes overtime showed that the majority returned to baseline after drug discontinuation and for some cases with <3xULN increase even with continuous treatment with duloxetine. (See section 7.3.5 for details.)

Discontinuations due to abnormal liver function

One person (0.2%) from duloxetine 60 mg a day treatment group discontinued during the first seven weeks of the treatment period and one person (0.6%) from duloxetine 120 mg a day treatment group discontinued during the last six weeks of the treatment period due to hepatic enzyme increase. No placebo treated subjects discontinued the study due to abnormal liver enzymes. See Section 7.3.5 for details and summary of the narratives for these patients.

One of the subjects (Subject 034-3431), who discontinued the trial due to drug induced hepatitis, experienced ALT elevation greater than 10 times the ULN two days after stopping duloxetine (ALT of 356 U/L; reference range: 6-34 U/L). Twenty three days after stopping duloxetine patient's hepatic enzymes returned to within normal range.

7.4.3 Vital Signs

The most recent label says that "...duloxetine treatment was associated with mean increase of up to 2.1 mm Hg in systolic blood pressure and up to 2.3 mm Hg in diastolic blood pressure. There was no significant difference in the frequency in sustained elevated (3 consecutive visits) blood pressure."

Analysis focused on measure of central tendency

A statistically significant greater mean decrease in diastolic blood pressure was observed in patients administered placebo compared with patients administered duloxetine 60 mg during the first seven weeks of treatment. Patients administered duloxetine 120 mg experienced an increase in diastolic blood pressure (mean of 1.55 mmHg during the first seven weeks of treatment and 1.18 mmHg during the second six weeks).

A greater mean increase in pulse was observed for patients taking duloxetine 60 mg and 120 mg compared with patients taking placebo.

For change in weight, a significant difference was observed where patients administered duloxetine 60 mg experienced a mean decrease in weight and patients administered placebo experienced a mean increase in weight. Patients administered duloxetine 20 mg and 120 mg also experienced a mean decrease in weight during this time period. During the second six weeks of treatment, no clear trend was observed.

Similar vital signs profile was observed in the all placebo-controlled analysis set.

These findings are consistent with what is already described in the product label.

Table 111: Mean change from baseline to endpoint for VS– Primary chronic pain trials – First 7 weeks of treatment

**Table 4.14. Vital Signs and Weight
 Change from Baseline to Endpoint
 All Randomized Patients
 Primary Placebo-Controlled Analyses Set - Chronic Pain (First 7 weeks)**

Vital	Therapy	N	Baseline		Change to Endpoint	
			Mean	SD	Mean	SD
Pulse (sitting)	Placebo	466	71.00	8.97	0.58	8.35
	DLX60QD	442	71.16	8.67	2.09	8.96
	DLX20QD	58	73.74	10.66	-0.05	12.18
	DLX120QD	108	74.04	11.30	1.63	9.59
Systolic BP (sitting)	Placebo	467	128.78	14.85	-1.64	12.12
	DLX60QD	442	128.18	14.65	-0.94	12.44
	DLX20QD	58	127.47	13.62	-2.22	13.23
	DLX120QD	108	125.81	12.72	0.01	13.15
Diastolic BP (sitting)	Placebo	467	79.49	9.47	-1.38	8.31
	DLX60QD	442	79.30	9.04	-0.26	8.14
	DLX20QD	58	79.60	8.67	-0.26	7.94
	DLX120QD	108	76.88	9.84	1.55	8.57
Weight (Kg)	Placebo	475	81.01	15.07	0.17	1.91
	DLX60QD	449	80.96	15.10	-0.67	1.96
	DLX20QD	58	85.46	13.76	-0.48	1.81
	DLX120QD	108	82.64	18.89	-0.76	1.64

(Source: Applicant's table 4.14 from 8/14/09 response to information request, p. 86)

Table 112: Mean change from baseline to endpoint for VS– Primary chronic pain trials – Last 6 weeks of treatment

**Table 4.15. Vital Signs and Weight
 Change from Baseline to Endpoint
 All Randomized Patients
 Primary Placebo-Controlled Analyses Set - Chronic Pain (Second 6 weeks)**

Vital	Therapy	N	Baseline		Change to Endpoint	
			Mean	SD	Mean	SD
Pulse (sitting)	Placebo	405	71.46	8.59	-0.56	8.49
	DLX60QD	256	73.56	9.02	-0.25	8.72
	DLX20QD	44	73.61	10.00	0.75	7.48
	DLX120QD	171	73.77	8.65	0.92	9.18
Systolic BP (sitting)	Placebo	405	127.27	15.07	0.71	11.75
	DLX60QD	256	125.94	13.72	0.63	13.03
	DLX20QD	44	125.68	15.67	0.25	11.45
	DLX120QD	171	127.63	14.28	0.35	12.73
Diastolic BP (sitting)	Placebo	405	78.27	8.88	0.67	8.02
	DLX60QD	256	79.11	8.50	-0.25	8.36
	DLX20QD	44	79.89	9.21	0.20	8.40
	DLX120QD	171	78.53	8.85	1.18	7.38
Weight (Kg)	Placebo	413	80.77	15.08	-0.06	1.36
	DLX60QD	263	79.04	14.79	0.13	1.50
	DLX20QD	44	85.86	14.28	-0.04	1.28
	DLX120QD	170	81.58	16.61	0.06	1.60

(Source: Applicant's table 4.15 from 8/14/09 response to information request, p. 87)

Analysis focused on outliers or shifts from normal to abnormal

No significant changes and differences between treatment groups were observed for blood pressure and pulse during the first seven weeks and the last 6 weeks of the treatment period.

At endpoint, significantly more patients administered duloxetine 60 mg (1.6%) than patients administered placebo (0.2%) experienced weight loss of $\geq 7\%$ (compared to baseline) during the first seven weeks of treatment. A similar frequency of patients administered duloxetine 120 mg (1.9%) experienced weight loss of $\geq 7\%$. During the second six weeks of treatment, no weight loss was observed for any treatment group.

Similar results were reported for treatment-emergent values at anytime.

Table 113: Shifts from baseline to “high” and “low” values at endpoint for VS– Primary chronic pain trials– First 7 weeks of treatment

Table 4.18. Vital Signs and Weight Treatment-Emergent Potentially Clinically Significant Values at Endpoint All Randomized Patients Primary Placebo-Controlled Analyses Set - Chronic Pain (First 7 Weeks)

Vital Statistic	Abnormality	Placebo			DLX20QD			DLX60QD			DLX120QD		
		N	n	%	N	n	%	N	n	%	N	n	%
Sitting Diastolic BP	High	461	1	0.2	58	0	0	436	0	0	108	0	0
	Low	466	1	0.2	57	0	0	442	1	0.2	108	0	0
Sitting Pulse	High	466	0	0	58	0	0	442	0	0	108	0	0
	Low	459	0	0	57	0	0	439	0	0	107	0	0
Sitting Systolic BP	High	467	1	0.2	58	0	0	441	0	0	108	0	0
	Low	464	0	0	58	0	0	440	0	0	107	0	0
Weight (kg) (10%)	Gain	475	3	0.6	58	0	0	449	0	0	108	0	0
	Loss	475	0	0	58	0	0	449	1	0.2	108	0	0
Weight (kg) (7%)	Gain	475	7	1.5	58	0	0	449	3	0.7	108	0	0
	Loss	475	1	0.2	58	0	0	449	7	1.6	108	2	1.9

(Source: Applicant’s table 4.18 from 8/14/09 response to information request, p. 90)

Table 114: Shifts from baseline to “high” and “low” values at endpoint for VS– Primary chronic pain trials– Last 6 weeks of treatment

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Table 4.19. Vital Signs and Weight
 Treatment-Emergent Potentially Clinically Significant Values at Endpoint
 All Randomized Patients
 Primary Placebo-Controlled Analyses Set - Chronic Pain (Second 6 weeks)

Vital Statistic	Abnormality	Placebo			DLX20QD			DLI60QD			DLI120QD		
		N	n	%	N	n	%	N	n	%	N	n	%
Sitting Diastolic BP	High	398	0	0	44	0	0	253	0	0	169	1	0.6
	Low	402	0	0	43	0	0	255	0	0	170	0	0
Sitting Pulse	High	405	0	0	44	0	0	256	0	0	171	0	0
	Low	398	0	0	43	0	0	253	0	0	171	0	0
Sitting Systolic BP	High	403	0	0	44	0	0	255	0	0	171	1	0.6
	Low	402	0	0	44	0	0	253	0	0	167	0	0
Weight (kg) (10%)	Gain	413	0	0	44	0	0	263	0	0	170	0	0
	Loss	413	0	0	44	0	0	263	0	0	170	0	0
Weight (kg) (7%)	Gain	413	0	0	44	0	0	263	0	0	170	0	0
	Loss	413	0	0	44	0	0	263	0	0	170	0	0

(Source: Applicant's table 4.19 from 8/14/09 response to information request, p. 91)

Marked Outliers and dropouts for vital signs abnormalities

Only one person (0.9%) from the 120 mg duloxetine treatment group discontinued the study during the first seven weeks of the treatment period due to high blood pressure.

Subject 301-3141 from Study HMEN was a 42-year-old male assigned to duloxetine 60 mg dose. His past medical history was significant for mild hypertension. No concomitant medication use was reported. Twenty days after the start of the study drug, patient presented with neurologic symptoms of unresponsiveness and left-sided hemiplegia. Blood pressure values were as follows: 145/90 mmHg (visit 1), 138/88 mmHg (visit 2) and 132/96 mmHg (visit 3). Patient was hospitalized with a suspected cerebral infarction and hypertensive encephalopathy. Laboratory data included: blood pressure - 260/150 mmHg; nuclear magnetic resonance (MRI) ruled out cerebral infarction. Final diagnosis of hypertensive encephalopathy was made. Corrective treatment in hospital included unspecified antihypertensive drugs. The patient recovered from the symptom of left-sided hemiplegia and hypertensive encephalopathy.

7.4.4 Electrocardiograms (ECGs)

In the four primary chronic pain trials, ECGs were only collected at baseline and thus no statistical analysis were conducted and submitted to the Agency for ECGs.

The most recent Cymbalta label says "No clinically significant differences were observed for QTc, QT, PR, and QRS intervals between duloxetine-treated and placebo-treated patients. There were no differences in clinically meaningful QTcF elevations between duloxetine and placebo. In a positive-controlled study in healthy volunteers using duloxetine up to 200 mg twice daily, no prolongation of the corrected QT interval was observed."

7.4.5 Special Safety Studies/Clinical Trials

No additional duloxetine safety studies/trials were performed during the chronic pain development program.

7.4.6 Immunogenicity

No new data regarding the immunogenic potential of duloxetine were included in this submission.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

Refer to Section 7.2.2

7.5.2 Time Dependency for Adverse Events

In general, the common TEAEs reported by duloxetine-treated patients occurred early in treatment (first week). For majority of the duloxetine-treated patients, these events resolved between 15 and 30 days after onset.

