Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

Australian Public Assessment Report for Duloxetine

Proprietary Product Name: Cymbalta

Sponsor: Eli Lilly Australia Pty Ltd

September 2012

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and Ageing, and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <www.tga.gov.au>.

About AusPARs

- An Australian Public Assessment Record (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations, and extensions of indications.
- An AusPAR is a static document, in that it will provide information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

I. Introduction to product submission

Submission details

Type of Submission	Extension of Indications
Decision:	Rejected
Date of Decision:	20 December 2011
Active ingredient(s):	Duloxetine
Product Name(s):	Cymbalta
Sponsor's Name and Address:	Eli Lilly Australia Pty Ltd 112 Wharf Rd, West Ryde, NSW 2114
Dose form(s):	Capsules
Strength(s):	30 and 60 mg
Container(s):	Blister pack
Pack size(s):	7 and 28's
Approved Therapeutic use:	Not applicable
Route(s) of administration:	Oral (PO)
Dosage:	60 mg once daily. Some patients may benefit from commencing with 30 mg once daily and increasing the dose to 60 mg once daily after one week as this may reduce the risk of nausea. Some patients may benefit from higher doses up to a maximum of 120 mg daily.
ARTG Number (s)	Not applicable

Product background

Serotonin (5-HT) and norepinephrine (NE) have been implicated as key neurotransmitters involved in pain modulation at the level of descending inhibitory pathways. Duloxetine (DLX) is a potent inhibitor of 5-HT and noradrenaline re-uptake *in vitro* and *in vivo* in the central nervous system (CNS).

Nonclinical studies have shown that duloxetine effectively reduces pain across a range of persistent neuropathic inflammatory chronic pain models in a dose range consistent with 5-HT and NE re-uptake inhibition and is considered to be a member of the Serotonin Noradrenalin Reuptake Inhibitor (SNRI) class. DLX is believed to have a central analgesic effect by the potentiation of activity in the descending pain inhibitory pathways. Because of this effect, DLX is expected to be effective against chronic pain states in humans with

various underlying aetiologies via a mechanism that differs from currently used analgesic drugs.

This AusPAR describes the application by the sponsor to register Cymbalta (duloxetine) for

Treatment of chronic somatic pain

Duloxetine was first registered in 2007. The initial indication was:

T*reatment of Major Depressive Disorder*

This was extended in 2009 to include

Treatment of Diabetic Peripheral Neuropathic Pain and

Treatment of Generalised Anxiety Disorder.

No antidepressant has an indication for treatment of somatic pain in Australia. Milnacipran, another SNRI, was approved for management of fibromyalgia in October 2011. Available treatments for chronic pain include paracetamol, non steroidal anti inflammatory drugs (NSAIDs) and opioids. Tramadol and tapentadol are also indicated for the treatment of moderate to severe pain. These are mu-opioid agonists and inhibitors of noradrenaline reuptake and/ or serotonin. The extended release form of tapentadol is approved for management of moderate to severe chronic pain un-responsive to non-narcotic analgesia with the rider that there are currently no clinical trial data available regarding the safety and efficacy in patients with pain due to malignancy.

The TGA has adopted the European Union (EU) Guideline *Note for Guidance on Clinical Investigation of Medicinal Products for Treatment of Nociceptive Pain*[1]. Aspects of that guideline particularly relevant to this submission include:

- Classifications of pain have been developed and different pain domains have been described: (1) nociceptive pain (pain evoked by a noxious stimulus, (2) neuropathic pain and (3) pain related to central sensitisation (the latter two are pain types evoked by non-noxious stimuli;
- Nociceptive pain can be somatic or visceral. Somatic pain is due to prolonged activation of the nociceptive receptors in somatic tissues such as bone, joint, muscle or skin;
- Somatic pain can be acute or chronic;
- Due to the high and variable placebo response rate, placebo-controlled designs with appropriate use of rescue medication are recommended for trials not aiming to show superior efficacy to an active comparator. For the full assessment of efficacy and safety 3-armed trials (that is, active/active comparator/placebo) are usually most informative;
- The choice of active comparator should be justified taking into account proposed indications, dose, mode of action, time to onset of efficacy, duration of action, safety etc depending on study objectives;
- Patients enrolled in clinical trials must represent the target population on demographic and clinical characteristics;
- Different models based on type of pain and pain intensity are recommended for study. Pain due to osteoarthritis and low back pain are provided as examples of conditions for assessment of chronic mild to moderate pain. The duration of these studies should

[1] CPMP/EWP/612/00 http://www.tga.gov.au/pdf/euguide/ewp061200final.pdf

be at least 3 months. Other models are acceptable provided that the applicant justifies the choice.

- In a general indication such as mild to moderate chronic pain, patients with a chronic visceral pain need to be included in clinical trials. For limited investigations in a specific model, only a limited indication can be obtained;
- Any other treatments that can modulate the perception of pain, such as physical techniques, surgery and psychological support, should be avoided during the trial, or comparable in study groups if unavoidable.

Regulatory status

The following is a summary of the international regulatory status of Cymbalta:

- Cymbalta received regulatory approval by the FDA for "Chronic muscoskeletal pain" in November 2010.
- On 21 July 2011, the Committee for Medicinal Products for Human Use (CHMP) adopted a negative opinion, recommending the refusal of a change to the marketing authorisations for the duloxetine-containing medicines Ariclaim, Cymbalta and Xeristar. The change concerned the addition of a new indication, the treatment of moderate to severe chronic somatic pain in patients not taking NSAIDs regularly. Lilly requested a re-examination of the opinion. After considering the grounds for this request, the CHMP re examined the initial opinion, and confirmed the refusal of the change to the marketing authorisations on 17 November 2011.
- An application was submitted in Canada to Health Canada for "Chronic Low Back Pain and Chronic Pain due to Osteoarthritis (OA)" in July 2009. The chronic low back pain indication was approved and the osteoarthritis indication was rejected by the Canadian agency (TPD) on April 11, 2011. Eli Lilly Canada refiled the OA submission following the results of a recently completed trial in OA patients (Study HMGL) on November 14, 2011. The submission included this new study as well as some reanalyses of previously submitted OA studies, which were recommended by Health Canada. The OA indication was approved by Health Canada on July 31, 2012.

II. Quality findings

There was no requirement for a quality evaluation in a submission of this type.

III. Nonclinical findings

There was no requirement for a nonclinical evaluation in a submission of this type.

IV. Clinical findings

Introduction

DLX is expected to act via a mechanism that differs from currently used analgesic drugs. To assess this hypothesis this application investigated DLX in prevalent disease states to represent two main types of chronic pain, namely inflammatory pain as represented by osteoarthritis (OA) of the knee and non-inflammatory/non-neuropathic pain as represented by idiopathic chronic low back pain (CLBP).

In this application a total of five placebo controlled studies to support the application of use of DLX in chronic somatic pain are presented. These studies comprise a total of 839 patients treated with DLX at doses 20, 60 and 120 mg once daily and 689 patients treated with placebo. Two of the studies were in patients with osteoarthritis of the knee referred to as OA-EP and OA-FG and three in patients with chronic lower back pain referred to as CLBP-EN and CLBP-EO and CLBP-GC. All five studies had a placebo controlled phase of 12 to 13 weeks, while study CLBP-EN had a long term uncontrolled extension phase of 41 weeks to assess maintenance of effect.

All studies were conducted in accordance with Good Clinical practice (GCP).

Pharmacokinetics

There were no studies in relation to clinical pharmacokinetics presented in this submission.

Pharmacodynamics

There were no studies in relation to clinical pharmacology presented in this submission.

Efficacy

All five studies included investigational sites from European countries except for Study CLBP-EO. Apart from Study CLBP-GC, patients were allowed to remain on their regular dose of NSAID provided they were using them at the time of enrolment. Randomisation for all studies was stratified by NSAID use and patients were instructed to remain on their regular dose throughout the course of the study. Patients with major depressive disorder (MDD) were excluded from all chronic somatic pain studies.

The severity criteria for entry in all the studies was the 24 average pain rating of at least four reflecting at least moderate pain. Subjects were required to have had chronic pain for at least three months in the OA patients or six months in the CLBP patients prior to entry into the study.

In view of the fact that all five studies are of a pivotal nature in relation to the evaluation of both efficacy and safety, it is considered appropriate to discuss all studies combining relevant data at the same time highlighting any differences with regards to study design and outcomes.

Elements of the study design which were common across these studies included:

- Double blind randomised placebo controlled.
- 12-13 weeks in duration.
- Excluded patients with MDD.
- Randomisation was stratified by NSAID used in all studies except for study CLBP-GC. A NSAID user was defined as a patient who takes an NSAID for at least 14 days per month for three months prior to study entry.
- Excluded the concomitant use of anti-convulsants, anti-depressants and anti-manics, anti-psychotics, Capsaicin, Cimetidine, Lignocaine, mono-aminooxydase inhibitors, psycho stimulants, Quinoline class of antibiotics, Triptans, Tryptophan and Tramadol[2].
- Required the following diagnostic criteria:

[2] Sponsor comment: St John's Wort use was also excluded. Muscle relaxants were excluded from all CLBP studies.

  - The same level of baseline pain for entry into the study with a 24 hour average pain ranking of ≥4 based on a 11 point numerical rating scale.
  - For the two OA studies the disease diagnosis was based upon American College of Rheumatology (ACR) clinical and radiographic criteria for classification of idiopathic OA of the knee.
  - Of the three CLBP studies patients were required to have a clinical diagnosis of CLBP with pain present on most days for at least six months. Pain was to be either restricted to lower back or associated with radiation to a proximal portion of the lower limb only. Patients could not have neurological radicular pain; presumptive compression of the spinal nerve root on simple radiogram; compression of a spinal nerve root confirmed by specific imaging techniques; spinal fracture; spondylolisthesis Grade III or IV, tumour, abscess or other acute pathology in the lower back/abdominal region.
- Evaluated duloxetine doses of 20 mg, 60 mg, 120 mg daily except for the fixed dose study of CLBP-GC which only included Duloxetine 60 mg per day.
- Used 24 hour average pain rating (either collected in patient daily diary or through brief pain inventory (BPI) at scheduled office visits) as primary efficacy outcomes. The weekly mean of 24 hour average pain was originally specified as the primary efficacy outcome for all chronic somatic pain studies except for Study CLBP-GC. However, after the interim review of the first two studies, namely OA-EP and CLBP-EO, it was recognised that diary compliance was low being 68% for Study OA-EP and 49% for Study CLBP-EO diminishing the potential value of diary entries. Accordingly the 24 hour average pain rating collected from BPI at study visits was pre-specified as the primary efficacy outcome for all other studies, that is, OA-FG, CLBP-EN and CLBP-GC.
- Employed a gatekeeper strategy for sequentially testing the following secondary objectives.
  - Evaluated the DLX versus placebo on patients perceived improvement during the treatment phase as measured by PGI improvement.
  - Evaluated DLX versus placebo on the change in patients physical function during the treatment phase as measured by the WOMAC physical function sub-scale[3] for studies OA-FG and OA-EP or by the RMDQ-24[4], a questionnaire addressing intensity of CLBP and interference with activities of daily living for study CLBP-EN, CLBP-EO and CLBP-GC.
- Included measurements of BPI severity and interference and clinical global impressions of severity (CGI-severity) ranges as well as quality of life measures such as the Euro Qol-5 dimensions (EQ-5D)[5] and 36 items on the short form health survey (SF-36[6]) scores.

[3] WOMAC assesses pain, stiffness, and physical function in patients with hip and / or knee osteoarthritis (OA). The WOMAC consists of 24 items divided into 3 subscales:

- **Pain (5 items):** during walking, using stairs, in bed, sitting or lying, and standing
- **Stiffness (2 items):** after first waking and later in the day
- **Physical Function (17 items):** stair use, rising from sitting, standing, bending, walking, getting in / out of a car, shopping, putting on / taking off socks, rising from bed, lying in bed, getting in / out of bath, sitting, getting on / off toilet, heavy household duties, light household duties

[4] Roland Morris Disability Questionnaire (RMDQ-24) is used as a health status measure for low back pain.

[5] Euro Qol-5 dimensions (EQ-5D) is a descriptive system of health-related quality of life states consisting of five dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression).

[6] The SF-36 is a multi-purpose, short-form health survey with only 36 questions. It yields an 8-scale profile of functional health and well-being scores as well as psychometrically-based physical and mental health summary measures and a preference-based health utility index. It is a generic measure, as opposed to one that targets a specific age, disease or treatment group.

Individual aspects of the various study designs

Study OA-FG, a Phase III parallel double-blind placebo controlled study in male and female patients at least 40 years with pain associated with OA of the knee. In order to assess the individually optimised dose at Week 7, DLX treated patients who did not meet the response criteria defined as at least 30% pain reduction of 24 hour average pain and were able to tolerate their current treatment had their dose increased to 120 mg per day for the remainder of the study. All other patients stayed on the originally assigned treatment. Analyses were performed on all randomised patients including patients who had their dose increased to DLX 120 mg or stayed on DLX 60 mg and were collectively referred to as DLX 60-120 mg treatment.

The primary objective for Study OA-FG was to assess the efficacy of combined DLX 60-120 mg on the reduction of pain severity as measured by the 24 hour average pain rating in patients with pain associated with OA of the knee during a 13 week double blind treatment period.

Study OA-EP was a Phase III parallel double blind placebo controlled study in male and female patients at least 40 years with pain associated with the OA of the knee. At Week 7 DLX treated patients were re-randomised to either 60 mg or 120 mg per day with the objective of exploring relative efficacy of 120 mg versus 60 mg. Analyses were performed on all randomised patients including patients who had their dose increased to DLX 120 mg or stayed on DLX 60 mg and are collectively referred to as DLX 60-120 mg treatment.

The primary objective was to assess the efficacy of DLX combined 60-120 mg per day on the reduction of pain severity as measured by the weekly mean of the 24 hour average pain ratings in patients with pain associated with OA of the knee during the 13 week double blind treatment period using the 11 point numerical rating scale collected from patient diaries.

Study CLBP-EN was a Phase III parallel double blind placebo controlled study in male and female patients of at least 18 years with CLBP as their primary painful condition. In order to assess the individually optimised doses at Week 7, DLX treated patients who did not meet the response criteria defined as at least 30% pain reduction of 24 hour average pain and were able to tolerate the current treatment had their dose increased to 120 mg per day for the remainder of the study. All other patients stayed on their original assigned treatment. Analyses were performed on all randomised patients including patients who had their dose increased and are collectively referred to as DLX 60-120 mg treatment.

The primary objective was to assess the efficacy of combined DLX 60-120 mg per day compared with placebo on the reduction of pain severity as measured by the 24 hour average pain rating in patients with CLBP during the 13 week double blind treatment period.

Study CLBP-EN also included a 41 week dose blinded (DLX 60 mg or 120 mg per day) extension phase to measure the maintenance of effect of DLX in these patients.

Study CLBP-EO was a Phase III, parallel, double blind, fixed dose including 20, 60 and 120 mg per day placebo controlled study in male and female patients of at least 18 years with CLBP as their primary painful condition. The primary objective were to assess the efficacy of DLX 60 mg per day compared with placebo on the reduction of pain severity as measured by the weekly mean of the 24 hour average pain rating in patients with CLBP during the 13 week double blind treatment period using the 11 point numerical rating scale collected from patient diaries.

Study CLBP-GC was a Phase III, randomised, double blind, parallel, placebo controlled study in male and female patients of at least 18 years, with CLBP their primary painful condition. The primary objective of the study was to assess the efficacy of DLX 60 mg per

day compared with placebo on the reduction of pain severity as measured by the 24 hour average pain score in patients with CLBP during a 12 week double blind treatment period.

Table 1 list the efficacy variables measured in the five primary chronic somatic pain studies and Table 2 outlines the definitions of these various efficacy indices.

Table 1. List of Efficacy Variables. Primary Chronic Somatic Pain Studies OA-EP, OA-FG, CLBP-EN, CLBP-EO and CLBP-GC.

Measure
Primary Variables
Weekly mean of the 24-hour average pain rating[a] (collected from **electronic patient diaries**) for Study **OA-EP** and Study **CLBP-EO**
24-hour average pain item rating [b] (collected from the Brief Pain Inventory **[BPI]** instrument **at study visits**) for Study **CLBP-EN**, Study **CLBP-GC**, and Study **OA-FG**
Secondary Gatekeeper Variables
Patient Global Impression of Improvement ratings
Western Ontario and McMaster Universities (WOMAC) Arthritis index, physical function subscale score[c]
Roland Morris Disability Questionnaire score[d]
Other (Non-Gatekeeper) Secondary Variables
30% response rate (at least 30% reduction from baseline on the 24-hour average pain rating)
50% response rate (at least 50% reduction from baseline on the 24-hour average pain rating)
Weekly mean of the 24-hour worst pain and night pain ratings (collected from electronic patient diaries)
BPI Severity and Interference
Clinical Global Impressions of Severity ratings
WOMAC pain and stiffness subscales and total[c]
Athens Insomnia Scale[d]
Beck Depression Inventory – II[e]
Hospital Anxiety and Depression Scale[e]
Euro-Quality of Life Questionnaire-5 Dimensions
36-Item Short Form Health Survey
Work Productivity and Activity Impairment Instrument[f]
Profile of Mood States – Brief Form[g]

[a] Primary efficacy measure in Study OA-EP, Study CLBP-EO. Secondary efficacy measure in Study CLBP-EN, Study CLBP-GC, and Study OA-FG.

[b] Primary efficacy measure in Study CLBP-EN, Study CLBP-GC, and Study OA-FG. Secondary efficacy measure in Study CLBP-EO and Study OA-EP.

[c] Collected in Study OA-EP and Study OA-FG only.

[d] Collected in Study CLBP-EN, Study CLBP-EO, and Study CLBP-GC.

[e] Used for path analysis to assess duloxetine's direct analgesic effect versus improvements in mood and anxiety. Collected in Study CLBP-EN, Study CLBP-EO, Study OA-EP, and Study OA-FG.

[f] Collected in Study CLBP-EN and CLBP-GC.

[g] Collected in Study CLBP-GC.

Reviewing statistical methods, all analyses were conducted along the intent to treat (ITT) basis unless otherwise specified. Treatment effects were evaluated through pair-wise comparisons with placebo and based on two-sided tests with a significance level of 0.05. The primary efficacy measure was the 24 hour average pain item on the 11 point numerical rating scale expressed as either weekly mean from patient daily diaries for Studies OA-EP and CLBP-EO or the single day report at study visit for Studies OA-FG, CLBP-EN and CLBP-GC.

Table 2. Efficacy Measures

Electronic patient diaries were used to collect **24-hour average, worst, and night pain ratings**. Patients rated their pain on an ordinal 11-point numerical rating scale, with ratings ranging from 0 (no pain) to 10 (worst possible pain). Weekly mean of the daily pain rating was computed by averaging the pain rating within each nominal week between scheduled visits (see the Clinical

The **BPI – Modified Short Form** (Cleeland and Ryan 1994) is a self-reported scale that measures the severity of pain and the interference of pain on function. The ratings range from 0 (no pain) to 10 (worst possible pain). There are 4 questions assessing worst pain, least pain, and average pain in the past 24 hours, and the pain right now. The Interference scores range from 0 (does not interfere) to 10 (completely interferes). There are 7 questions assessing the interference of pain in the past 24 hours, including general activity, mood, walking ability, normal work, relations with other people, sleep, and enjoyment of life. The average interference score was calculated by averaging the score of all 7 interference items.

The **PGI-Improvement scale** (Guy 1976) is completed by the patient and measures the degree of change at the time of assessment. The score ranges from 1 (very much better) to 7 (very much worse) with a score of 4 being no change.

The **WOMAC index** (pain, stiffness, physical function subscales) (Bellamy et al. 1988) is completed by the patient. The index has 24 questions (5 on pain, 2 on stiffness, and 17 on physical function). Each question is answered using a 5-point numerical scale (0 through 4) where a higher number indicates more functional impairment. WOMAC total score was calculated as the sum of 3 subscales and range from 0 to 96.

The **RMDQ-24** (Roland and Morris 1983) is completed by the patient and measures the degree of disability due to back pain. The questionnaire consists of 24 statements, and the patient is instructed to put a mark next to each appropriate statement. The number of statements marked is added up by the clinician and a total score is given. The total score ranges from 0 (no disability) to 24 (severe disability).

The **CGI-Severity scale** (Guy 1976) evaluates the severity of illness at the time of assessment. The score ranges from 1 (normal, not at all ill) to 7 (among the most extremely ill patients). The CGI-Severity is administered by a study physician in the presence of the patient or after having been in the presence of the patient.

The **Athens Insomnia Scale (AIS)** is a self-administered psychometric instrument used to quantify sleep difficulty based on the International Classification of Diseases, Version 10 (ICD-10) criteria (Soldatos et al. 2000) and is completed by the patient. The AIS consists of 8 items and each item can be rated 0 (no problem at all) to 3 (very serious problem). The total score ranges from 0 to 24 with higher score indicating greater difficulty.

The **Beck Depression Inventory-II (BDI-II)** is a 21-item, patient-completed questionnaire designed to assess characteristics of depression (Beck et al. 1979; Beck and Steer 1991). Each item ranges in score from 0 to 3, for a possible total score ranging from 0 to 63 (higher scores indicate more severe depression).

The **HADS** (Zigmond and Snaith 1983) is a self-reported questionnaire. The HADS contains 14 items and consists of 2 subscales: anxiety (HADS-A) and depression (HADS-D). Each item is rated on a 4-point scale (0 through 3), giving maximum scores of 21 for anxiety and depression. Scores of 11 or more on either subscale are considered to be a significant "case" of psychological morbidity, while scores of 8 to 10 represent "borderline" and 0 to 7, "normal."

The patient-rated **SF-36** (Ware et al. 1993) consists of 36 questions covering 8 health domains: physical functioning, bodily pain, role limitations due to physical problems, role limitations due to emotional problems, general health perceptions, mental health, social function, and vitality. Each domain is scored by summing the individual items and transforming the scores into a 0-to-100 scale, with higher scores indicating better health status or functioning. Two summary scores are constructed based on the 8 SF-36 domains.

Table 2 continued.