7.5.3 Drug-Demographic Interactions

The applicant performed analyses of TEAEs by demographic subgroups to determine whether a particular demographic subgroup experiences a higher frequency of TEAEs than another. Specifically, analyses by the demographic subgroups of age (<65 years strata versus ≥65 years strata), origin (Caucasian strata versus other strata), and gender were performed.

For the primary placebo-controlled analysis set, with respect to age, no significant treatment-by-strata interactions were observed. Patients on duloxetine experienced at least one TEAE with a similar frequency, whether <65 years (62.4%) or ≥65 years of age (57.7%) and with a frequency significantly greater than patients on placebo.

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With respect to gender, for dry mouth, the duloxetine/placebo difference in females was significantly greater than the duloxetine/placebo difference in males. For libido decrease, the duloxetine/placebo difference in males was significantly higher than the duloxetine/placebo difference in females.

With respect to ethnic origin, for all patients experiencing at least 1 TEAE, no significant treatment-by-strata interaction was observed.

Table 115: Common AEs by demographic subgroups – Primary chronic pain trials

Table 2.7.4.12. Common Adverse Events by Demographics Subgroups
 MedDRA Preferred Term
 All Randomized Patients
 Primary Placebo-Controlled Analyses Set

Strata	Age			Gender			Origin								
	<65 %		≥65 %		Female %		Male %		Caucasian %		Other %				
Event ^a	PBO N=353	DLX N=452	PBO N=133	DLX N=189	Trt- by-Str p-val ^b	PBO N=325	DLX N=398	PBO N=161	DLX N=243	Trt- by-Str p-val ^b	PBO N=408	DLX N=534	PBO N=78	DLX N=107	Trt- by- Str p-val ^b
ANY EVENT	45.6	62.4	43.6	57.7	.688	47.4	59.5	40.4	63.4	.030	45.3	60.9	43.6	61.7	.766
Nausea	2.0	13.9	3.8	10.1	.121	2.5	13.3	2.5	11.9	.909	2.5	12.4	2.6	15.0	.846
Insomnia	2.3	8.8	3.0	5.3	.242	3.1	7.3	1.2	8.6	.113	2.2	7.7	3.8	8.4	.539
Dry mouth	1.1	6.9	3.0	7.9	.245	1.2	9.5	2.5	3.3	.037	1.7	8.1	1.3	2.8	.543
Dizziness	1.4	6.2	3.0	5.3	.231	1.5	4.8	2.5	7.8	.916	2.0	6.0	1.3	5.6	.751
Fatigue	0.8	6.2	0.0	3.7	.284	0.9	5.3	0.0	5.8	.103	0.7	5.4	0.0	5.6	.302
Somnolence	0.6	5.8	2.3	6.3	.188	1.2	7.3	0.6	3.7	.995	0.7	5.4	2.6	8.4	.426
Constipation	0.6	5.3	1.5	11.6	.903	0.9	8.5	0.6	4.9	.866	0.7	7.9	1.3	3.7	.318

(Source: Applicant's table 2.7.4.12 form SCS, page 42)

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7.5.4 Drug-Disease Interactions

Duloxetine is used as first line therapy for major depressive disorder (MDD). Subjects with MDD were excluded from OA and CLBP trials. No specific drug-disease interaction was noticed for the OA and CLBP population.

7.5.5 Drug-Drug Interactions

The Cymbalta labeling notes the potential for drug-drug interactions with inhibitors of CYP1A2, inhibitors of CYP2D6, MAO inhibitors, and other serotonergic drugs. No new interaction studies have been conducted in support of this application.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

No new carcinogenicity studies were performed during the chronic pain development program. Previous studies mentioned in the duloxetine label found that in female mice receiving duloxetine at 140 mg/kg/day (11 times the maximum recommended human dose) there was an increase incidence of hepatocellular adenomas and carcinomas. No effects were seen at 50 mg/kg/day (4 times the maximum recommended human dose and 2 times the human dose of 120 mg/day). Also, in vitro studies did not find duloxetine to be mutagenic, clastogenic, or genotoxic.

7.6.2 Human Reproduction and Pregnancy Data

Pregnancy Category C has been assigned to duloxetine. When administered to rats and rabbits during organogenesis, there was no evidence of teratogenicity at doses up to 45 mg/kg/day (7 times the maximum recommended human dose). However, fetal weights were decreased at this dose, with a no-effect dose of 10 mg/kg (2 times the maximum recommended human dose).

A total of 84 pregnancies possibly exposed to duloxetine at various doses were reported in clinical trials since the first patient exposure to duloxetine and up to 20 November 2008. All exposures were in the first trimester. Fifteen women were lost to follow-up, 14 women elected to have therapeutic abortions, and 14 women experienced spontaneous abortions, of which one took mifepristone (RU-486) two months prior to the loss of the pregnancy, and one woman experienced a spontaneous abortion in the first trimester after a rock-climbing accident. Four women had ectopic pregnancies. Thirty women delivered normal babies at term. Four women delivered after premature rupture of membranes and/or preterm labor, with none of the infants surviving. One woman delivered a term infant with congenital abnormalities: a 29 year-old woman who delivered a full-term male infant at 38 weeks gestation. The infant experienced foramen persistence versus interauricular communication, was asymptomatic, and did not receive corrective therapy. There are six ongoing pregnancies for which the applicant is obtaining follow-up information.

Table 116: Pregnancy exposure to duloxetine

Table 2.7.4.35. Summary of Pregnancies Exposed to Duloxetine in the First Trimester

Outcome	N	%
Ectopic pregnancy	4	5
Spontaneous abortion	14	17
Therapeutic abortion	14	17
Lost to follow-up	15	18
Ongoing	2	2
Preterm delivery with fetal demise	4	5
Normal term infant	30	35
Term infant with congenital abnormalities	1	1
Total	84	100

(Source: Applicant's table 2.7.4.35 from CSS, p. 103)

The applicant is sponsoring a pregnancy registry as a post-marketing commitment. The proposal has been reviewed by the Agency Maternal Health Team, with comments conveyed to the sponsor in an advice letter. The registry is scheduled to begin in August, 2009.

7.6.3 Pediatrics and Assessment of Effects on Growth

Safety and efficacy in pediatrics has not been established for duloxetine.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

There is limited clinical experience with duloxetine overdose in humans. The product label states that in clinical trials, there were cases of acute ingestions up to 3 grams, alone or in combination with other drugs, none of which were fatal. However, in post-marketing experience, there have been reports of fatal outcomes with acute ingestion of doses lower than 3 grams. Signs and symptoms of overdose, at doses as low as 1000 mg, include serotonin syndrome, somnolence, vomiting, and seizures. However, most of these events involve polypharmacy.

Duloxetine is not a controlled substance and the product label states that animal studies have not indicated that there is any abuse potential. Nevertheless, upon abrupt discontinuation, the following symptoms have been reported in placebo-controlled trials: dizziness, nausea, paresthesia, vomiting, irritability, nightmares, insomnia, diarrhea, anxiety, hyperhidrosis, and vertigo. Other SSRIs and SNRIs have spontaneously reported withdrawal symptoms which include dysphoric mood, irritability, agitation, dizziness, sensory disturbances, anxiety, confusion, headache, lethargy, emotional lability, insomnia, hypomania, tinnitus, and seizures.

7.7 Additional Submissions / Safety Issues

7.7.1 120-day Safety Update

The information submitted with the 120-day Safety Update is not incorporated into the rest of the review but is discussed separately in this section.

The Safety Update includes the following new information:

- Full report from a new lower back pain trial (HMGC), a fixed dose (60 mg vs. placebo) double-blind, randomized 12-week trial.
- New duloxetine clinical trial safety information between the data lock on 20 November 2008 and 15 May 2009 and reports of deaths and serious AEs from ongoing trials up until 14 August 2009.
- Comments on proposed labeling.

7.7.1.1 HMGC Trial

Title: "Effect of duloxetine 60 mg once daily versus placebo in patients with chronic low back pain."

The HMGC trial design and applicant's efficacy results are described in detail in Section 5.3.4 of this review. The analyses of safety data is presented in this section. Overall the toxicity profile for duloxetine in this trial was similar to what was found in the rest of the chronic pain trials.

Safety analyses and findings

Deaths

No deaths occurred during the trial.

Serious Adverse Events

During the double-blind treatment phase, a total of five patients in the duloxetine treatment group reported one SAE each. No patient in the placebo treatment group reported an SAE. While there was a significant treatment group difference in the incidence of SAEs, no individual SAE term was reported more than once. During the taper phase, one patient in the placebo treatment group reported one SAE (abdominal pain) and no patient in the duloxetine treatment group reported an SAE.

Table 117: TEAE during DB treatment phase - HMGC

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Preferred Term	PLACEBO (N=203)		DLX60QD (N=198)		Total (N=401)	
	n	(%)	n	(%)	n	(%)
Patients with >= 1 SAE	0	(0.0)	5	(2.5)	5	(1.2)
Acute myocardial infarction	0	(0.0)	1	(0.5)	1	(0.2)
Alcohol poisoning	0	(0.0)	1	(0.5)	1	(0.2)
Asthma	0	(0.0)	1	(0.5)	1	(0.2)
Myopathy toxic	0	(0.0)	1	(0.5)	1	(0.2)
Vertigo	0	(0.0)	1	(0.5)	1	(0.2)

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(Source: Applicant's table from HMGC trial report, p. 177)

Discontinuations due to adverse events

Significantly more patients in the duloxetine treatment group reported adverse events as the reason for discontinuation, compared with patients in the placebo treatment group. Nausea was the only adverse event term that was reported significantly more frequently as a reason for discontinuation in the duloxetine treatment group compared with the placebo treatment group (6% vs. 1%). No subjects discontinued because of hepatic-related adverse event or LFT abnormalities.