The **EQ-5D** (Kind 1996) is a generic, multidimensional, health-related, quality-of-life instrument. The profile allows patients to rate their health state in 5 health domains: mobility, self-care, usual activities, pain/discomfort, and mood. A single rating between 1 and 3 is generated for each domain. For each patient, the outcome rating on the 5 domains is mapped to a single index through an algorithm. The index ranges between 0 and 1, with the higher values indicating a better health state perceived by the patient.

The **Work Productivity and Activity Impairment Instrument (WPAI)** is a self-administered instrument used to measure the effect of general health and symptom severity on work productivity and regular activities (Reilly et al. 1993). The WPAI yields 4 types of scores: Absenteeism (work time missed); Presenteeism (impairment at work/reduced on-the-job effectiveness); Work Productivity Loss (overall work impairment/absenteeism plus presenteeism); and Activity Impairment. Subscale scores in the chronic pain studies were based on a scale of 0 to 1. Higher scores indicate greater impairment.

The Profile of Mood States – Brief Form (POMS–Brief Form) is completed by the patient and consists of 30 items that measures both positive and negative aspects of 6 mood states (tension-anxiety, depression-dejection, anger-hostility, vigor-activity, fatigue inertia, and confusion-bewilderment) (MHS Systems 2003). The score for each of the 6 mood states ranges from 0 to 20. The total score is sum of all factor scores minus the factor score for vigor and ranges from 0 (least disturbed) to 80 (most disturbed).

The primary efficacy analysis tested the null-hypothesis that the difference for the 24 hour average pain rating between the DLX and placebo treatment groups at the last time point of the placebo controlled treatment phase is zero. All studies were powered at 80% or above to detect treatment group differences for both the analysis of mean change from baseline to endpoint and the response rate analysis with the exception of study CLBP-GC. Analysis of co-variance (ANCOVA) was performed for the mean change from baseline to endpoint of the primary efficacy measures and other secondary efficacy measures. Stratifying variable NSAID use (Yes/No) was also added to the above ANCOVA model for all efficacy analyses except for CLBP-GC in which NSAID routine users were excluded from the study.

A gatekeeper strategy was employed in all studies for sequentially testing the secondary hypothesis. If the primary hypothesis was statistically significant at the 0.05 two-sided level, the first secondary gatekeeper hypothesis was tested. If this comparison was statistically significant subsequent secondary hypotheses were tested in sequence until a null-hypothesis in the sequence failed to be rejected.

Clinically significant response rates were defined as either at least 50% or at least 30% pain reduction in 24 hour average pain from baseline to endpoint. Proportions of response were analysed using Fischer's exact test.

Reviewing patient disposition, a total of 839 patients were randomly assigned to DLX and 689 patients assigned to placebo in the five chronic somatic studies. The two placebo controlled trials in patients with OA pain, namely Studies OA/EP and OA/FG included 239 DLX treated patients and 248 placebo treated patients while the three placebo controlled trials in patients with CLBP, that is, Studies CLBP-EN, CLBP-EO and CLBP-GC included 600 DLX treated patients and 441 placebo treated patients. Table 3 summarises patient disposition for the five studies. There were no statistically significant differences between DLX and placebo treatment groups in terms of early discontinuation due to any reason from the study expect for Studies OA-FG and CLBP-EO.

In Studies OA-FG, CLBP-EN, CLBP-EO and CLBP-GC a statistically significant and larger percentage of DLX patients discontinued due to adverse events compared with placebo treated patients. Discontinuation due to lack of efficacy was infrequent in all five studies. In Study CLBP-GC a statistically significant smaller percentage of DLX patients discontinued due to lack of efficacy compared with placebo treated patients.

Reviewing patient demographics and baseline characteristics, DLX and placebo treated groups were generally well balanced within studies with no clinically relevant treatment group differences observed in patient characteristics or in baseline severity of illnesses.

In all five studies patients were required to have the 24 hour average pain rating of at least 4 to enter the study and the observed mean average pain rating of approximately 6 points denotes pain classified as moderately severe. The baseline characteristic of the study population generally reflected those of the overall population with OA pain and CLBP. The overall percentage of concomitant NSAID users at study entry ranged from 31.36% in Study CLBP-EN to 50.65% in Study OA-EP. The baseline scores for the WOMAC physical function subscale and RMDQ-24 suggests moderately impaired functional status of patients.

Table 3. Summary of Patient Disposition. All randomised patients. Acute treatment phase. Studies OA-FG, OA-EP, CLBP-EN, CLBP-EO and CLBP-GC. Table continued across two pages.

Primary Reason for Discont.	OA-FG			OA-EP			CLBP-EN*		
	DLX 60/120 QD	PBO	p-Value[a]	DLX 60/120 QD	PBO	p-Value[a]	DLX 60/120 QD	PBO	p-Value[a]
	N=128 (%)	N=128(%)		N=111 (%)	N=120 (%)		N=115 (%)	N=121 (%)	
Completed	72.7	86.7	.008	69.4	80.0	.070	73.0	81.0	.165
Discont due to any reason	27.3	13.3	.008	30.6	20.0	.070	27.0	19.0	.165
Adverse event	18.8	5.5	.002	13.5	5.8	.071	13.9	5.8	.047
Subject decision	3.1	1.6	.684	7.2	7.5	1.000	7.0	5.0	..588
Lack of efficacy	0.8	3.9	.213	1.8	2.5	1.000	2.6	4.1	.723
Lost to follow up	0.8	0.0	1.00	3.6	0.0	.052	0.9	0.8	1.00
Protocol violation	2.3	1.6	1.00	1.8	0.8	.609	2.6	2.5	1.00
Physician Decision	1.6	0.0	.498	2.7	1.7	.673	0.0	0.8	1.00
Entry criteria not met	0.0	0.8	1.00	0.0	0.8	1.00	0.0	0.0	NA
Sponsor Decision	0.0	0.0	NA	0.0	0.8	1.00	0.0	0.0	NA

Primary Reason for Discont.	CLBP-EO					CLBP-GC		
	1)DLX 20 QD	2)DLX 60 QD	3)DLX 120 QD	PBO	p-Value[a]	DLX 60 QD	PBO	p-Value[a]
	N=59 (%)	N=116 (%)	N=112 (%)	N=117 (%)		N=198 (%)	N=203 (%)	
Completed	72.9	69.0	55.4	70.1	1) .729 2) .887 3) .028	74.2	76.8	.563
Discont due to any reason	27.1	31.0	44.6	29.9	1) .729 2) .887 3) .028	25.8	23.2	.563
Adverse event	15.3	14.7	24.1	8.5	1) .202 2) .158 3) .002	15.2	5.4	.002
Subject decision	5.1	5.2	5.4	12.0	1) .182 2) .100 3) .101	4.0	6.4	.371
Lack of efficacy	3.4	3.4	4.5	5.1	1) .720 2) .748 3) 1.00	0.5	4.4	.020
Lost to follow up	1.7	5.2	4.5	1.7	1) 1.00 2) .171 3) .272	0.5	2.0	.372
Protocol violation	0.0	2.6	3.6	2.6	1) .552 2) 1.00 3) .717	3.0	2.5	.769
Physician Decision	1.7	0.0	2.7	0.0	1) .335 2) NA 3) .115	2.0	1.5	.721
Entry criteria not met	0.0	0.0	0.0	0.0	NA	0.5	0.5	1.00
Sponsor Decision	0.0	0.0	0.0	0.0	NA	0.0	0.5	1.00

Table 3 continued.

Abbreviations: Discont. = discontinuation; DLX = duloxetine; N = number of randomized patients ; NA = not applicable; PBO = placebo; QD = once daily.

* For Study CLBP-EN, summary of patient disposition is a post hoc analysis based on the database from the final datalock after the extension treatment period . The frequencies of discontinuation due to subject decision, lack of efficacy, physician decision, and lost to follow up were different from the numbers documented in the Study CLBP-EN interim clinical study report (which was based on the database from the interim datalock after the placebo-controlled treatment period) because of corrections made in the source data during the final lock.

[a] P-value comparison with placebo.

The actual numerical p value results of the primary key efficacy findings are given in Table 4. As described earlier, the primary endpoint (24 hour average pain rating) was collected from patient diaries and expressed as a weekly mean in Studies OA-EP and CLBP-EO and collected at study visits in Studies OA-FG, CLBP-EN and CLBP-GC. All five studies used the same 11 point numerical rating scale for rating pain severity. Results based on the protocol specified primary collection method are given in Table 5. In Studies OA-FG, OA-EP, CLBP-EN and CLBP-GC patients on DLX (ranging from 60-120 mg per day) had statistically significantly greater improvement based on the pre-specified primary efficacy analysis using Mixed Model Repeated Measures (MMRM) analysis. Sensitivity analysis of both Last Observation Carried Forward (LOCF) and Baseline Observation Carried Forward (BOCF) endpoint confirmed the MMRM analysis results except for Study OA-EP where BOCF analysis did not demonstrate a statistically significant difference.

Table 4. Numerical p values for the key efficacy measures.

Efficacy Endpoint	Method	Study/Dose						
		OA-EP 60/120mg	OA-FG 60/120mg	CLBP-EO 20mg	CLBP-EO 60mg	CLBP-EO 120mg	CLBP-GC 60mg	CLBP-EN 60/120mg
24-hour average pain rating	MMRM	<.001	<.001	.243	.110	.236	.001	.004
	BOCF	.086	.013	.621	.228	.893	.004	.019
30% Response[a]	LOCF	.033	<.001	.869	.141	.033	.108	.060
	BOCF	.228	.031	1.000	.277	.679	.161	.056
50% Response[a]	LOCF	.006	.068	.356	.472	.255	.006	.087
	BOCF	.067	.289	.562	.546	.761	.002	.039
PGI-I	LOCF	.001	.164	.318	.005	.124	.011	.014
	BOCF	.026	.074	.285	.019	.569	.003	.001
WOMAC physical function	LOCF	.001	.016	N/A	N/A	N/A	N/A	N/A
	BOCF	.028	.149	N/A	N/A	N/A	N/A	N/A
RMDQ-24 total	LOCF	N/A	N/A	.161	.019	.010	.255	.009
	BOCF	N/A	N/A	.089	.023	.191	.073	.042

Abbreviations: BOCF = baseline observation carried forward; LOCF = last observation carried forward; MMRM = mixed model repeated measures; N/A = not applicable; PGI I = Patient's Global Impressions of Improvement; RMDQ-24 = Roland-Morris Disability Questionnaire; WOMAC = Western Ontario and McMaster Universities Arthritis Index.

[a] Response was defined based on change in 24-hour average pain rating.

Table 5. Primary efficacy outcome (24 h average pain). All randomised patients. Acute treatment phase. Studies OA-FG, OA-EP, CLBP-EN, CLBP-EO and CLBP-GC.

	24-hour average pain (collected at study visits)			
Study	**Analysis**	**Treatment Group[a]**	**LSMean Change (SE)**	**p-Value[b]**
OA-FG[c]	MMRM	DLX 60/120 QD Placebo	-2.72 (0.20) -1.88 (0.18)	<.001
	BOCF	DLX 60/120 QD Placebo	-2.23 (0.20) -1.63 (0.19)	.013
	LOCF	DLX 60/120 QD Placebo	-2.51 (0.20) -1.72 (0.18)	<.001
CLBP-EN[e]	MMRM	DLX 60/120 QD Placebo	-2.32 (0.22) -1.50 (0.21)	.004
	BOCF	DLX 60/120 QD Placebo	-1.86 (0.20) -1.25 (0.20)	.019
	LOCF	DLX 60/120 QD Placebo	-2.09 (0.21) -1.45 (0.21)	.019
CLBP-GC[f]	MMRM	DLX 60 QD Placebo	-2.48 (0.16) -1.80 (0.15)	.001
	BOCF	DLX 60 QD Placebo	-1.92 (0.15) -1.37 (0.15)	.004
	LOCF	DLX 60 QD Placebo	-2.25 (0.15) -1.65 (0.15)	.002

Table 5. Continued. Primary efficacy outcome (24 h average pain). All randomised patients. Acute treatment phase. Studies OA-FG, OA-EP, CLBP-EN, CLBP-EO and CLBP-GC.

OA-EP[d]	MMRM	DLX 60/120 QD	-2.92 (0.17)	<.001
		Placebo	-2.08 (0.16)	
	BOCF	DLX 60/120 QD	-2.20 (0.20)	.086
		Placebo	-1.75 (0.19)	
	LOCF	DLX 60/120 QD	-2.64 (0.19)	.006
		Placebo	-1.93 (0.18)	
CLBP-EO[g]	MMRM	DLX 20 QD	-1.74 (0.25)	.243
		DLX 60 QD	-2.50 (0.18)	.110
		DLX 120 QD	-2.42 (0.20)	.236
		Placebo	-2.10 (0.18)	
	BOCF	DLX 20 QD	-1.37 (0.27)	.621
		DLX 60 QD	-1.86 (0.20)	.228
		DLX 120 QD	-1.50 (0.20)	.893
		Placebo	-1.54 (0.19)	
	LOCF	DLX 20 QD	-1.59 (0.28)	.482
		DLX 60 QD	-2.27 (0.20)	.104
		DLX 120 QD	-2.21 (0.20)	.167
		Placebo	-1.82 (0.20)	

Abbreviations: BOCF = baseline observation carried-forward; DLX = duloxetine; LOCF = last observation carried forward; LSMean = least-squares mean; MMRM = mixed-models repeated measures; QD = once daily; SE = standard error.

[a] Study OA-EP: N (DLX 60/120 QD) = 111, N (Placebo) = 120
Study OA-FG: N (DLX 60/120) = 128, N (Placebo) = 128
Study CLBP-EN: N (DLX 60/120 QD) = 115, N (Placebo) = 121
Study CLBP-EO: N (DLX 20 QD) = 59, N (DLX 60 QD) = 116, N (DLX 120 QD) = 112, N (Placebo) = 117.
Study CLBP-GC: N (DLX 60 QD) = 198, N (Placebo) = 203

[b] P-value comparison with placebo.

[c] Baseline score (standard deviation): DLX 60/120 QD = 6.07 (1.39), Placebo = 6.14 (1.27).

[d] Baseline score (standard deviation): DLX 60/120 QD = 6.10 (1.34), Placebo = 6.18 (1.32).

[e] Baseline score (standard deviation): DLX 60/120 QD = 5.91 (1.59), Placebo = 5.96 (1.66).

[f] Baseline score (standard deviation): DLX 60 QD = 5.84 (1.43), Placebo = 5.75 (1.37).

[g] Baseline score (standard deviation): DLX 20 QD = 6.42 (1.39), DLX 60 QD = 6.18 (1.44), DLX 120 QD = 6.06 (1.45), Placebo = 6.18 (1.25).

Table 6 shows the treatment differences, associated 95% confidence intervals (CIs) and p values from MMRM-LOCF-BOCF analysis of 24 hour average pain collected from both diary and study visits for Studies OA-FG, OA-EP, CLBP-EN and CLBP-GC.

Table 6. 24 h average pain score. DLX-placebo differences in least-squares mean changes from baseline to endpoint with 95% CI. All randomised patients. All randomised patients. Acute treatment phase. Studies OA-FG, OA-EP, CLBP-EN and CLBP-GC.

	24-hour average pain (*collected from patient diaries*)			24-hour average pain (*collected at study visits*)		
	Difference (DLX 60/120 QD - PBO)[c]	95% CI	p-Value[a]	Difference (DLX 60/120 QD - PBO)[c]	95% CI	p-Value[a]
OA-FG						
MMRM[b]	-0.72	(-1.12, -0.31)	<.001	-0.84	(-1.32, -036)	<.001
BOCF	-0.40	(-0.85, 0.04)	.077	-0.59	(-1.06, -0.13)	.013
LOCF	-0.58	(-1.01, -0.15)	.008	-0.78	(-1.24, -0.32)	<.001
OA-EP						
MMRM[b]	-0.84	(-1.29, -0.39)	<.001	-1.12	(-1.69, -0.55)	<.001
BOCF	-0.45	(-0.96, 0.06)	.086	-0.63	(-1.18, -0.09)	.024
LOCF	-0.70	(-1.20, -0.21)	.006	-0.97	(-1.52, -0.42)	<.001
CLBP-EN						
MMRM[b]	-1.00	(-1.46, -0.55)	<.001	-0.82	(-1.37, -0.27)	.004
BOCF	-0.58	(-1.06, -0.10)	.019	-0.61	(-1.11, -0.10)	.019
LOCF	-0.77	(-1.26, -0.28)	.002	-0.64	(-1.18, -0.11)	.019
CLBP-GC						
MMRM[b]	-0.77	(-1.15, -0.39)	<.001	-0.68	(-1.09, -0.26)	.001
BOCF	-0.65	(-1.00, -0.30)	<.001	-0.55	(-0.93, -0.18)	.004
LOCF	-0.70	(-1.05, -0.35)	<.001	-0.60	(-0.97, -0.22)	.002

Abbreviations: BOCF = baseline observation carried forward; BPI = Brief Pain Inventory; CI = confidence interval; Differences = differences in least-squares mean changes from baseline to endpoint; DLX = duloxetine; LOCF = last observation carried forward; MMRM = mixed-models repeated measures; PBO = placebo; QD = once daily .

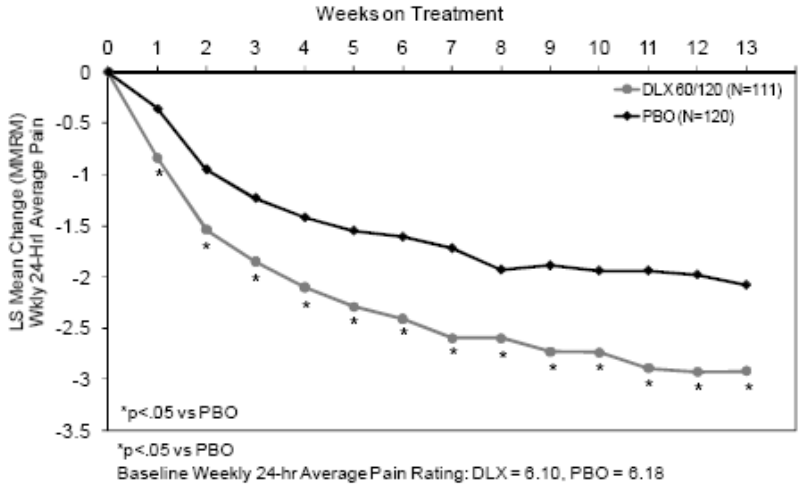
a P-value comparison with placebo.

b Primary efficacy analysis used weekly mean from diary in Study OA-EP, and used BPI collected at study visits in Studies OA-FG and CLBP-EN.

c Study CLBP-GC only included DLX 60 mg.

Statistically significant pain reductions were observed as early as one week on DLX 60 mg per day in four studies and were maintained for the duration of three month placebo controlled treatment phase as illustrated in Figure 1. Study CLBP-EO did not achieve the primary objective but had a numerically greater average pain reduction in favour of DLX at 60 mg and 120 mg. There was also a statistically significant separation between DLX 60 mg/120 mg and placebo between Weeks 3-11. This was however not demonstrated at Week 13 as indicated Figure 2. Table 7 shows the treatment differences and the associated 95% CI for Study CLBP-EO.

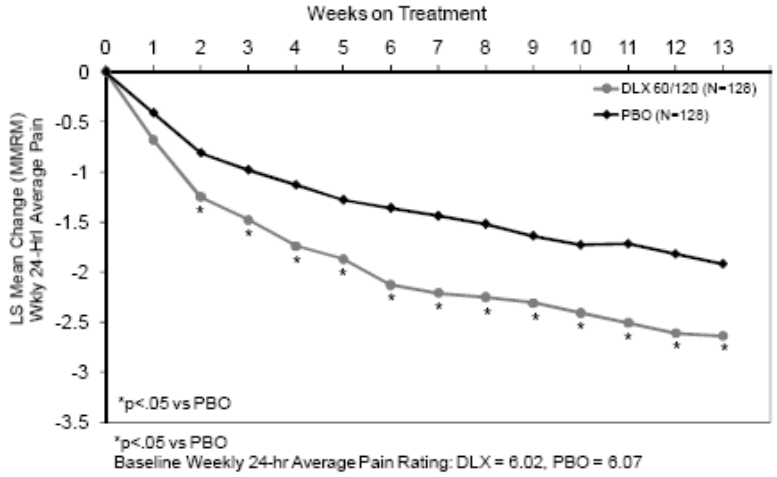
Figure 1(a). Studies OA-EP (a), OA-FG (b), CLBP-EN (c), CLBP-GC (d). MMRM analysis of weekly mean of 24 h average pain severity (a-d).



*p<.05 vs PBO

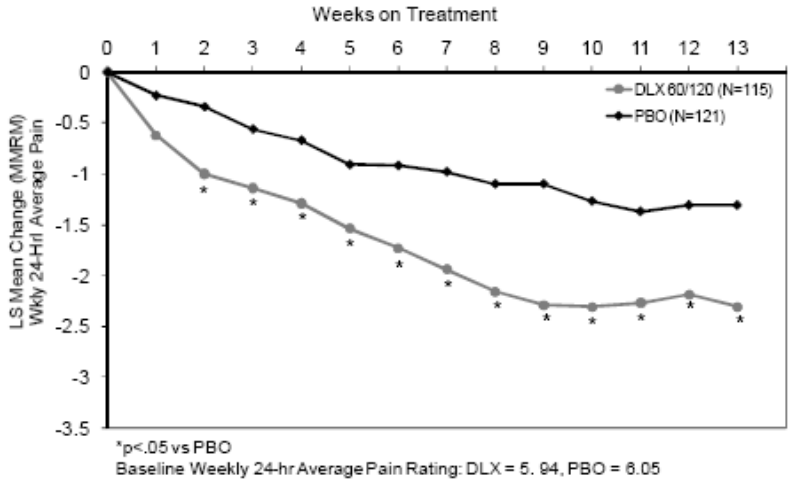
Baseline Weekly 24-hr Average Pain Rating: DLX = 6.10, PBO = 6.18

Figure 1(b).