Table 118: Discontinuations due to AEs - HMGC

Preferred Term	PLACEBO (N=203)		DLX60QD (N=198)		Total (N=401)	
	n	(%)	n	(%)	n	(%)
Patients with >= 1 Event	11	(5.4)	30	(15.2)	41	(10.2)
Nausea	2	(1.0)	12	(6.1)	14	(3.5)
Dizziness	1	(0.5)	2	(1.0)	3	(0.7)
Headache	1	(0.5)	1	(0.5)	2	(0.5)
Vertigo	0	(0.0)	2	(1.0)	2	(0.5)
Vomiting	1	(0.5)	1	(0.5)	2	(0.5)
Acute myocardial infarction	0	(0.0)	1	(0.5)	1	(0.2)
Akathisia	0	(0.0)	1	(0.5)	1	(0.2)
Asthma	0	(0.0)	1	(0.5)	1	(0.2)
Diarrhoea	0	(0.0)	1	(0.5)	1	(0.2)
Dyspepsia	0	(0.0)	1	(0.5)	1	(0.2)
Ejaculation failure	0	(0.0)	1	(0.5)	1	(0.2)
Helicobacter infection	1	(0.5)	0	(0.0)	1	(0.2)
Hyperkalaemia	1	(0.5)	0	(0.0)	1	(0.2)
Hypertensive crisis	1	(0.5)	0	(0.0)	1	(0.2)
Insomnia	1	(0.5)	0	(0.0)	1	(0.2)
Malaise	0	(0.0)	1	(0.5)	1	(0.2)
Myopathy toxic	0	(0.0)	1	(0.5)	1	(0.2)
Rash pruritic	1	(0.5)	0	(0.0)	1	(0.2)
Sedation	0	(0.0)	1	(0.5)	1	(0.2)
Somnolence	0	(0.0)	1	(0.5)	1	(0.2)
Tachycardia	1	(0.5)	0	(0.0)	1	(0.2)
Urinary retention	0	(0.0)	1	(0.5)	1	(0.2)
Vomiting projectile	0	(0.0)	1	(0.5)	1	(0.2)

(Source: Applicant's table from HMGC trial report, pp. 180-181)

Treatment-emergent adverse events

During the double-blind phase, a total of 59% of patients reported one or more TEAEs (55% for the placebo group and 63% for the DLX 60 mg group). Significantly more patients in the duloxetine treatment group than in the placebo treatment group reported the following TEAEs: nausea, dry mouth, and somnolence. The majority of the events were mild or moderate in severity. These findings are consistent with the known drug side effect profile and the safety findings from the other chronic pain trials.

Table 119: TEAE by PT - HMGC

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**Table HMGC.12.3. Treatment-Emergent Adverse Events
 Occurring by Preferred Term
 All Randomized Patients
 Double-Blind Treatment Period**

Preferred Term	PLACEBO (N=203)		DLX60QD (N=198)		Total (N=401)	
	n	(%)	n	(%)	n	(%)
Patients with >= 1 TEAE	112	(55.2)	125	(63.1)	237	(59.1)
Headache	25	(12.3)	26	(13.1)	51	(12.7)
Nausea	6	(3.0)	35	(17.7)	41	(10.2)
Constipation	7	(3.4)	12	(6.1)	19	(4.7)
Dry mouth	4	(2.0)	13	(6.6)	17	(4.2)
Diarrhoea	6	(3.0)	9	(4.5)	15	(3.7)
Dizziness	3	(1.5)	10	(5.1)	13	(3.2)
Insomnia	6	(3.0)	5	(2.5)	11	(2.7)
Somnolence	2	(1.0)	9	(4.5)	11	(2.7)
Upper respiratory tract infection	7	(3.4)	4	(2.0)	11	(2.7)
Fatigue	3	(1.5)	7	(3.5)	10	(2.5)
Nasopharyngitis	4	(2.0)	5	(2.5)	9	(2.2)
Vertigo	3	(1.5)	6	(3.0)	9	(2.2)
Arthralgia	7	(3.4)	1	(0.5)	8	(2.0)
Influenza	5	(2.5)	3	(1.5)	8	(2.0)
Hyperhidrosis	2	(1.0)	5	(2.5)	7	(1.7)
Abdominal pain upper	4	(2.0)	2	(1.0)	6	(1.5)
Back pain	3	(1.5)	3	(1.5)	6	(1.5)
Musculoskeletal pain	4	(2.0)	2	(1.0)	6	(1.5)
Flatulence	2	(1.0)	3	(1.5)	5	(1.2)
Libido decreased	1	(0.5)	4	(2.0)	5	(1.2)
Vomiting	3	(1.5)	2	(1.0)	5	(1.2)

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Anorexia	0	(0.0)	4	(2.0)	4	(1.0)
Anxiety	2	(1.0)	2	(1.0)	4	(1.0)
Bronchitis	4	(2.0)	0	(0.0)	4	(1.0)
Rhinitis	2	(1.0)	2	(1.0)	4	(1.0)
Sciatica	3	(1.5)	1	(0.5)	4	(1.0)
Sinusitis	3	(1.5)	1	(0.5)	4	(1.0)
Yawning	0	(0.0)	4	(2.0)	4	(1.0)
Abdominal distension	2	(1.0)	1	(0.5)	3	(0.7)
Blood creatine phosphokinase increased	3	(1.5)	0	(0.0)	3	(0.7)
Hypertension	2	(1.0)	1	(0.5)	3	(0.7)
Hypertriglyceridaemia	3	(1.5)	0	(0.0)	3	(0.7)
Migraine	1	(0.5)	2	(1.0)	3	(0.7)
Neck pain	1	(0.5)	2	(1.0)	3	(0.7)
oropharyngeal pain	2	(1.0)	1	(0.5)	3	(0.7)
Pain in extremity	2	(1.0)	1	(0.5)	3	(0.7)
Pruritus	1	(0.5)	2	(1.0)	3	(0.7)
Rash	2	(1.0)	1	(0.5)	3	(0.7)
Respiratory tract infection viral	3	(1.5)	0	(0.0)	3	(0.7)
Tachycardia	3	(1.5)	0	(0.0)	3	(0.7)
Tension headache	3	(1.5)	0	(0.0)	3	(0.7)
Vision blurred	1	(0.5)	2	(1.0)	3	(0.7)
Weight increased	2	(1.0)	1	(0.5)	3	(0.7)
Abdominal pain	2	(1.0)	0	(0.0)	2	(0.5)

 (Source: Applicant's table from HMGC trial report, pp. 167-168)

During the taper phase, a total of 4% of all patients (duloxetine and placebo) experienced at least one taper-emergent adverse event. There were no significant treatment group differences in either the overall or individual incidences of taper-emergent adverse events.

Table 120: TEAEs – Taper phase HMGC

Table HMGC.12.7. Taper-Emergent Adverse Events Occurring by Preferred Term All Randomized Patients Taper Phase

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Preferred Term	PLACEBO (N=165)		DLX30QD (N=157)		Total (N=322)	
	n	(%)	n	(%)	n	(%)
Patients with >= 1 TPEAE	7	(4.2)	6	(3.8)	13	(4.0)
Headache	1	(0.6)	1	(0.6)	2	(0.6)
Abdominal pain	1	(0.6)	0	(0.0)	1	(0.3)
Abnormal dreams	0	(0.0)	1	(0.6)	1	(0.3)
Ear infection	1	(0.6)	0	(0.0)	1	(0.3)
Gastroenteritis	0	(0.0)	1	(0.6)	1	(0.3)
Gastroenteritis viral	1	(0.6)	0	(0.0)	1	(0.3)
Gastrooesophageal reflux disease	0	(0.0)	1	(0.6)	1	(0.3)
Haemorrhoids	1	(0.6)	0	(0.0)	1	(0.3)
Hypercreatinaemia	1	(0.6)	0	(0.0)	1	(0.3)
Hypertriglyceridaemia	0	(0.0)	1	(0.6)	1	(0.3)
Myalgia	0	(0.0)	1	(0.6)	1	(0.3)
Tooth infection	1	(0.6)	0	(0.0)	1	(0.3)
Upper respiratory tract infection	1	(0.6)	0	(0.0)	1	(0.3)

(Source: Applicant’s table from HMGC trial report, p. 183)

Clinical laboratory evaluations

Per trial schedule, only chemistry analytes and hemoglobin A1c were collected at both baseline and post-baseline visits. Other laboratory tests, such as hematology and serology tests, were collected at baseline visit only.

Analysis focused on measures of central tendency

Significant differences in mean change of alkaline phosphatase ALT, and AST were observed, where patients taking duloxetine experienced a mean increase while patients taking placebo experienced a mean decrease. Other significant differences between treatment groups were observed with uric acid, total protein, and albumin, where patients taking duloxetine experienced a greater decrease in these analyte levels than patients on placebo. These findings are consistent with the results from the other chronic pain trials.

Table 121: Mean change from baseline to LOCF endpoint - HMGC

**Table HMGC.12.9. Laboratory Analysis – Chemistry Analytes
 Change from Baseline to Last-Observation-Carried-Forward Endpoint
 All Randomized Patients
 Double-Blind Treatment Period**

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Treatment	N	Baseline		Last Observation		Change to Last Observation		LSMean	SE
		Mean	SD	Mean	SD	Mean	SD		
Variable analyzed: ALBUMIN(gram/Liter)									
PLACEBO	194	40.92	3.04	40.83	2.94	-0.09	3.00	-0.12	0.23
DLX60QD	190	41.28	2.56	40.51	3.06	-0.78	2.75	-0.76	0.23
Variable analyzed: ALKALINE PHOSPHATASE(Units/Liter)									
PLACEBO	194	71.75	21.80	70.30	20.96	-1.45	10.56	-1.85	0.94
DLX60QD	190	70.44	22.76	72.33	22.89	1.89	12.52	1.59	0.94
Variable analyzed: ALT/SGPT(Units/Liter)									
PLACEBO	194	25.11	15.16	23.21	12.99	-1.90	12.61	-1.71	1.01
DLX60QD	190	24.86	14.19	26.43	15.78	1.57	12.76	1.51	1.01
Variable analyzed: AST/SGOT(Units/Liter)									
PLACEBO	191	22.09	6.87	21.66	6.46	-0.43	6.51	-0.54	0.92
DLX60QD	186	22.11	7.06	24.34	15.90	2.23	14.73	1.90	0.92
Variable analyzed: BICARBONATE, HCO3(millimole/Liter)									
PLACEBO	193	25.43	2.55	25.28	2.51	-0.15	2.87	-0.16	0.22
DLX60QD	190	25.53	2.37	25.46	2.40	-0.07	2.79	-0.11	0.22
Variable analyzed: BILIRUBIN, DIRECT(micromole/Liter)									
PLACEBO	191	2.09	1.00	2.00	0.97	-0.09	0.87	-0.09	0.07
DLX60QD	186	2.02	1.10	1.87	0.90	-0.15	0.78	-0.15	0.07
Variable analyzed: BILIRUBIN, TOTAL(micromole/Liter)									
PLACEBO	194	9.02	4.57	8.64	4.31	-0.37	3.99	-0.40	0.30
DLX60QD	190	8.95	5.27	8.31	4.25	-0.64	3.54	-0.68	0.30
Variable analyzed: CALCIUM(millimole/Liter)									
PLACEBO	194	2.42	0.09	2.41	0.10	-0.01	0.10	-0.01	0.01
DLX60QD	190	2.44	0.11	2.42	0.12	-0.03	0.10	-0.03	0.01
Variable analyzed: GAMMA GLUTAMYLTRANSFERASE (GGT)(Units/Liter)									
PLACEBO	194	27.78	28.03	26.44	27.30	-1.34	19.32	-0.89	1.72
DLX60QD	190	29.79	24.95	30.26	36.48	0.47	22.89	0.85	1.71
Variable analyzed: POTASSIUM(millimole/Liter)									
PLACEBO	194	4.39	0.44	4.38	0.38	-0.01	0.43	-0.03	0.04
DLX60QD	189	4.43	0.42	4.40	0.43	-0.03	0.48	-0.05	0.04
Variable analyzed: SODIUM(millimole/Liter)									
PLACEBO	194	141.29	2.25	141.08	2.20	-0.21	2.30	-0.15	0.21
DLX60QD	190	141.57	2.56	140.97	2.59	-0.60	3.09	-0.52	0.21
Variable analyzed: TOTAL PROTEIN(gram/Liter)									
PLACEBO	194	71.97	4.23	71.63	3.98	-0.34	3.50	-0.43	0.30
DLX60QD	190	72.65	4.11	71.35	4.47	-1.29	3.91	-1.34	0.30

(Source: Applicant's table 12.9 from HMGC trial report, pp.186-191)

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Analysis focused on outliers or shifts from normal to abnormal

No significant differences or clinically relevant findings were observed between treatment groups.

Table 122: Shifts from baseline to “high” or “low” - HMGC

**Table HMGC.12.10. Treatment-Emergent Abnormal Laboratory Values at Anytime
 Frequency of Patients with Abnormal Values after Baseline
 All Randomized Patients
 Double-Blind Treatment Period**

Laboratory Test (unit)	Abnormality Direction	Treatment	N	n	(%)
ALBUMIN (gram/Liter)	Low	PLACEBO	199	1	(0.5)
		DLX60QD	192	2	(1.0)
	High	PLACEBO	197	1	(0.5)
		DLX60QD	191	1	(0.5)
ALKALINE PHOSPHATASE (Units/Liter)	Low	PLACEBO	198	2	(1.0)
		DLX60QD	191	1	(0.5)
	High	PLACEBO	195	4	(2.1)
		DLX60QD	185	2	(1.1)
ALT/SGPT (Units/Liter)	Low	PLACEBO	199	0	(0.0)
		DLX60QD	192	0	(0.0)
	High	PLACEBO	175	20	(11.4)
		DLX60QD	171	22	(12.9)
AST/SGOT (Units/Liter)	Low	PLACEBO	196	1	(0.5)
		DLX60QD	188	1	(0.5)
	High	PLACEBO	187	11	(5.9)
		DLX60QD	176	18	(10.2)
BASOPHILS (BILL/L)	Low	PLACEBO	1	0	(0.0)
		DLX60QD	3	0	(0.0)
	High	PLACEBO	1	0	(0.0)
		DLX60QD	3	0	(0.0)
BILIRUBIN, TOTAL (micromole/Liter)	Low	PLACEBO	193	15	(7.8)
		DLX60QD	185	17	(9.2)
	High	PLACEBO	193	2	(1.0)
		DLX60QD	183	4	(2.2)
CALCIUM (millimole/Liter)	Low	PLACEBO	199	0	(0.0)
		DLX60QD	192	1	(0.5)
	High	PLACEBO	198	4	(2.0)
		DLX60QD	185	6	(3.2)
CHLORIDE (millimole/Liter)	Low	PLACEBO	199	0	(0.0)
		DLX60QD	192	1	(0.5)
	High	PLACEBO	199	1	(0.5)
		DLX60QD	191	1	(0.5)
POTASSIUM (millimole/Liter)	Low	PLACEBO	198	1	(0.5)
		DLX60QD	191	5	(2.6)
	High	PLACEBO	193	7	(3.6)
		DLX60QD	189	7	(3.7)

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SODIUM (millimole/Liter)	Low	PLACEBO	198	2	(1.0)
		DLX60QD	192	3	(1.6)
	High	PLACEBO	194	10	(5.2)
		DLX60QD	188	9	(4.8)
TOTAL PROTEIN (gram/Liter)	Low	PLACEBO	199	1	(0.5)
		DLX60QD	192	2	(1.0)
	High	PLACEBO	197	2	(1.0)
		DLX60QD	188	2	(1.1)

(Source: Derived from applicant's table 12.10 from HMGC trial report, pp.193-200)

Liver Function tests abnormalities

Similar incidence of transaminase elevations was observed for the DLX 60 mg and placebo-treated patients. No bilirubin elevations were reported in patients who experienced transaminase elevations. One patient experienced an ALT elevation of 3X ULN during the double-blind treatment period. The ALT level decreased to normal values during follow-up visits and was not accompanied by increases in bilirubin levels. No patients discontinued the trial due to LFT abnormalities.

Table 123: LFTs abnormalities - HMGC

Table HMGC.12.12. Treatment-Emergent Elevation of Bilirubin Patients With Abnormal Liver Function Tests All Randomized Patients Double-Blind Treatment Period

Elevated Lab Analyte : BILIRUBIN, TOTAL

LAB ANALYTE	TREATMENT	Elevated		Normal		Total N
		N1	Percent	N2	Percent	
ALKALINE PHOSPHATASE	PLACEBO	0	0.00	4	100.00	4
	DLX60QD	0	0.00	2	100.00	2
ALT/SGPT	PLACEBO	0	0.00	19	95.00	20
	DLX60QD	0	0.00	20	90.91	22
AST/SGOT	PLACEBO	0	0.00	10	90.91	11
	DLX60QD	0	0.00	15	83.33	18
CREATINE PHOSPHOKINASE (CK/CPK)	PLACEBO	0	0.00	28	96.55	29
	DLX60QD	0	0.00	21	95.45	22
GAMMA GLUTAMYLTRANSFERASE (GGT)	PLACEBO	0	0.00	8	100.00	8
	DLX60QD	0	0.00	5	100.00	5

N: number of randomized patients with treatment-emergent abnormal LFTs

N1: number of randomized patients with elevated bilirubin and treatment-emergent abnormal LFTs

N2: number of randomized patients with normal bilirubin and treatment-emergent abnormal LFTs

(Source: Applicant's table 12.12 from HMGC trial report, p.210)

Vital Signs

No significant differences or clinically relevant findings were observed between treatment groups for vital sign parameters, mean change and shifts from normal to abnormal (tables located in appendix 9.6).

7.7.1.2 Safety from ongoing trials

A table located in Appendix 9.7 lists patients who experienced a death or other SAE in ongoing trials between the data cutoffs of 20 November 2008 and 15 May 2009. No additional patient deaths were reported after 15 May 2009 and up to 30 days prior to the submission of this safety update.

One patient (HMGB, US200904006865) died due to cervical vertebral fracture. The trial is blinded and treatment assignment is not available. A narrative was not submitted.

With regard to the SAEs reported, there is no pattern for a particular system organ class involvement.

8 Postmarketing Experience

Duloxetine is not approved for the treatment of chronic pain in any country. However, duloxetine has been approved and marketed in the United States and other countries for other indications:

- For treatment of Major depressive disorder (MDD), duloxetine was approved in the United States since August, 2004. As of March 1, 2009, duloxetine was approved for use in MDD in 94 countries.
- For the treatment of generalized anxiety disorder (GAD), duloxetine was approved in the United States since February 2007. As of March 1, 2009, duloxetine was approved for use in GAD in 54 countries.
- For treatment of diabetic peripheral neuropathic pain (DPNP), duloxetine was approved in the United States since September 2004. As of March 1, 2009, duloxetine was approved for use in DPNP in 82 countries.
- For the treatment of women with stress urinary incontinence (SUI) under the name Yentreve® and Ariclim, duloxetine was approved in August 2004 by the European Medicines Evaluation Agency (EMA). Duloxetine has not been approved for this indication in the United States. As of March 1, 2009, duloxetine was approved for use in SUI in 48 countries.
- For the treatment of fibromyalgia, duloxetine was recently approved in the United States on June 13, 2008. As of March 1, 2009, duloxetine was approved for use in FM in 10 countries.
- For the treatment of chronic pain, duloxetine was approved in Mexico in November 2008.

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Periodic Safety Reports for duloxetine are completed every 6 months as of 3/8/2004. A total of eight PSURs have been completed, representing six 6-month periods. The last report was submitted to regulatory agencies in October of 2008.

For a listing of major regulatory actions taken for safety reasons since the original approval of Cymbalta (August 2004) through February 2009, see Appendix 9.4. The major actions taken were related to hepatic safety and suicidality.

Exposure

Since initial approval through February 2, 2009 the estimated exposure to duloxetine is 14,059,000 patients in the US and 19,417,000 patients (6,382,000 patient years) worldwide. A total of 89,701 AEs in 37,266 cases have been reported as of February 2, 2009.

Adverse Events

The most frequently reported events by SOC were Psychiatric disorders (16,201); Nervous system disorders (15,386); GI disorders (14,259); General disorders and administration site conditions (12,591); Investigations (5780); and Skin and subcutaneous tissue disorders (5070).

The most frequently reported events were nausea (5639), dizziness (3056), insomnia (2274), headache (2272), fatigue (1994), hyperhidrosis (1899), feeling abnormal (1896), drug ineffective (1868), somnolence (1772), diarrhea (1599), vomiting (1575), anxiety (1466), tremor (1395), constipation (1043), weight increased (1014), dry mouth (965), blood pressure increased (855), depression (849), suicidal ideation (847), paresthesia (815), malaise (814), agitation (713), vision blurred (704), and asthenia (638). All of these events are listed in the CCDS (approved on 03 December 2008).

Drug Interactions

Through the most current PSUR cut-off date, 2/2/2009, there have been 275 drug interactions reported for duloxetine. The most commonly reported drug interactions have been warfarin (5.5%), tramadol (4.7%), fluoxetine (3.6%).

Over dosage

Fatal outcomes have been reported for acute overdoses with duloxetine alone or with mixed drugs at doses as low as 1000mg. The signs and symptoms of overdose reported included somnolence, coma, serotonin syndrome, seizures, vomiting, and tachycardia.

Special Topics

Hepatotoxicity: There have been a total of 1094 reports of hepatic-related adverse events (reporting rate: 0.0056%) and 492 of these were related to isolated enzyme elevations (45%).

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Although no fatalities have been definitively attributed to duloxetine, the applicant reports that there have been 11 cases of severe hepatic injury that were probably attributed to duloxetine. Of the 162 clinically significant cases, 33 met the definition of Hy's rule. For details, see table below.

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Table 124: Clinical significance of hepatic events

Table 8.1. Clinical Significance of Hepatic Events

Clinical Significance Category	Etiologic Classification				Total
	Unlikely	Possible	Probable	Indeterminate	
Fatality	18	5	0	8	31
Hepatic failure	12	7	0	5	24
Severe hepatic injury	25	52	11	19	107

(Source: Applicant's Table, Page 4, Post-marketing Report, page 58)

Ongoing pharmacovigilance activities include:

- Targeted questionnaire for follow-up investigation of hepatic events
- Genotyping of patients
- Quarterly FDA AERS analysis of hepatic adverse events for all cases and fatal case series, both in overall database and against antidepressant-only background. AERS fatal case series followed by individual case expert review to evaluate causality.
- Continued assessment of hepatic-related adverse event data and laboratory data at the time of completion of each clinical trial. Sites instructed to use the Hepatic Monitoring Plan Guidance for further course of action upon clinical suspicion of potential liver damage.
- Periodic review of the clinical trial database and spontaneous AE data for hepatotoxicity.
- Updates provided in PSURs as applicable.