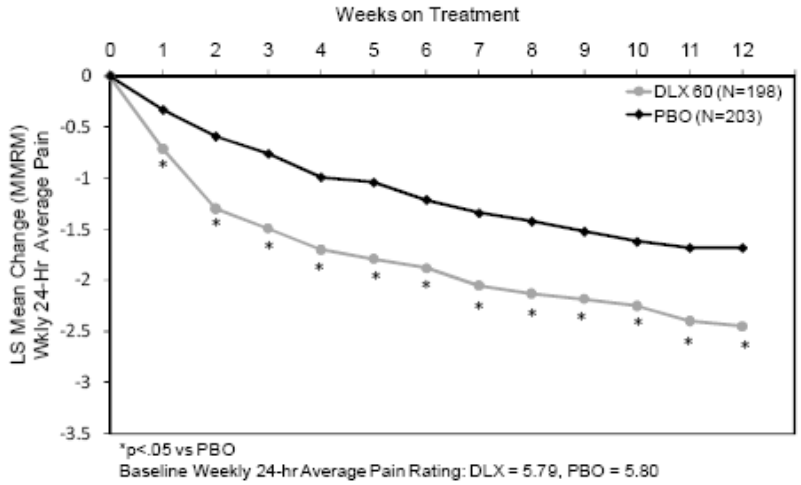
*p<.05 vs PBO
Baseline Weekly 24-hr Average Pain Rating: DLX = 6.02, PBO = 6.07

Figure 1(c).



*p<.05 vs PBO
Baseline Weekly 24-hr Average Pain Rating: DLX = 5. 94, PBO = 6.05

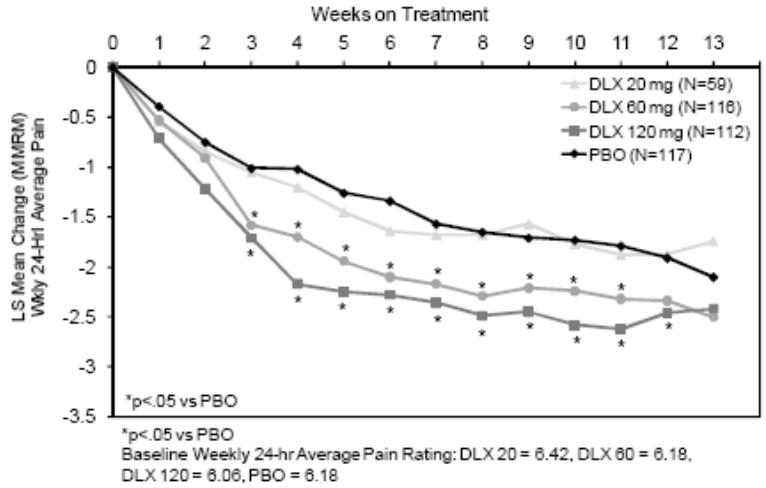
Figure 1(d).



*p<.05 vs PBO
Baseline Weekly 24-hr Average Pain Rating: DLX = 5.79, PBO = 5.80

Abbreviations: DLX = duloxetine; LS Mean = least-squares mean; MMRM = mixed-model repeated measures; PBO = placebo.

Figure 2. Study CLBP-EO. MMRM analysis of weekly mean of 24 h average pain severity.



*p<.05 vs PBO
Baseline Weekly 24-hr Average Pain Rating: DLX 20 = 6.42, DLX 60 = 6.18, DLX 120 = 6.06, PBO = 6.18

Abbreviations: DLX = duloxetine; LS Mean = least-squares mean; MMRM = mixed-model repeated measures; PBO = placebo.

Table 8 show 30% and 50% response rates based on 24 hour average pain in the five primary studies. Based on the LOCF approach a statistically significantly greater percentage of DLX treated patients were responders compared with placebo treated patients in Studies OA-EP, OA-FG, CLBP-EO and CLBP-GC. Sensitivity analysis using the BOCF approach confirmed the statistically significant findings in Studies OA-FG and CLBP-GC. In addition BOCF analysis showed statistically significant difference in favour of DLX 60/120 mg but only based on 50% pain reduction criteria even though LOCF analysis only showed a numerical difference in Study CLBP-EN. Figures 3 and 4 are graphical presentations of the response rate results.

Table 7. 24 h average pain score. DLX-placebo differences in least-squares mean changes from baseline to endpoint with 95% CI. All randomised patients. All randomised patients. Acute treatment phase. Study CLBP-EO.

	Difference (DLX 20 QD - PBO)	95% CI	p-Value[a]	Difference (DLX 60 QD - PBO)	95% CI	p-Value[a]	Difference (DLX 120 QD - PBO)	95% CI	p-Value[a]
Weekly mean 24-hour average pain (Diary)									
MMRM[b]	0.36	(-0.24, 0.95)	.243	-0.40	(-0.89, 0.09)	.110	-0.32	(-0.84, 0.21)	.236
BOCF	0.16	(-0.48, 0.81)	.621	-0.32	(-0.85, 0.20)	.228	0.04	(-0.50, 0.57)	.893
LOCF	0.23	(-0.42, 0.89)	.482	-0.44	(-0.98, 0.09)	.104	-0.38	(-0.92, 0.16)	.167
24-hour average pain (BPI collected at study visits)									
MMRM	0.16	(-0.6, 0.94)	.672	-0.58	(-1.21, 0.05)	.070	-0.59	(-1.25, 0.07)	.078
BOCF	0.10	(-0.60, 0.79)	.784	-0.45	(-1.02, 0.12)	.125	-0.02	(-0.60, 0.55)	.933
LOCF	0.09	(-0.63, 0.80)	.813	-0.63	(-1.21, -0.04)	.035	-0.58	(-1.17, 0.01)	.054

Abbreviations: BOCF = baseline observation carried forward; BPI = Brief Pain Inventory; CI = confidence interval; Difference = differences in least-squares mean changes from baseline to endpoint between duloxetine and placebo; DLX = duloxetine; LOCF = last observation carried forward; MMRM = mixed-models repeated measures; PBO = placebo; QD = once daily.

a P-value comparison with placebo.

b Primary efficacy analysis in Study CLBP-EO.

Table 8. Response rates for the 24 h average pain score. All randomised patients. 13 week treatment phase. Studies OA-FG, OA-EP, CLBP-EN, CLBP-EO and CLBP-GC.

Study	Analysis	Treatment Group[a]	30% Response Rate (%)	p-Value[b]	50% Response Rate (%)	p-Value[b]
OA-FG[c]	BOCF	DLX 60/120 mg QD	57.0	.031	38.0	.289
		Placebo	42.5		31.5	
	LOCF	DLX 60/120 mg QD	65.3	<.001	43.8	.068
		Placebo	44.1		32.3	
OA-EP[c]	BOCF	DLX 60/120 mg QD	48.1	.228	39.8	.067
		Placebo	39.5		27.7	
	LOCF	DLX 60/120 mg QD	59.3	.033	47.2	.006
		Placebo	44.5		29.4	
CLBP-EN[c]	BOCF	DLX 60/120 mg QD	45.9	.056	35.8	.039
		Placebo	33.0		22.6	
	LOCF	DLX 60/120 mg QD	53.2	.060	38.5	.087
		Placebo	40.0		27.0	
CLBP-EO[c]	BOCF	DLX 20 mg QD	35.7	1.000	19.6	.562
		DLX 60 mg QD	43.6	.277	29.1	.546
		DLX 120 mg QD	39.4	.679	26.6	.761
		Placebo	36.3		24.8	
	LOCF	DLX 20 mg QD	41.1	.869	21.4	.356
		DLX 60 mg QD	53.6	.141	34.5	.472
		DLX 120 mg QD	57.8	.033	36.7	.255
		Placebo	43.4		29.2	
CLBP-GC[c]	BOCF	DLX 60 mg QD	48.0	.161	42.9	.002
		Placebo	40.9		28.1	
	LOCF	DLX 60 mg QD	56.9	.108	48.7	.006
		Placebo	48.7		34.7	

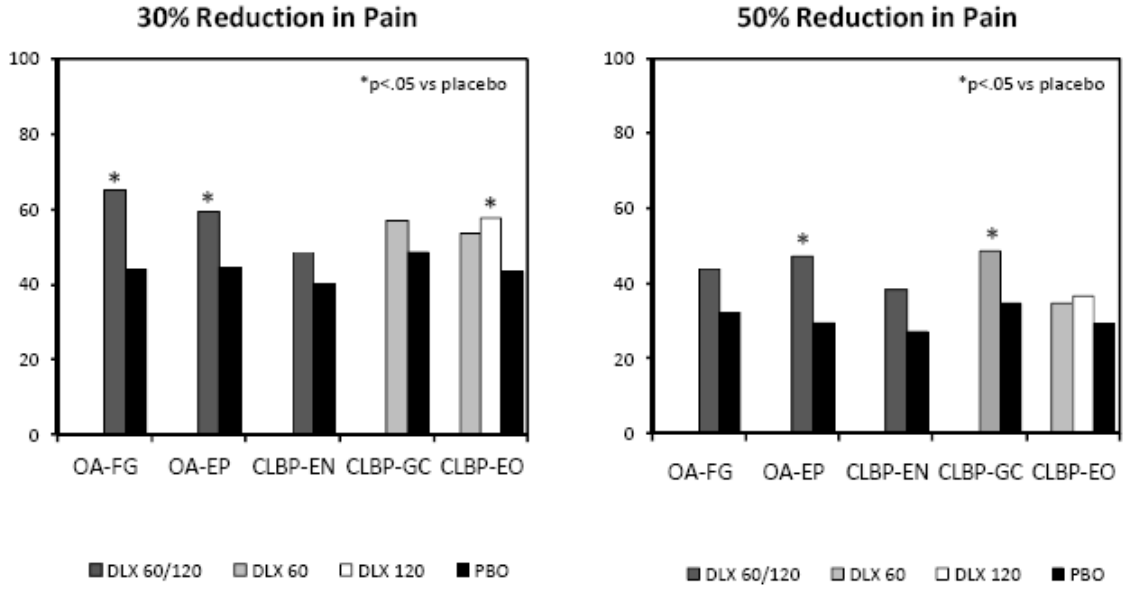
Abbreviations: BOCF = baseline observation carried forward; BPI = Brief Pain Inventory; DLX = duloxetine; LOCF = last observation carried forward; N = all randomized patients; QD = once daily.

[a] Study OA-FG: N (DLX 60/120) = 128, N (Placebo) = 128
Study OA-EP: N (DLX 60/120 QD) = 108, N (Placebo) = 119;
Study CLBP-EN: N (DLX 60/120 QD) = 111, N (Placebo) = 116;
Study CLBP-EO: N (DLX 20 QD) = 59, N (DLX 60 QD) = 116, N (DLX 120 QD) = 112, N (Placebo) = 117;
Study CLBP-GC: N (DLX 60 QD) = 198, N (Placebo) = 203.

[b] Versus placebo using Fisher's exact test.