Suicidality: There have been 2806 reports of suicidality and based on patient exposures of approximately 19,417,000 patients worldwide as of 2/2/2009, the suicide behavior and ideation rate was 0.01%. The majority of these reports were in patients with psychiatric conditions such as depression (91.4%) and anxiety (8.6%). For details, see table below.

Table 125: Number of Suicidality Events by Diagnostic Category

Table 8.2. Number of Suicidality Events by Diagnostic Category

Diagnostic Category	Diagnosis Description	Total
1	Completed suicide, fatal	255
2	Suicide attempt, nonfatal	426
3	Preparatory acts towards imminent suicidal behavior	10
4	Suicidal ideation	810
		<i>Total: 1501</i>

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(Source: Applicant's Table 8.2, Page 60, Post-marketing report)

Ongoing pharmacovigilance activities include:

- General Practice Research Database (GPRD) analysis of suicidality in SUI patients
- Study F1J-MC-B027: A retrospective cohort study of suicide attempts leading to hospitalization in depressed adult patient population using a large US medical claims database.
- Targeted questionnaire for follow-up investigation of suicide-related events
- Active monitoring of suicidal ideation by including the Beck Depression Inventory (BDI-II) Suicidality Item or the Columbia Suicide Severity Rating Scale (C-SSRS) in clinical trials for all nonpsychiatric indications.
- Study F1J-SB-B007 (DUROSA study). Overall safety assessment completed
- Continued assessment of all suicidality at the time of completion of each clinical trial.
- Periodic review of the clinical trial database and spontaneous AE data for suicidality.
- Updates provided in PSURs as applicable.

Stevens-Johnson Syndrome: There have been 17 cases of Stevens-Johnson Syndrome (reporting rate 0.00009%), five cases of erythema multiforme (reporting rate 0.00003%), and one case reported of Toxic Epidermal Necrolysis. The TEN case also reported SJS, and the reporting physician at the time of the initial report did not make a diagnosis but felt that the serious skin reaction was secondary to pregablin use.

Upper Gastrointestinal Tract Bleeding: There have been 688 cases describing bleeding events. In thirty-three of the 81 upper gastrointestinal bleeding cases (40.1%) the bleeding event resulted in a hospitalization. Three of the 81 cases (3.7%) resulted in a fatality. All three fatal cases were reported by the applicant as confounded by use of concomitant medications and underlying comorbid conditions.

Cardiovascular Events: Hypertensive crisis has rarely been reported (<.01%). There have been 69 cases of myocardial infarction and 58 cases of ventricular arrhythmias.

9 Appendices

9.1 Literature Review/References

No literature review was performed for this application.

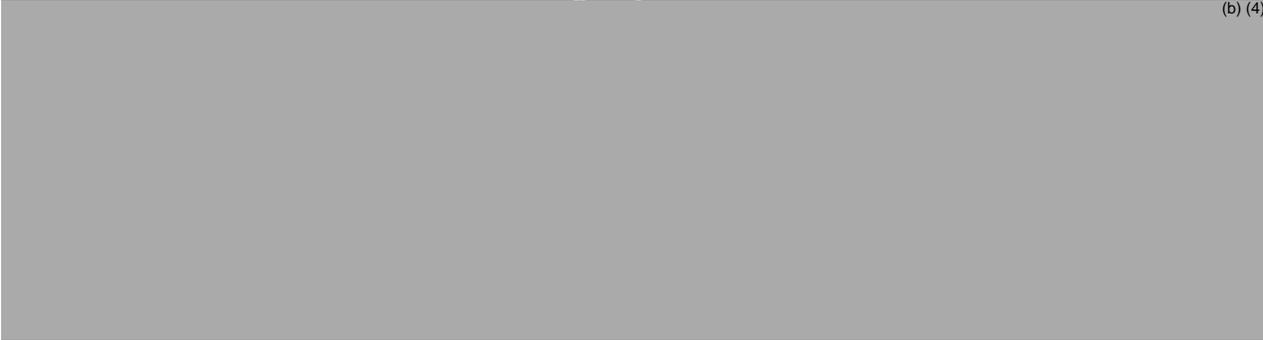
9.2 Labeling Recommendations

The proposed label will require changes prior to approval. At the time of this review, the negotiations with the applicant are still ongoing.

The following are the main outstanding issues:

1. Benefit from dose increase to 120 mg/day.

(b) (4)



Dr. Yongman Kim's analysis of the efficacy data did not show a benefit of duloxetine dose increase to 120 mg/day for patients who did not respond to duloxetine 60 mg/day. Therefore, statements that the duloxetine dose of 120 mg/day confers additional benefit to the 60 mg/day dose should not be included in the label.

(b) (4)



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(b) (4). The efficacy findings from this open-label extension phase do not support findings of efficacy for duloxetine because there was a lack of placebo control.

3. The clinical trial section of the label should include information about the negative fixed-dose OA trial (HMEO).

4. Adverse reactions occurring at an incidence of 2% or more are presented separately as Pooled analysis for 1) MDD and GAD and 2) Chronic pain, including DPN, FM, OA, and CLBP. Because the safety profile of Cymbalta was similar in all four chronic pain populations studied, it is acceptable to present TEAE that occurred at an incidence of 2% or more as a pooled analysis data.

5. A labeling supplement including changes to the fibromyalgia section of the label was submitted to the Division of Psychiatric Products (DPP), NDA 21-427/S-033, on September 22, 2009. Because the review of the fibromyalgia application was performed by DAARP and our division is familiar with the labeling issues raised by the applicant, review of the proposed changes to the fibromyalgia section of the label will be incorporated within the review of this chronic pain NDA application.

The proposed changes affect the following sections of the Cymbalta USPI:

1. Section 6.2. Adverse Reactions Reported as Reasons for Discontinuations of Treatment in Placebo-Controlled Trials – Change in the number of discontinuations due to an adverse event.
2. Section 14.4 Fibromyalgia – Change of the definition of responders for HMEH, long-term trial.

The applicant's proposed label revisions are described below. Language added to the PI is underlined. Language deleted from the PI is ~~struck through~~.

1. Section 6.2. Adverse Reactions Reported as Reasons for Discontinuations of Treatment in Placebo-Controlled Trials.

The applicant requests that the number of FM patients who discontinued treatment due to an adverse reaction reflects what was listed in the Integrated Summary of Safety (Section 5.3.5.3) submitted with the NDA 22-516 application. The proposed change for the number of discontinued patients is from (b) (4) (NDA 22-148) to (b) (4) (NDA 22-516) with adjustments to the accompanying percentage (b) (4). The applicant explains that the reason for the number change (b) (4) in NDA 22-148 to (b) (4) in NDA 22-516 is due to the fact that a different database for HMCJ trial was used for those two submissions. For NDA 22-148, data from an interim lock (for the acute, placebo-controlled period only) was used, and patient HMCJ-112-2203 was recorded as discontinued due to subject decision in that interim database. HMCJ trial had an extension phase and final data locked occurred after the original FM submission (22-148). In the final database, the disposition reason for patient HMCJ-112-2203 was

changed to discontinued due to adverse events. For NDA 22-516, data from the HMCJ final lock was used, resulting in 172 patients discontinued due to adverse event from FM trials.

“Fibromyalgia – Approximately 19^{(b)(4)}6% (17^{(b)(4)}2/876) of the patients who received duloxetine in 3 to 6 month placebo-controlled trials for FM discontinued treatment due to an adverse reaction, compared with 11.8% (63/535) for placebo...”

Comments

The reviews of Dr. Ricardo Dent and Dr. Celia Winchell of the original fibromyalgia NDA application documented the numbers that are currently in the label. However, the change requested reflects information from the final data lock analysis that was used for the chronic pain indication, NDA 22-516. It does not change the meaning of the information that is being conveyed to the reader and is in a direction that is unfavorable to the drug. Therefore, the change requested can be allowed.

2. Section 14.4. Fibromyalgia.

(b) (4)

“Additionally, the benefit of up-titration in non-responders to Cymbalta at 60 mg/day was evaluated in a separate study. Patients were initially treated with Cymbalta 60 mg once daily for eight weeks in open-label fashion. Subsequently, completers of this phase were randomized to double-blind treatment with Cymbalta at either 60 mg once daily or 120 mg once daily. Those patients who were considered non-responders, where response was defined as at least a 30^{(b)(4)}% reduction in pain score from baseline at the end of the 8-week treatment, were no more likely to meet response criteria at the end of 60 weeks of treatment if blindly titrated to Cymbalta 120 mg as compared to those who were blindly continued on Cymbalta 60 mg.”

Comments

As described in the reviews of Dr. Ricardo Dent and Dr. Celia Winchell, the trial in question (HMEH) involved eight weeks of open-label treatment with duloxetine 60 mg/day followed by randomization to double-blind treatment with either 60 mg/day or 120 mg/day. All completers of the open-label phase, whether responders or non-responders, were randomized into the double-blind phase of the trial. Dr. Buenconsejo, the statistical reviewer for the FM application, performed an analysis to determine whether non-responders benefited from up-titration, using both the 50% improvement definition of responder at the end of the open-label treatment, and using the less stringent 30% definition. One can assume that subjects who had not gotten even 30% improvement on 60 mg, would have a greater potential to get better. Nevertheless, using either approach, patients who were non-responders to the initial treatment were