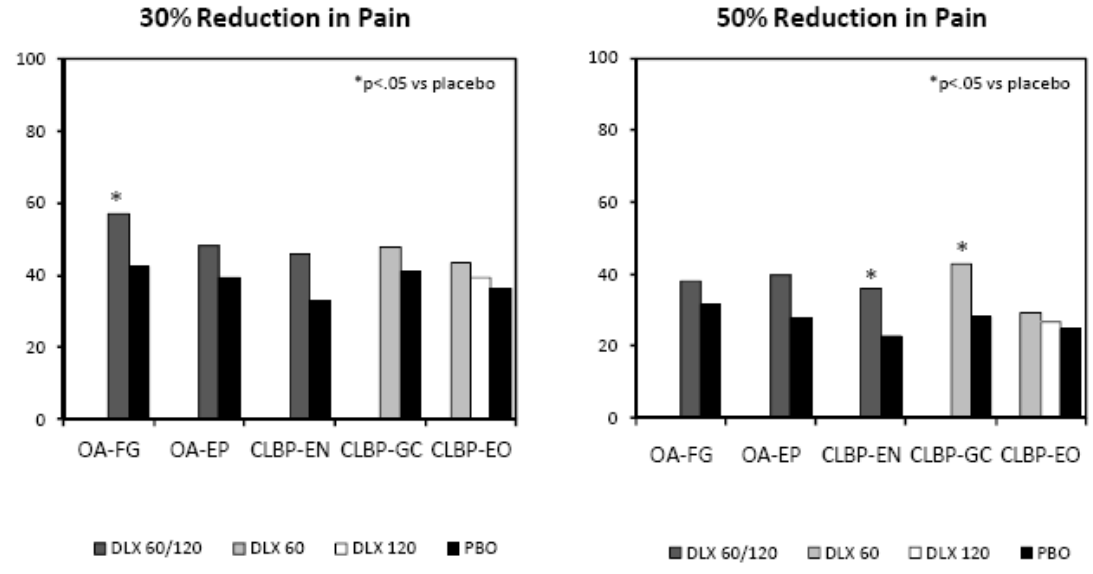
[c] Response rate based on: 1) the weekly mean of 24-hour average pain rating from patient diaries (the primary outcome) in Study OA-EP and Study CLBP-EO, and 2) daily average from BPI instrument collected at study visits (the primary outcome) in Study OA-FG, Study CLBP-EN, and Study CLBP-GC.

Figure 3. Response rate at 3 months using LOCF.



Abbreviations: DLX = duloxetine; LOCF = last observation carried forward; PBO = placebo.

Figure 4. Response rate at 3 months using BOCF.



Abbreviations: BOCF = baseline observation carried forward; DLX = duloxetine; PBO = placebo.

Time to response was statistically significantly earlier for DLX treatment groups when compared with placebo treatment groups in all 5 studies with the exception of DLX 20 mg per day in Study CLBP-EO. Table 9 summarises the mean time to 30% reduction from baseline to LOCF endpoint in a 24 hour average pain rating by treatment in each of five studies.

Table 9. Time to response (30% reduction in 24 h average pain). All randomised patients. 13 week treatment phase. Studies OA-FG, OA-EP, CLBP-EN, CLBP-EO and CLBP-GC.

Study	Mean (SD) Days to 30% Response		p-Value[a]
	Duloxetine	Placebo	
OA-FG (60/120QD)	51 (2.81)	68 (2.95)	<.001
OA-EP (60/120QD)	33 (2.42)	57 (3.30)	<.001
CLBP-EN (60/120QD)	61 (3.02)	76 (3.02)	.003
CLBP-EO (60/120QD)[b]	44 (2.35)	62 (3.76)	<.001
CLBP-GC (60QD)	53 (2.12)	64 (2.03)	.003

Abbreviations: LOCF = last observation carried forward; QD = once daily; SD = standard deviation.

a Versus placebo using log-rank test.

b Study CLBP-EO Duloxetine 20 mg QD was excluded from this analysis.

Response defined as >=30% reduction from baseline to LOCF endpoint based on the weekly mean of 24-hour average pain rating from patient diaries.

Regarding the response rates for the three CLBP studies, the 30 and 50% response rate outcomes are indicated in Table 10. Table 11 shows the 30% and 50% response rates combining data from the two OA studies.

Table 10. Response rates for the 24 h average pain score. All randomised patients. 13 week treatment phase. Studies CLBP-EN, CLBP-EO and CLBP-GC.

Analysis	Treatment Group	30% Response Rate (%)	p-Value[a]	50% Response Rate (%)	p-Value[a]
BOCF	DLX 60/120 mg QD (N=541)	239 (44.2%)	.021	203 (37.5%)	<.001
	Placebo (N=441)	164 (37.2%)		117 (26.5%)	
LOCF	DLX 60/120 mg QD (N=520)	291 (56.0%)	.002	240 (46.2%)	<.001
	Placebo (N=428)	194 (45.3%)		140 (32.7%)	

Abbreviations: BOCF = baseline observation carried forward; BPI = Brief Pain Inventory; CLBP = chronic low back pain; DLX = duloxetine; LOCF = last observation carried forward; QD = once daily.

Response defined based on data from BPI.

[a] p-value is based on Cochran Mantel-Haenszel test.

Table 11. Response rates for the 24 h average pain score. All randomised patients. 13 week treatment phase. Pooled OA studies (OA-EP and OA-FG).

Analysis	Treatment Group	30% Response Rate (%)	p-Value[a]	50% Response Rate (%)	p-Value[a]
BOCF	DLX 60/120 mg QD (N=239)	125 (52.3%)	.011	92 (38.5%)	.021
	Placebo (N=248)	101 (40.7%)		71 (28.6%)	
LOCF	DLX 60/120 mg QD (N=229)	148 (64.6%)	<.001	108 (47.2%)	<.001
	Placebo (N=244)	109 (44.7%)		75 (30.7%)	

Abbreviations: BOCF = baseline observation carried forward; BPI = Brief Pain Inventory; DLX = duloxetine; LOCF = last observation carried forward; OA = osteoarthritis; QD = once daily.

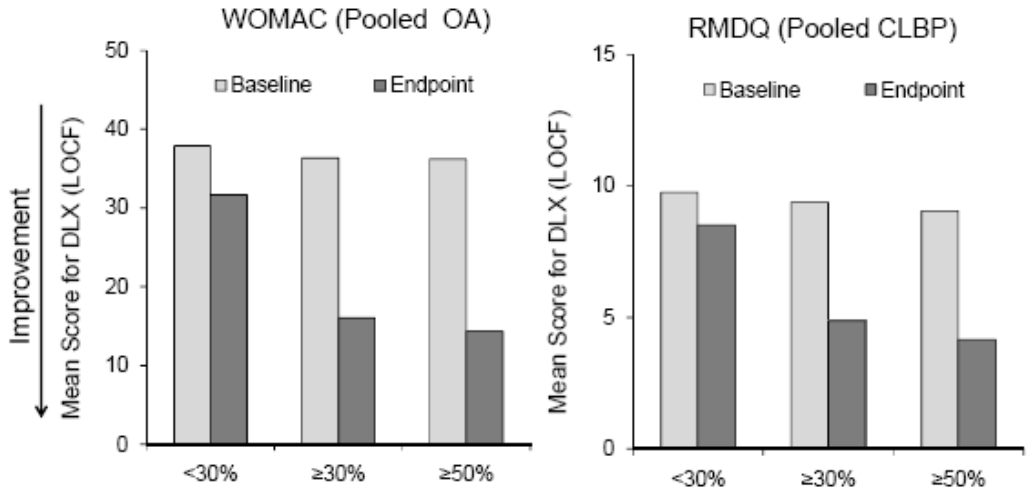
Response defined based on data from BPI.

[a] p-value is based on Cochran Mantel-Haenszel test.

For the all the studies, physical function was assessed using disease specific scales with WOMAC physical function subscale for OA pain and RMDQ-24 for CLBP. Figure 5 presents the mean change in physical function score from baseline to LOCF endpoint by response status defined as either at least 30% or 50% improvement in average pain from study

baseline for the DLX treated patients in the pooled OA and CLBP studies. Notably patients with a clinically significant pain reduction also reported a clinically significant improvement in physical function. Specifically at the group mean level, there was an approximate 50% improvement ranging from 48% to 60% in physical function for patients who reported at least 30% and 50% average pain reduction. On the contrary, for patients who reported <30% average pain reduction there was only a <20% improvement in physical function score.

Figure 5. Mean change in physical function score.



Abbreviations: % = percent decrease in pain severity as measured by the Brief Pain Inventory – Severity scale; CLBP = chronic low back pain; DLX = duloxetine; LOCF = last observation carried forward analysis; OA = osteoarthritis of the knee; RMDQ = Roland-Morris Disability Questionairre-24; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index.

Table 12 summarises the key secondary efficacy findings across the four studies. On both of their pre-specified secondary gatekeeper objectives, DLX treated patients in Studies OA-EP and CLBP-EN demonstrated statistically significant improvement when compared with placebo. Study CLBP-GC met the first gatekeeper secondary objective based on PGI improvement but did not meet the second gatekeeper secondary objective based on RMDQ. Study OA-FG did not meet the first gatekeeper secondary objective based on PGI-Improvement. Study CLBP-EO did not meet its primary objective and per the gatekeeper strategy the data are not presented.

Table 12. Key Secondary Assessment of Efficacy. All randomised patients, Acute treatment phase. Table continued across two pages.

Study OA-FG, Study OA-EP, Study CLBP-EN, and Study CLBP-GC

Study	Measure	Analysis	Treatment Group[a]	LSMeang (SE)	p-Value
OA-FG	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)	
	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)	
OA-EP	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)	
	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)	

Table 12 continued.

Study	Measure	Analysis	Treatment Group[a]	LSMean[g] (SE)	p-Value
CLBP-EN	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)	
	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)	
CLBP-GC	PGI-Improvement	LOCF[b]	DLX 60 QD	2.88 (0.09)	.011
			Placebo	3.19 (0.09)	
		BOCF[c]	DLX 60 QD	2.88 (0.08)	.003
			Placebo	3.22 (0.08)	
		MMRM	DLX 60 QD	2.70 (0.09)	.002
			Placebo	3.09 (0.09)	
	RMDQ-24 total score[e,f]	LOCF[b]	DLX 60 QD	-2.69 (0.31)	.255
			Placebo	-2.22 (0.32)	
		BOCF[c]	DLX 60 QD	-2.44 (0.29)	.073
			Placebo	-1.76 (0.29)	

Abbreviations: BOCF = baseline observation carried forward; DLX = duloxetine; LOCF = last observation carried forward; LSMean = least-squares mean; MMRM = mixed-models repeated measures; PGI-Improvement = Patient's Global Impressions of Improvement; N = all randomized patients; QD = once daily; RMDQ-24 = Roland-Morris Disability Questionnaire; SE= standard error; WOMAC = Western Ontario and McMaster Universities Arthritis Index.

[a] Study OA-EP: N (DLX 60/120 QD) = 111, N (Placebo) = 120.
Study CLBP-EN: N (DLX 60/120 QD) = 115, N (Placebo) = 121.
Study OA-FG: N (DLX 60/120) = 128, N (Placebo) = 128.
Study CLBP-GC: N (DLX 60 QD) = 198, N (Placebo) = 203.

[b] The prespecified analysis for the gatekeeper assessment.

[c] Post-hoc analysis.

[d] Baseline score (standard deviation): DLX 60/120 QD = 39.10 (11.06), Placebo = 38.50 (10.12).

[e] Baseline score (standard deviation): DLX 60/120 QD = 10.39 (4.78), Placebo = 10.87 (5.12).

[f] No MMRM analysis was performed for the RMDQ-24 total score because only baseline and endpoint values were collected.

[g] For PGI-Improvement, endpoint was used, and for RMDQ-24 and WOMAC, change from baseline was used.

[h] Baseline score (standard deviation): DLX 60/120 QD = 35.05 (9.63), Placebo = 36.82 (8.15).

Overall DLX 60 mg and 120 mg daily treated patients had statistically significantly greater improvements when compared with placebo across other secondary efficacy assessments.

The independence of the effect on pain from effects on depression and anxiety: although patients with MDD were excluded from the primary chronic somatic pain studies the relationship between the effect of DLX on mood and anxiety symptoms and the effect on pain relief were evaluated to assess the direct analgesic effect of DLX. Path analysis was used to test the null-hypothesis that the change in 24 hour average pain severity depends on the improvement of BDI-II or HADS-A (see Table 2 above for definition) versus the alternative that the improvement in 24 hour average pain severity is due to a direct analgesic effect of the treatment and not dependent upon the improvement in mood and anxiety symptoms. Regression models were used to estimate the direct effect of treatment and the indirect effect of change in BDI and change in HADS-A on the change in the 24 hour average pain rating and to test the null-hypothesis. Path analyses were performed in 4/5 studies, the exception being Study CLBP-GC where HADS and BDI were not collected, using the HADS-A, BDI-II and the 24 hour average pain rating from patient diary for Studies OA-EP and CLBP-EO and from the BPI for Studies OA-FG and CLBP-EN.

The data showed that the effects of DLX on pain reduction were attributable to a direct analgesic effect, independent of its effect on mood or anxiety. In the three positive studies the direct analgesic effects for DLX was 95.48% of the total effect in Study OA-FG, 95.14% of the total effect in Study OA-EP and 80.44% of the total effect of Study CLBP-EN. In Study CLBP-EO for the DLX 60 mg group, 82.3% of the total effects were due to a straight analgesic effect for the DLX 120 mg group, the percentage of the total effect could not be calculated due to at least one of the effects going in the opposite direction.

Reviewing the change of average pain by baseline depression severity, using the recommended major depressive episode detection cut-off value of HADS-D of at least eight, sub-group analysis of the change from baseline to endpoint in the BPI average pain score by HADS-depression baseline severity was conducted to assess whether the analgesic effect was consistent across different baseline depression severity levels. The ANCOVA model was used which contained effects for treatment group, HADS sub-group and the treatment by sub-group interaction with BPI average pain baseline value included as a covariate. Study CLBP-GC did not collect HADS-D data and was not included in the sub-group analysis. For the pooled CLBP studies and the pooled OA studies there was no statistically significant treatment by sub-group interaction. The effect of DLX in the reduction of BPI average pain appears to be similar in patients regardless of the HADS-D score at baseline.

Reviewing the change of average pain by baseline anxiety severity using the recommended general anxiety disorder detection value of HADS-A of at least eight, a sub-group analysis by HADS-anxiety baseline severity was conducted to assess whether the analgesic effect was consistent across different baseline anxiety severity levels.[7] As demonstrated by the results, there was no statistically significant treatment by sub-group interaction in the pooled CLBP studies. However, analysis of the pooled OA studies (Table 13) showed a statistically significant treatment by sub-group interaction with a p value = 0.029. The effect of DLX in the reduction of BPI average pain appears to be greater in patients whose HADS-A baseline score was <8 (indicating patients without a general anxiety disorder) compared to patients whose HADS-A baseline score was >8 (indicting patients with a general anxiety disorder).

[7] Sponsor comment: Study CLBP-GC did not collect HADS-A data and was not included in this subgroup analysis.

Table 13. Subgroup analysis of BPI average pain. Mean change from baseline to LOCF. By baseline HADS Anxiety Score. All randomised patients in Studies OA-EP and OA-FG Acute phase.

Subgroup	Treatment by Subgroup p-Value	Sub-group p-Value	Strata	N	Treatment	n	Baseline Mean	Baseline SD	Change Mean	Change SD	Change LSMean	Change SE	*p-Value
Baseline HADS anxiety score	.029	.401	<8	374	PLACEBO	191	6.13	1.40	-1.69	2.11	-1.65	0.14	
					DLX60/120QD	183	6.09	1.45	-2.75	2.15	-2.74	0.15	<.001
			>=8	93	PLACEBO	49	6.47	1.37	-2.12	2.25	-2.06	0.31	
					DLX60/120QD	44	6.39	1.56	-2.18	2.31	-2.21	0.32	.741

N=all randomized patients with non-missing baseline and endpoint.
Model 1 = Treatment, NSAID use, Protocol, and Baseline for within-stratum p-values.
Model 2 = Treatment, NSAID use, Protocol, Baseline, Subgroup and Treatment*Subgroup for interaction and subgroup p-values.
*p-Value for LSMean difference between Duloxetine and Placebo.

Sub-group analyses were conducted to examine treatment effect by patient demographic or baseline illness characteristics including age, gender, race, baseline average pain severity, duration of CLBP or OA pain, history of back surgery, NSAID use and geographic region. There was no statistically significant treatment by sub-group interactions for any of the sub-groups analysed. These results suggest that the efficacy of DLX in 24 hour average pain reduction from baseline to endpoint was similar in patients regardless of routine NSAID use status, baseline pain severity, geographic region, demographics and other disease specific characteristics across the placebo controlled studies.

Since study CLBP-GC did not enrol patients on routine NSAID use, sub-group analysis of NSAID use was performed for Studies CLBP-EN and CLBP-EO only. There was no statistically significant treatment by sub-group interactions by 'NSAID use' sub-group.

Reviewing the data on dose response effect, it is noted that all the primary chronic somatic pain studies required patients to start on DLX 30 mg per day before increasing the dose during a one week titration period except for Study CLBP-GC where DLX patients directly started on 60 mg per day. Of the two studies with a fixed dose design, that is, Studies CLPB-GC and CLPB-EO only CLBP-GC showed statistically significant separation from placebo with the DLX 60 mg per day dose on primary efficacy outcome and a number of secondary efficacy outcomes.

Study CLBP-EO did not show statistically significant separation on its endpoint based primary outcome measure. In the other two flexible dose design studies, OA-FG and CLBP-EN, DLX 60 mg non-responders who had no tolerability concerns were titrated up to 120 mg per day for the last six weeks of a thirteen week acute treatment period. However, patients randomised to placebo at study entry remained on placebo. To assess the treatment effect of DLX 60 mg per day compared to placebo, the non-responders at Visit 4 (regardless of the treatment assignment) were treated as discontinued from treatment due to the lack of efficacy at the visit for dose titration, that is, Week 7. Data were analysed using BOCF approach, that is, the baseline average pain rating was assigned 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. This data is presented in Table 14. The results using this analysis showed that the DLX 60 mg per day had statistically significantly greater pain reduction over the 13 week period compared to placebo in patients with OA pain and patients with CLBP. This analysis is not applicable to the other flexible dose design study, OA-EP because (per protocol) all DLX patients were re-randomised to DLX 60 mg per day and 120 mg per day without considering their response status at Week 7.

Table 14. 24 h average pain score. All randomised patients (DLX 60 mg versus placebo). 13 week treatment phase.

Study OA-FG and Study CLBP-EN

Study	Analysis	Treatment Group	LSMean Change (SE)	p-Value
OA-FG	BOCF	DLX 60 QD	-1.81 (0.20)	.007
		Placebo	-1.17 (0.19)	
CLBP-EN	BOCF	DLX 60 QD	-1.56 (0.19)	
		Placebo	-0.90 (0.18)	.006

Abbreviations: BOCF = baseline-observation-carried-forward; DLX 60 QD = duloxetine 60 mg once daily; LSMean = least-squares mean; SE = standard error; vs = versus.

Reviewing the rationale for dose adjustment at Week 7 in the three flexible dose studies (CLBP-EN, OA-EP and OA-FG), patients randomised to DLX treatment received DLX 60 mg per day for first seven weeks and patients were either re-randomised to DLX 60 mg or 120 mg (in Study OA-EP) or titrated to DLX 120 mg per day (Studies CLBP-EN and OA-FG) if not responding to DLX 60 mg per day. A post-hoc analysis was conducted for patients who stayed on DLX 60 mg during the entire placebo control 13 week treatment phase to show that pain reduction from baseline to the Week 7 time-point begin at the end of treatment phase. Table 15 and Figure 6 show that the DLX 60 mg per day treatment group had experienced statistically significant and clinically meaningful improvement in BPI average pain rating by Week 7. Further within group changes observed beyond a nominal seven weeks of study before patients continued on DLX 60 mg per day had no other statistical significance except for Study CLBP-GC and were not clinically meaningful. This result indicates that the majority of pain reduction was gained during the first seven weeks of treatment and there was little or no further pain reduction after the initial response is reached.

Reviewing the supporting data for evidence of additional benefit of DLX 120 mg once daily; In the re-randomised phase of Study OA-EP, patients re-randomised to DLX 120 mg per day had statistically significantly greater pain reduction compared with patients who stayed on DLX 60 mg per day during the six week treatment period based upon the analysis of mean change from re-randomisation baseline, that is, Week 7 to LOCF endpoint at Week 13.

In the re-randomised phase of Study OA-EP the analysis of mean change from re-randomisation baseline, that is, Week 7 to LOCF endpoint Week 13 of weekly mean of the 24 hour range pain score by the response status at the re-randomisation visit, found that there was statistically significant interaction between DLX dose and response status. Specifically non-responders to DLX 60 mg per day benefited more from the dose titration to DLX 120 mg per day than responders, with a difference between DLX 120 mg and DLX 60 mg per day on the mean change was 1.65 for non-responders and only 0.14 for responders.

Table 15. BPI average pain item. Between and within treatment change during and after the initial 2 month treatment period. All chronic pain studies that included DLX 60 mg treatment.

Study/Treatment	N	Baseline BPI 24-hour average pain score	Change at Week 7[a]		Change between Week 7 to Week 13[a]
		Mean (SD)	Mean (SD) within-group p-value*	p-val** (DLX vs PBO)	Mean (SD) within-group p-value*
OA-FG					
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
OA-EP					
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
CLBP-EN					
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
CLBP-GC					
DLX60QD	158	5.84 (1.30)	-2.23 (1.97); p<.001	<.001	-0.47 (1.53); p<.001
PLACEBO	169	5.66 (1.33)	-1.41 (1.64); p<.001		-0.50 (1.38); p<.001
CLBP-EO					
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

Abbreviations: ANCOVA = analysis of covariance; BPI = Brief Pain Inventory; DLX60QD = duloxetine 60 mg once daily; LOCF = last observation carried forward; N = number of randomized patients; PBO = placebo; QD = once daily; SD = standard deviation; vs = versus.

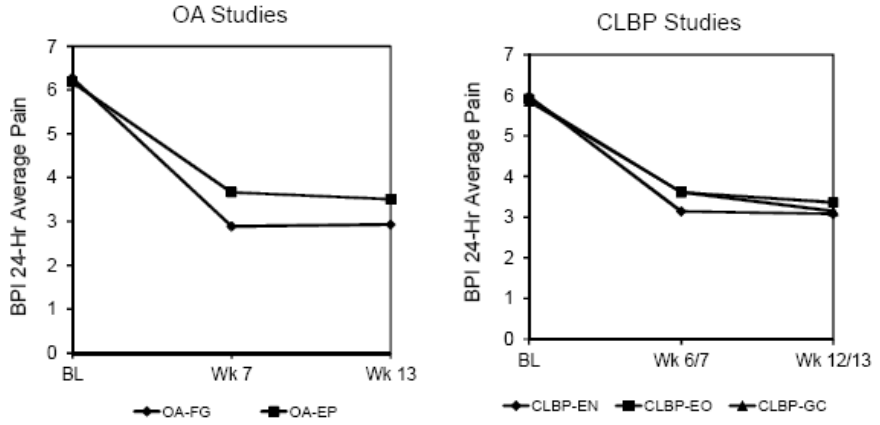
[a] In Study CLBP-GC, Week 6 and Week 12 data was used due to different study design.