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Serotonin syndrome	United States	On 09 May 2006, the FDA requested class labeling for all selective serotonin reuptake inhibitors (SSRI)/serotonin norepinephrine reuptake inhibitors (SNRI) and triptans regarding drug-drug interactions of these compounds and the potential development of serotonin syndrome. Following discussions with the FDA, Lilly submitted a CBE sNDA labeling change adding the class labeling on 30 August 2006.	May to September, 2006 The FDA approved this CBE on 20 September 2006.
Orthostatic hypotension, Syncope, Blood pressure	United States	On 22 May 2006, the FDA requested revised wording on orthostatic hypotension, syncope and blood pressure. Following discussions with the FDA, Lilly submitted a revised CBE on 04 October 2006 which included agreed upon language on hypotension/syncope, blood pressure, and hyponatremia.	Initiated May 2006, FDA approved on 23 February 2007
Fibromyalgia New Indication	United States	The Division of Anesthesia, Analgesia and Rheumatology Products approved the new indication for the management of fibromyalgia	13 June 2008
Medication Guide	United States	The Division of Psychiatry Products requested Lilly to update the current Medication Guide to make it more comprehensive than the current document, which only addresses suicidality	Request by FDA received on 16 April 2009
Hepatic safety	South Africa	Medicines Control Council requested that Lilly provide a "Dear Healthcare Professional" letter to healthcare providers informing them of the hepatic effects of duloxetine based upon information collected from spontaneous reporting. Lilly prepared a "Dear Healthcare Professional" that was approved by Medicines Control Council and was distributed to health care providers in February 2007.	Request from Medicines Control Council - January 2007
Pediatric suicidality	European Union	All duloxetine products (Cymbalta/Xeristar/Ariclaim/Yentreve): A Referral procedure (Articles 18 and 31) was initiated in January 2005 by the CHMP with regards pediatric suicidality for all SSRIs and SNRIs. A class-labeling warning regarding suicide-related behaviors in children and adolescents was requested (CHMP Opinion of 22 April).	Completed September 2005 The European Commission approved this label change in September 2005
SUI and suicidality	European Union	<u>Duloxetine in SUI (Yentreve/Ariclaim):</u> The Marketed Authorization Holder (MAH) was requested to provide a written answer to a list of question including all data available for duloxetine regarding suicide attempt in the indication of SUI and its potential impact on the risk-benefit balance. After reviewing this data the CHMP requested the MAH submit an application to amend the label accordingly on 5 August 2005.	Completed November 2005 The European Commission approved this label change in November 2005.
Hyponatremia, gastrointestinal hemorrhage, Adverse drug reactions	European Union	<u>All duloxetine products:</u> Following a request of the CHMP in its conclusion of the review of PSUR 01, a type II variation was submitted in August 2005 to update the SPC with: Section 4.4 - Precaution for patients at increased risks of hyponatremia, reported cases of GI hemorrhage. Section 4.8 -Adverse drug reactions.	Completed March 2006 The European Commission approved this label change in March 2006
Heart Rate, Blood pressure, Withdrawal symptoms, Akathisia, Psychomotor restlessness	European Union	<u>All duloxetine products:</u> Following a request of the CHMP in its conclusion of the review of PSUR 02, a type II variation was submitted in February 2006 to updated Section 4.4 of the SPC with: - A precaution for use in patients whose conditions could be compromised by an increased heart rate or by an increase in blood pressure, - A class labeling warning on withdrawal symptoms, - A class labeling warning on akathisia and psychomotor restlessness.	Completed May 2006 The European Commission approved this label change in May 2006.

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Hypertension, Hypertensive crisis, Renal impairment, Akathisia/psychomotor restlessness, Hepatic failure	European Union	<p><u>All duloxetine products:</u></p> <p>Following a request of the CHMP in its conclusion of the review of PSUR 03, a type II variation was submitted in August 2006 to update the SPC with:</p> <p>Section 4.3:</p> <ul style="list-style-type: none"> - A contraindication for the initiation of treatment in patients with uncontrolled hypertension that could expose patients to a potential risk of hypertensive crisis. - A contraindication for patients with severe renal impairment (Ventrevé and Ariclain only). <p>Section 4.4:</p> <ul style="list-style-type: none"> - Updated class labeling wording on Akathisia/psychomotor restlessness. - Reported cases of clinically significant hypertension and hypertensive crisis. <p>Section 4.8:</p> <ul style="list-style-type: none"> - The adverse event hepatic failure. 	<p>Completed November 2006</p> <p>The European Commission approved this label change in November 2006.</p>
Suicidality	United States	<p>The FDA issued a press release and posted information on the FDA website, describing the revised class labeling language on suicidality and antidepressant use required for all antidepressants. The FDA sent manufacturers of all antidepressants revised class labeling for the use of antidepressants (including duloxetine) and the risk of suicidality for patients aged 18 to 24 years. The new class labeling also states that there is no demonstrated risk for patients beyond 24 years and that there is a decrease in risk of suicidality for patients greater than 65 years. This information was revised in both the boxed warning at the beginning of labeling as well as in the "Warnings" section of the labeling. The Medication Guide was also updated to contain this information. Manufacturers were given 30 days to implement this new labeling. Lilly submitted this CBE sNDA labeling change to the FDA on 31 May 2007. On 21 June 2007, the FDA notified all anti-depressant manufacturers that they were requiring changes to their proposed class labeling. Lilly has agreed to this revised wording.</p>	<p>02 May 2007</p> <p>Labeling supplement approved by the FDA on August 2, 2007.</p>
Suicide related events, bleeding events	European Union	<p><u>All duloxetine products:</u></p> <p>Following a request of the CHMP in its conclusion of the review of PSUR 04, a type II variation was submitted in March 2007 to update the SPC with:</p> <p>Section 4.4:</p> <ul style="list-style-type: none"> - Update of warning on suicide with increased risk of suicide-related events for patients having pre-existing suicidal ideation or young adults. <p>Section 4.8:</p> <ul style="list-style-type: none"> - Bleeding events (Gastrointestinal haemorrhage, haematochezia, epistaxis, gynaecological haemorrhage). 	<p>Completed August 2007</p> <p>The European Commission approved this label change in August 2007.</p>
Abnormal bleeding, Urinary retention and hesitation.	United States	<p>Following a request from the FDA the US label was updated on 28 November 2007 to include to two addition to the Warning and Precautions section:</p> <ul style="list-style-type: none"> - Abnormal bleeding (class labeling required for all SSRIs/SNRIIs). - Urinary retention and hesitation (previously listed as ADRs). 	<p>Completed 28 November 2007</p>
Hepatic	Canada	<p>Following a request from Health Canada who approved MDD and DPNP on November 1, 2007, a launch DHPL will be issued in Canada on January 28, 2008 to announce that Cymbalta is now available and for physicians to be aware of potential hepatic effects.</p> <p>Lilly Canada issued a "Dear Healthcare Professional" letter to inform healthcare professionals that the product is available in Canada and to highlight the warning of potential hepatic events</p>	<p>Planned 28 January 2008</p> <p>28 January 2008</p>
GAD and DPNP	Taiwan	<p>GAD and DPNP submissions were rejected. Appeals are in progress</p>	<p>September 2008 and March 2009</p>
Aggression and anger	Europe	<p>Following review of PSUR 6, a type II variation was submitted in November 2007 to update the SPC with: Section 4.8: Aggression and anger.</p> <p>Section 4.9: Updated symptoms of overdose</p>	<p>Completed April 2008</p> <p>The European Commission approved this label change in April 2008</p>
Restless legs syndrome and convulsions upon discontinuation	Europe	<p>Following review of PSUR 8, a type II variation was submitted in December 2008 to update the SPC with (Section 4.8):</p> <ul style="list-style-type: none"> - Restless legs syndrome and convulsions upon treatment discontinuation <p>Section 4.9 of the SPC: New maximum overdose reported (4800 mg).</p>	<p>Positive opinion in February 2009</p>

(Source: Applicant's table 7.1 from 5.3.6 Post-Marketing Experience, pp.52-57)

9.5 Tables of TEAEs for the primary chronic pain trials (HMEN, HMEP, HMFG, and HMEO)

Table 127: TEAEs $\geq 1\%$ by treatment group for the first 7 weeks of the treatment phase – primary chronic pain trials

Table 3.7. Treatment-Emergent Adverse Event $\geq 1\%$ in Any Treatment Group By Decreased Frequency and by Randomized Dose MedDRA Preferred Term All Randomized Patients Primary Placebo-Controlled Analyses Set - Chronic Pain (First 7 Weeks)

MedDRA Preferred Term	PLACEBO	DLX20QD	DLX60QD	DLX120QD	TOTAL
	(N=496) n (%)	(N=59) n (%)	(N=470) n (%)	(N=112) n (%)	(N=1127) n (%)
Patients with ≥ 1 TEAE	181 (37.2)	35 (59.3)	247 (52.6)	80 (71.4)	543 (48.18)
Nausea	10 (2.1)	9 (15.3)	54 (11.5)	12 (10.7)	85 (7.54)
Insomnia	7 (1.4)	5 (8.5)	21 (4.5)	19 (17.0)	52 (4.61)
Diarrhoea	14 (2.9)	2 (3.4)	27 (5.7)	6 (5.4)	49 (4.35)
Dry mouth	5 (1.0)	3 (5.1)	29 (6.2)	11 (9.8)	48 (4.26)
Constipation	3 (0.6)	2 (3.4)	28 (6.0)	12 (10.7)	45 (3.99)
Headache	18 (3.7)	1 (1.7)	16 (3.4)	9 (8.0)	44 (3.90)
Somnolence	4 (0.8)	2 (3.4)	19 (4.0)	13 (11.6)	38 (3.37)
Fatigue	2 (0.4)	0 (0.0)	24 (5.1)	10 (8.9)	36 (3.19)
Dizziness	7 (1.4)	3 (5.1)	16 (3.4)	7 (6.3)	33 (2.93)
Hyperhidrosis	3 (0.6)	0 (0.0)	14 (3.0)	5 (4.5)	22 (1.95)
Influenza	6 (1.2)	3 (5.1)	8 (1.7)	2 (1.8)	19 (1.69)
Arthralgia	7 (1.4)	2 (3.4)	9 (1.9)	0 (0.0)	18 (1.60)
Decreased appetite	1 (0.2)	0 (0.0)	10 (2.1)	5 (4.5)	16 (1.42)
Nasopharyngitis	7 (1.4)	1 (1.7)	7 (1.5)	1 (0.9)	16 (1.42)
Abdominal pain upper	3 (0.6)	0 (0.0)	9 (1.9)	2 (1.8)	14 (1.24)
Erectile dysfunction	0 (0.0)	1 (1.7)	10 (2.1)	3 (2.7)	14 (1.24)
Dyspepsia	4 (0.8)	1 (1.7)	5 (1.1)	3 (2.7)	13 (1.15)
Hypertension	3 (0.6)	1 (1.7)	4 (0.9)	5 (4.5)	13 (1.15)
Anorexia	1 (0.2)	0 (0.0)	8 (1.7)	3 (2.7)	12 (1.06)
Libido decreased	1 (0.2)	2 (3.4)	5 (1.1)	4 (3.6)	12 (1.06)
Asthenia	0 (0.0)	0 (0.0)	8 (1.7)	3 (2.7)	11 (0.98)
Sleep disorder	3 (0.6)	0 (0.0)	5 (1.1)	3 (2.7)	11 (0.98)
Back pain	4 (0.8)	1 (1.7)	5 (1.1)	0 (0.0)	10 (0.89)
Vomiting	2 (0.4)	2 (3.4)	4 (0.9)	2 (1.8)	10 (0.89)
Abdominal pain	4 (0.8)	1 (1.7)	3 (0.6)	1 (0.9)	9 (0.80)
Hot flush	1 (0.2)	0 (0.0)	7 (1.5)	1 (0.9)	9 (0.80)
Dysgeusia	2 (0.4)	0 (0.0)	5 (1.1)	1 (0.9)	8 (0.71)
Flatulence	1 (0.2)	0 (0.0)	6 (1.3)	1 (0.9)	8 (0.71)
Sedation	2 (0.4)	0 (0.0)	3 (0.6)	3 (2.7)	8 (0.71)
Urinary tract infection	3 (0.6)	2 (3.4)	1 (0.2)	2 (1.8)	8 (0.71)
Abdominal distension	2 (0.4)	0 (0.0)	3 (0.6)	2 (1.8)	7 (0.62)
Lethargy	2 (0.4)	0 (0.0)	3 (0.6)	2 (1.8)	7 (0.62)
Myalgia	2 (0.4)	1 (1.7)	3 (0.6)	1 (0.9)	7 (0.62)
Rash	4 (0.8)	1 (1.7)	2 (0.4)	0 (0.0)	7 (0.62)
Vision blurred	0 (0.0)	1 (1.7)	4 (0.9)	2 (1.8)	7 (0.62)

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Stomach discomfort	0 (0.0)	1 (1.7)	0 (0.0)	2 (1.8)	3 (0.27)
Acne	1 (0.2)	1 (1.7)	0 (0.0)	0 (0.0)	2 (0.18)
Cystitis	1 (0.2)	1 (1.7)	0 (0.0)	0 (0.0)	2 (0.18)
Dehydration	1 (0.2)	1 (1.7)	0 (0.0)	0 (0.0)	2 (0.18)
Hyperglycaemia	0 (0.0)	1 (1.7)	0 (0.0)	1 (0.9)	2 (0.18)
Hypokalaemia	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.8)	2 (0.18)
Testicular pain	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.8)	2 (0.18)
Aphonia	0 (0.0)	1 (1.7)	0 (0.0)	0 (0.0)	1 (0.09)
Breast cyst	0 (0.0)	1 (1.7)	0 (0.0)	0 (0.0)	1 (0.09)
Cardiac ablation	0 (0.0)	1 (1.7)	0 (0.0)	0 (0.0)	1 (0.09)
Colonic polyp	0 (0.0)	1 (1.7)	0 (0.0)	0 (0.0)	1 (0.09)
Drug hypersensitivity	0 (0.0)	1 (1.7)	0 (0.0)	0 (0.0)	1 (0.09)
Epistaxis	0 (0.0)	1 (1.7)	0 (0.0)	0 (0.0)	1 (0.09)
Folliculitis	0 (0.0)	1 (1.7)	0 (0.0)	0 (0.0)	1 (0.09)
Groin pain	0 (0.0)	1 (1.7)	0 (0.0)	0 (0.0)	1 (0.09)
Haemarthrosis	0 (0.0)	1 (1.7)	0 (0.0)	0 (0.0)	1 (0.09)
Joint injury	0 (0.0)	1 (1.7)	0 (0.0)	0 (0.0)	1 (0.09)
Kidney infection	0 (0.0)	1 (1.7)	0 (0.0)	0 (0.0)	1 (0.09)
Anxiety	0 (0.0)	1 (1.7)	3 (0.6)	2 (1.8)	6 (0.53)
Increased appetite	4 (0.8)	1 (1.7)	0 (0.0)	1 (0.9)	6 (0.53)
Musculoskeletal pain	3 (0.6)	1 (1.7)	1 (0.2)	1 (0.9)	6 (0.53)
Nocturia	0 (0.0)	0 (0.0)	2 (0.4)	4 (3.6)	6 (0.53)
Palpitations	0 (0.0)	0 (0.0)	4 (0.9)	2 (1.8)	6 (0.53)
Ejaculation disorder	0 (0.0)	0 (0.0)	3 (0.6)	2 (1.8)	5 (0.44)
Irritability	1 (0.2)	1 (1.7)	1 (0.2)	2 (1.8)	5 (0.44)
Paraesthesia	0 (0.0)	0 (0.0)	3 (0.6)	2 (1.8)	5 (0.44)
Pruritus	2 (0.4)	0 (0.0)	1 (0.2)	2 (1.8)	5 (0.44)
Muscle spasms	0 (0.0)	1 (1.7)	2 (0.4)	1 (0.9)	4 (0.35)
Pollakiuria	0 (0.0)	0 (0.0)	2 (0.4)	2 (1.8)	4 (0.35)
Anorgasmia	0 (0.0)	0 (0.0)	0 (0.0)	3 (2.7)	3 (0.27)
Asthma	0 (0.0)	2 (3.4)	1 (0.2)	0 (0.0)	3 (0.27)
Confusional state	0 (0.0)	1 (1.7)	2 (0.4)	0 (0.0)	3 (0.27)
Ejaculation delayed	0 (0.0)	0 (0.0)	1 (0.2)	2 (1.8)	3 (0.27)
Hypersomnia	0 (0.0)	1 (1.7)	1 (0.2)	1 (0.9)	3 (0.27)
Loss of libido	1 (0.2)	0 (0.0)	0 (0.0)	2 (1.8)	3 (0.27)
Pharyngitis	0 (0.0)	2 (3.4)	1 (0.2)	0 (0.0)	3 (0.27)
Nasal congestion	0 (0.0)	1 (1.7)	0 (0.0)	0 (0.0)	1 (0.09)
Neurological examination abnormal	0 (0.0)	1 (1.7)	0 (0.0)	0 (0.0)	1 (0.09)
Non-cardiac chest pain	0 (0.0)	1 (1.7)	0 (0.0)	0 (0.0)	1 (0.09)
Pruritus generalised	0 (0.0)	1 (1.7)	0 (0.0)	0 (0.0)	1 (0.09)
Psoriasis	0 (0.0)	1 (1.7)	0 (0.0)	0 (0.0)	1 (0.09)
Therapeutic response unexpected	0 (0.0)	1 (1.7)	0 (0.0)	0 (0.0)	1 (0.09)
Vaginal haemorrhage	0 (0.0)	1 (1.7)	0 (0.0)	0 (0.0)	1 (0.09)
Vulvovaginal pruritus	0 (0.0)	1 (1.7)	0 (0.0)	0 (0.0)	1 (0.09)

(Source: Applicant's table 3.7 from 8/14/09 response to information request, pp. 27-31)

Table 128: TEAEs $\geq 1\%$ by treatment group for the last 6 weeks of the treatment phase – primary chronic pain trials

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**Table 3.8. Treatment-Emergent Adverse Event ≥1% in Any Treatment Group
 By Decreased Frequency by Randomized Dose
 MedDRA Preferred Term
 All Randomized Patients
 Primary Placebo-Controlled Analyses Set - Chronic Pain (Second 6 Weeks)**

MedDRA Preferred Term	PLACEBO	DLX20QD	DLX60QD	DLX120QD	TOTAL
	(N=423) n (%)	(N=45) n (%)	(N=268) n (%)	(N=173) n (%)	(N=909) n (%)
Patients with ≥ 1 Treatment-Emergent Event	87 (20.6)	12 (26.7)	68 (25.4)	45 (26.0)	212 (23.32)
Dizziness	2 (0.5)	0 (0.0)	7 (2.6)	5 (2.9)	14 (1.54)
Headache	4 (0.9)	1 (2.2)	6 (2.2)	3 (1.7)	14 (1.54)
Insomnia	6 (1.4)	0 (0.0)	2 (0.7)	4 (2.3)	12 (1.32)
Influenza	3 (0.7)	0 (0.0)	4 (1.5)	4 (2.3)	11 (1.21)
Arthralgia	6 (1.4)	0 (0.0)	3 (1.1)	1 (0.6)	10 (1.10)
Nausea	3 (0.7)	2 (4.4)	2 (0.7)	3 (1.7)	10 (1.10)
Diarrhoea	3 (0.7)	0 (0.0)	1 (0.4)	4 (2.3)	8 (0.88)
Somnolence	1 (0.2)	1 (2.2)	3 (1.1)	1 (0.6)	6 (0.66)
Constipation	1 (0.2)	0 (0.0)	1 (0.4)	3 (1.7)	5 (0.55)
Pain in extremity	1 (0.2)	0 (0.0)	2 (0.7)	2 (1.2)	5 (0.55)
Gastroenteritis	0 (0.0)	1 (2.2)	3 (1.1)	0 (0.0)	4 (0.44)
Conjunctivitis	1 (0.2)	2 (4.4)	0 (0.0)	0 (0.0)	3 (0.33)
Neck pain	0 (0.0)	0 (0.0)	3 (1.1)	0 (0.0)	3 (0.33)
Non-cardiac chest pain	2 (0.5)	1 (2.2)	0 (0.0)	0 (0.0)	3 (0.33)
Pharyngitis	0 (0.0)	2 (4.4)	0 (0.0)	1 (0.6)	3 (0.33)
Pruritus	0 (0.0)	0 (0.0)	1 (0.4)	2 (1.2)	3 (0.33)
Sinusitis	1 (0.2)	1 (2.2)	1 (0.4)	0 (0.0)	3 (0.33)
Anorexia	0 (0.0)	1 (2.2)	1 (0.4)	0 (0.0)	2 (0.22)
Gastritis	1 (0.2)	1 (2.2)	0 (0.0)	0 (0.0)	2 (0.22)
Muscle strain	1 (0.2)	1 (2.2)	0 (0.0)	0 (0.0)	2 (0.22)
Osteoarthritis	0 (0.0)	1 (2.2)	1 (0.4)	0 (0.0)	2 (0.22)
Tremor	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.2)	2 (0.22)
Irritability	0 (0.0)	1 (2.2)	0 (0.0)	0 (0.0)	1 (0.11)
Tooth abscess	0 (0.0)	1 (2.2)	0 (0.0)	0 (0.0)	1 (0.11)

(Source: Applicant's table 3.7 from 8/14/09 response to information request, pp. 32-33)

9.6 Tables of Vital Sign Parameters changes for HMGC trial

Table 129: Mean change from baseline to endpoint – HMGC

**Table HMGC.12.15. Vital Signs
 Mean Change from Baseline to LOCF Endpoint
 All Randomized Patients
 Double-Blind Treatment Period**

Variable Analyzed: BP Systolic (mm Hg)																
Treatment	n	Baseline					Last Observation					Change to Last Observation				
		Mean	SD	Median	Min	Max	Mean	SD	Median	Min	Max	Mean	SD	Median	Min	Max
PLACEBO	198	128.44	13.44	130.00	92.00	170.00	128.09	14.08	128.00	98.00	180.00	-0.35	11.88	0.00	-36.00	37.00
DLX60QD	194	128.90	14.40	130.00	95.00	189.00	129.41	14.62	130.00	95.00	176.00	0.51	10.51	0.00	-25.00	43.00

Variable Analyzed: BP Diastolic (mm Hg)																
Treatment	n	Baseline					Last Observation					Change to Last Observation				
		Mean	SD	Median	Min	Max	Mean	SD	Median	Min	Max	Mean	SD	Median	Min	Max
PLACEBO	198	79.71	8.46	80.00	58.00	106.00	79.37	8.30	80.00	60.00	100.00	-0.34	8.98	0.00	-28.00	30.00
DLX60QD	194	80.01	8.44	80.00	55.00	105.00	80.26	8.96	80.00	50.00	101.00	0.25	8.74	0.00	-23.00	26.00

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 Variable Analyzed: Pulse rate (bpm)

Treatment	n	Baseline					Last Observation					Change to Last Observation				
		Mean	SD	Median	Min	Max	Mean	SD	Median	Min	Max	Mean	SD	Median	Min	Max
PLACEBO	198	72.14	9.41	72.00	44.00	105.00	72.14	8.47	72.00	54.00	100.00	0.01	8.97	0.00	-34.00	36.00
DLX60QD	194	72.21	7.45	71.50	58.00	99.00	72.57	7.54	72.00	47.00	96.00	0.36	7.49	0.00	-31.00	29.00

 Variable Analyzed: Weight (kg)

Treatment	n	Baseline					Last Observation					Change to Last Observation				
		Mean	SD	Median	Min	Max	Mean	SD	Median	Min	Max	Mean	SD	Median	Min	Max
PLACEBO	199	79.44	14.76	78.70	47.00	114.40	79.49	14.75	78.40	48.50	116.50	0.05	1.85	0.00	-5.60	5.50
DLX60QD	194	78.29	15.97	76.95	43.70	127.70	77.99	15.77	76.60	44.00	128.30	-0.30	2.38	0.00	-13.40	6.30

**Table HMGC.12.16. Vital Signs
 Mean Change from Baseline to LOCF Endpoint
 All Randomized Patients
 Taper Phase**

 Variable Analyzed: BP Systolic (mm Hg)

Treatment	n	Baseline					Last Observation					Change to Last observation				
		Mean	SD	Median	Min	Max	Mean	SD	Median	Min	Max	Mean	SD	Median	Min	Max
PLACEBO	160	127.38	13.46	129.00	98.00	170.00	127.21	12.54	128.00	91.00	170.00	-0.17	9.69	0.00	-28.00	28.00
DLX30QD	155	128.96	13.85	130.00	95.00	170.00	126.99	12.49	128.00	90.00	160.00	-1.97	9.04	-1.00	-40.00	24.00

 Variable Analyzed: BP Diastolic (mm Hg)

Treatment	n	Baseline					Last Observation					Change to Last observation				
		Mean	SD	Median	Min	Max	Mean	SD	Median	Min	Max	Mean	SD	Median	Min	Max
PLACEBO	160	79.29	8.30	80.00	60.00	100.00	78.91	8.07	80.00	51.00	100.00	-0.38	7.21	0.00	-24.00	18.00
DLX30QD	155	79.92	8.95	80.00	50.00	101.00	79.70	7.70	80.00	60.00	107.00	-0.22	7.18	0.00	-20.00	20.00

 Variable Analyzed: Pulse rate (bpm)

Treatment	n	Baseline					Last Observation					Change to Last observation				
		Mean	SD	Median	Min	Max	Mean	SD	Median	Min	Max	Mean	SD	Median	Min	Max
PLACEBO	160	71.71	7.90	72.00	54.00	100.00	72.50	8.18	72.00	52.00	96.00	0.79	7.21	0.00	-28.00	26.00
DLX30QD	155	72.32	7.20	72.00	56.00	94.00	73.26	8.21	72.00	53.00	100.00	0.95	5.93	0.00	-13.00	26.00

 Variable Analyzed: Weight (kg)

Treatment	n	Baseline					Last Observation					Change to Last observation				
		Mean	SD	Median	Min	Max	Mean	SD	Median	Min	Max	Mean	SD	Median	Min	Max
PLACEBO	159	78.43	14.46	78.00	48.50	114.00	78.53	14.55	77.50	48.30	115.30	0.10	0.78	0.00	-3.00	3.60
DLX30QD	156	78.00	15.06	77.30	50.00	128.30	78.08	15.07	77.00	50.00	129.10	0.08	0.88	0.00	-4.50	3.30

(Source: Applicant's tables from HMGC trial report, pp. 216-223)

Table 130: Sustained elevations in blood pressure - HMGC

**Table HMGC.12.17. Sustained Elevation in Blood Pressure
 All Randomized Patients
 Double-Blind Treatment Period**

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Variable Analyzed : Sustained Elevation in Blood Pressure
-----
Treatment                N                n    (%)
-----
PLACEBO                  198                3   (1.5)
DLX60QD                  194                3   (1.5)
  
```

(Source: Applicant's table form HMGC trial report, p. 224)

Table 131: Orthostatic hypotension - HMGC

**Table HMGC.12.18. Treatment-Emergent Orthostatic Hypotension
 All Randomized Patients
 Double-Blind Treatment Period**

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-----
Variable Analyzed : Treatment Emergent Orthostatic Hypotension
-----
Treatment                N                n    (%)
-----
PLACEBO                  190                9   (4.7)
DLX60QD                  181                9   (5.0)
  
```

(Source: Applicant's table form HMGC trial report, p. 225)

9.7 Listing of Serious Adverse Events from Ongoing Trials submitted with the 120-day safety update

Table 132: SAEs – ongoing trials

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Table 6.1. Listing of Serious Adverse Events from Ongoing Studies

Patient Number	Treatment Group/Dose	Event Term	Outcome
HMEZ-0062-6203 (CA200902000091)	Open-Label 30mg QD – 60mg QD	Lacunar infarction	SAE
HMEZ-0080-8008 (DE200904005754)	Open-Label 30mg QD – 60mg QD	Adverse drug reaction	SAE
HMEZ-0081-8145 (DE200904006656)	Open-Label 30mg QD – 60mg QD	Atrioventricular block complete	SAE
HMFA-0007-0704 (US200901002596)	Blinded	Head injury	SAE
HMFA-0013-1318 (US200902007194)	Blinded	Toe amputation	SAE
HMFA-0034-03409 (US200902000814)	Blinded	Interstitial lung disease Dyspnoea Spinal osteoarthritis	SAE
HMFQ-0018-1812 (IT200902000042)	Open-Label 30mg QD – 60mg QD	Atrial fibrillation	SAE
HMFR-0004-0401 (US200903006333)	Blinded	Pneumonia Urinary tract infection	SAE
HMFS-0013-1341 (US200812005107)	Blinded	Asthma	SAE
HMFT-0013-1316 (US200901004800)	Open-Label 30mg QD – 120mg QD	Suicidal ideation	SAE
HMFT-0032-3207 (US200812003163)	Open-Label 30mg QD – 120mg QD	Pneumonia	SAE
HMFT-0041-4120 (US200812002488)	Open-Label 30mg QD – 120mg QD	Pneumonia	SAE
HMFT-0042-4230 (US200812001541)	Open-Label 30mg QD – 120mg QD	Nephrolithiasis	SAE
HMFT-0048-4804 (US200901002494)	Open-Label 30mg QD – 120mg QD	Post-traumatic stress disorder	SAE

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HMFY-051-2 (JP200811006304)	Blinded	Arthritis bacterial Osteomyelitis Renal failure acute Sepsis Pathological fracture	SAE
HMFY-071-3 (JP200902002513)	Blinded	Cerebral infarction	SAE
HMFY-095-3 (JP200903001115)	Blinded	Contusion	SAE
HMFY-163-2 (JP200902002587)	Blinded	Hepatic function abnormal Tuberculous pleurisy Gamma-glutamyltransferase increased C-reactive protein increased Blood bilirubin increased Blood alkaline phosphatase increased Platelet count increased Urine albumin/creatinine ratio increased	SAE
HMFY-011-4 (JP200905003006)	Open-Label 40mg QD – 60mg QD	Cerebral infarction	SAE
HMFY-018-2 (JP200903004615)	Open-Label 40mg QD – 60mg QD	Lymphoma	SAE
HMFY-019-4 (JP200904003254)	Open-Label 40mg QD – 60mg QD	Generalized oedema Cardiac failure	SAE
HMFY-022-1 (JP200903006473)	Open-Label 40mg QD – 60mg QD	Infected epidermal cyst	SAE
HMFY-047-3 (JP200901001151)	Open-Label 40mg QD – 60mg QD	Clavicle fracture Thoracic vertebral fracture Lung injury Pneumothorax	SAE
HMFY-078-2 (JP200904007013)	Open-Label 40mg QD – 60mg QD	Ileus	SAE
HMFY-087-1 (JP200904002336)	Open-Label 40mg QD – 60mg QD	Pyonephrosis	SAE
HMFY-088-1 (JP200901004811)	Open-Label 40mg QD – 60mg QD	Lymphoma	SAE
HMFY-090-2 (JP200902003476)	Open-Label 40mg QD – 60mg QD	Carotid artery stenosis Disuse syndrome	SAE
HMFY-099-1 (JP200902001215)	Open-Label 40mg QD – 60mg QD	Colon cancer	SAE
HMFY-103-4 (JP200904002919)	Open-Label 40mg QD – 60mg QD	Hypoglycaemia	SAE

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HMFY-129-4 (JP200904007014)	Open-Label 40mg QD – 60mg QD	Colonic polyp	SAE
HMFY-136-1 (JP200904003250)	Open-Label 40mg QD – 60mg QD	Diabetic gangrene	SAE
HMFY-143-3 (JP200902007593)	Open-Label 40mg QD – 60mg QD	Bronchopneumonia	SAE
HMFY-169-4 (JP200904005514)	Open-Label 40mg QD – 60mg QD	Pelvic fracture Rib fracture	SAE
HMFY-170-3 (JP200905001405)	Open-Label 40mg QD – 60mg QD	Metastases to Liver	SAE
HMGB-0108-1807 (US200901003564)	Blinded	Anaesthetic complication	SAE
HMGB-0111-2125 (US200812000972)	Blinded	Chest pain	SAE
HMGB-0110-2005 (US200903006077)	Blinded	Pneumonia	SAE
HMGB-0112-2218 (US200901001893)	Blinded	Non-cardiac chest pain	SAE
HMGB-0119-2909 (US200901000597)	Blinded	Headache	SAE
HMGB-0124-3405 (US200811005396)	Blinded	Intervertebral disc protrusion	SAE
HMGB-0136-4621 (US200904006865)	Blinded	Cervical vertebral fracture	Death
HMGB-0142-5210 (US200903003532)	Blinded	Muscle spasms	SAE
HMGB-0145-5502 (US200812002028)	Blinded	Postoperative fever Post procedural infection	SAE
HMGB-0146-5624 (US200904002744)	Blinded	Pneumonia	SAE
HMGB-0151-6108 (US200812001661)	Blinded	Suicidal ideation	SAE
HMGB-0152-6216 (US200904002741)	Blinded	Migraine with aura	SAE
HMGD-0008-0802 (FR200903005904)	Blinded	Dysphagia	SAE
HMGD-0046-4603 (NL200902000070)	Blinded	Suicidal ideation	SAE
HMGD-0053-5303 (RO200904007052)	Blinded	Crohn's disease	SAE
HMGD-0058-5806 (SI200903006359)	Blinded	Insomnia	SAE

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HMGD-0071-7109 (ES200905001431)	Blinded	Abnormal behavior	SAE
HMGD-0082-8205 (SE200903002257)	Blinded	Major depression	SAE
HMGD-6501 (ES200904001653)	Blinded	Suicide attempt	SAE

(Source: Applicant's table 6.1 from the 120-day safety update submission)

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22516	ORIG-1	ELI LILLY AND CO	CYMBALTA

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/s/

ANJELINA K POKROVNICHKA
02/02/2010

ELLEN W FIELDS
02/02/2010
Refer to CDTL review for additional details