* Within-group p-value from Wilcoxon signed rank test.

** Between-treatment group p-value was from ANCOVA model with terms for treatment, baseline, pooled investigator.

Note: The sample includes only those patients who remained on duloxetine 60 mg QD during the placebo-controlled study period (that is, patients who switched to duloxetine 120 mg QD were excluded from the analysis), completed the first 7 weeks of studies, and had at least 1 BPI measure after 7 weeks. The analyses use an LOCF approach.

Figure 6. Temporal profile of change in average pain ratings (from BPI collected at study visits) for Studies OA-FG, OA_EP, CLBP-EN and CLBP-EO.



Abbreviations: BPI = Brief Pain Inventory; CLBP = chronic low back pain; DLX = duloxetine; OA = osteoarthritis.

Table 16 shows the comparison of efficacy of DLX 60 mg per day or DLX 120 mg per day during the re-randomisation phase of Study OA-EP. Patients re-randomised to DLX 120 mg per day in Week 7 had statistically significantly greater 24 hour average pain reduction

based on mean change from study baseline to LOCF endpoint at Week 13 when compared with those re-randomised to DLX 60 mg per day.

Table 16. Efficacy Analysis of patients re-randomised to DLX 60 mg or 120 mg once daily. Study OA-EP.

Measure	Analysis	DLX 60 mg QD N=46	DLX 120 mg QD N=43	p-Value
Weekly mean change in 24-hour average pain score[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

Abbreviations: DLX = duloxetine; LOCF = last observation carried forward; MMRM = mixed-models repeated measures; SE = standard error; QD = once daily.

[b] Baseline score (standard deviation): DLX 60 QD = 5.96 (1.41), DLX 120 QD = 6.22 (1.37).

In Study OA-FG, 33 patients who did not respond to DLX 60 mg per day after the initial seven weeks of treatment had their dose escalated to 120 mg per day and achieved statistically significant improvement during the subsequent six weeks of treatment with a mean change in BPI average pain rating of -0.76, p=0.04.

A further 13 of the 33 non-responder subjects became responders after six weeks of DLX 120 mg per day treatment.

Similarly in Study CLBP-EN, 27 patients who did not respond to DLX 60 mg per day after the initial seven weeks of treatment had their dose escalated to 120 mg per day and had a statistically significant improvement during the subsequent six weeks of treatment with a mean change of -0.56 with a p value = 0.011. A further 6/27 non-responder subjects became responders after six weeks of DLX 120 mg per day treatment.

Persistence of efficacy and/or tolerance effects from the extension phase of Study CLBP-EN (41 week extension phase during which all patients received either DLX 60 mg or 120 mg DLX) were assessed: patients who had received placebo during the acute treatment phase received 30 mg of DLX for a week and were then titrated up to 60 mg per day during the two week titration treatment study. Patients who had received either DLX 60 mg or 120 mg during the acute treatment phase remained on their respective dose of DLX during these two weeks providing they had met response criteria of at least 30% pain reduction on BPI average pain relative to baseline. Those who had not met these criteria had their dose increased to 120 mg per day and remained on 120 mg per day for the remainder of the extension treatment phase.

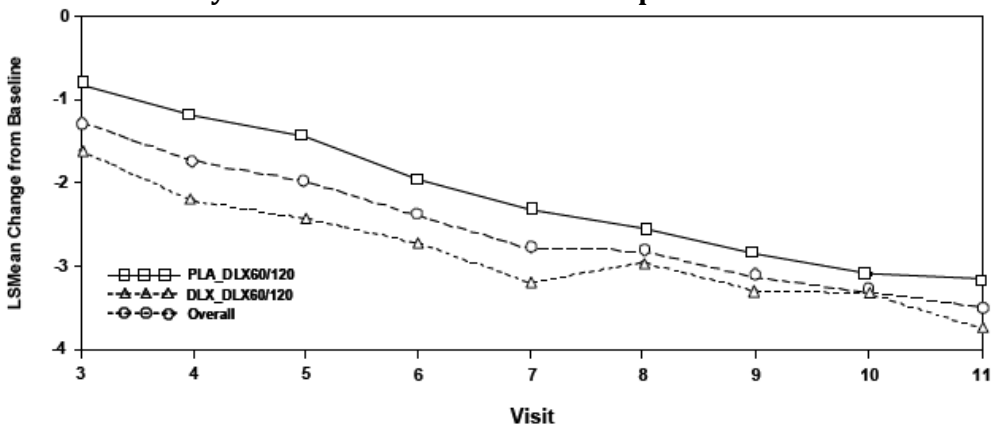
The main efficacy objective of the extension treatment phase was to evaluate whether the treatment effect of DLX 60 or 120 mg was maintained over a 41 week period in patients with CLBP and is measured by change from baseline to endpoint in BPI average pain.

Non-inferiority analysis from the extension period of Study CLBP-EN; during the 41 week extension period the change of BPI 24 hour average pain from baseline, that is, Week 13 to endpoint for the responders, was -0.97 with -0.45 as the upper bound of the 97.5% CI which was less than the pre-specified non-inferiority margin of 1.5 ($p<0.001$). The result demonstrates that the treatment effect of DLX 60 mg or 120 mg per day on pain reduction in acute period DLX responders were maintained throughout the extension period.

The secondary efficacy analyses of the extension phase study shows the mean change from baseline to endpoint during the extension treatment phase for the BPI average pain severity and RMDQ-24 total scores. The results show statistically significant pain reductions and improvement in physical function regardless of their initial treatment assignments during the acute treatment period.

Figure 7 shows the LS mean changes and BPI average pain from study baseline, that is, Visit 2, at each visit from the MMRM analysis during the entire 54 week study duration. There was a continuous reduction in pain during the extension period, including patients who had 13 weeks of DLX treatment during the acute treatment period. Generally, the longer the randomised patients stayed in the study the lower the mean BPI average pain rating at each subsequent visit, with the lowest ratings reported after 54 weeks of DLX treatment.

Figure 7. BPI average pain. Least squares mean changes during the acute and extension treatment phases from the MMRM analysis for randomised patients entered the Study CLBP-EN extension treatment phase.



Abbreviations: DLX = duloxetine; LSMean = least-squares mean; MMRM = mixed-models repeated measures; PLA = placebo.
Model Change = NSAIDUSE Baseline Visit Polled Investigator Baseline*visit.
Covariance Structure = unstructured.

Evaluator comment

These five studies, which together could be considered as overall pivotal trials involving evaluation of DLX for the treatment of moderate chronic somatic pain for patients with osteoarthritis of the knee and chronic lower back pain, have demonstrated significant reduction in 24 average pain ratings as the primary efficacy measure from an overall mean at baseline of approximately 6 points (equivalent to moderate pain) to below 4 points (equivalent to mild pain). For 4 of the 5 studies, the pain reduction was statistically significant when comparing the DLX treated patients to placebo treated patients. These significant benefits remained apparent by several methods of analysis. Evaluation of pooled response rates showed that about 60% of DLX treated patients reported moderate pain improvement, which was defined at least 30% pain reduction, while about 45% of DLX treated patients reported substantial pain improvement defined as at least 50% pain reduction. This is accompanied by an associated improvement in physical function.

It is noted that the pain reduction commenced within the first or second week of evaluation of a 12-13 week trial period with gradual increase in analgesic effect up to Week 7 and maintenance of this effect throughout the remainder of the trials. It was also noted that on those patients who had their doses increased from 60 mg to 120 mg per day, either by re-randomisation after inadequate response to 60 mg or planned re-randomisation, there was a moderate indication of dose response effect.

It is also noteworthy that assessment in relation to ensuring no influence of DLX on mood and anxiety was relevant to these studies; appropriate assessment clarified that the analgesic effect was independent of mood and anxiety phenomena. Assessment of secondary efficacy parameters also demonstrated significant benefit favouring DLX over placebo and there was no evidence that sub-group factors including age, gender, race and use of NSAIDs influenced the effect of DLX.

These studies were generally well conducted and carefully evaluated. They represent solid evidence of efficacy for DLX as an agent with a novel mechanism of action for the management of moderate somatic chronic pain.

Responding to the issues raised in the Statement of Requirements:

- The severity of pain in the patient population.

  The severity of pain in the patient population evaluated involved those who had been classified as having moderate chronic somatic pain. This is in line with the expected level of pain associated with inflammatory conditions such as osteoarthritis of the knee and a mixed non-inflammatory/non-neuropathic condition such as CLBP. Entry criteria for the study were clearly indicated in relation to this level of pain.

- The number needed to treat to achieve 50% or 30% reduction in baseline pain severity.

  The levels of reduction in pain severity to 30% from baseline or 50% from baseline were determined by appropriate standard criteria established for assessment of pain. The number of patients who achieved significant reduction in pain of at least 30% below baseline and 50% below baseline were significantly in favour of DLX over placebo.

- The correlation between baseline measures of depression and efficacy.

  All patients with a diagnosis of major depressive disorder were excluded from studies. Appropriate analysis were undertaken to assess the influence of mood and anxiety on the studies and none were demonstrated.

- Co-morbidities of the patients.

  Full evaluation of co-morbidities of the patients was not undertaken in these studies but it was clear that patients with major depressive disorders were specifically excluded from trial.

  Whether there are active comparative products approved for chronic pain in any of the studies.

  In 4/5 of the studies patients who were on NSAIDs remained on these at a stable dose. In one study, patients who were on chronic use of NSAIDs were excluded from trial[8]. There was no other active comparison undertaken in these studies.

- Duration of assessment of analgesic effect.

  For all five pivotal trials the initial evaluation period was 12-13 weeks. For one study there was an extension period of up to 42 weeks evaluation. It is noteworthy that the analgesic effect obtained with DLX in the initial phase of Study CLBP-EN was maintained throughout the extension period up to 42 weeks.

- Use of concomitant analgesics.

  Concomitant NSAIDs were maintained in 4/5 studies while the last study (CLBP-GC) excluded patients on chronic NSAIDs[8]. Accordingly only one of the studies can be definitely considered to be representative of DLX as monotherapy. Nevertheless the influence of DLX on analgesia was clear.

- Comment on study design and extent of patient dropouts/follow-ups.

  Study designs were precise and generally similar for each trial. Proportion of patient dropouts was small. Follow up was only truly maintained for one of the studies (CLBP-

[8] Sponsor comment: Chronic NSAID users were not excluded. They were included providing they washed out of NSAIDs.

EN) over the 41 week extension period. Throughout this period of time patients remained on DLX obtaining ongoing therapeutic benefit in a significant proportion.

- What would be the placement of this product in the management of patients with chronic pain?

  The data provided indicates a definite analgesic effect for DLX as a novel agent for analgesia with a different mechanism of action. Accordingly it would seem appropriate that this represents an adjunct to the current available therapies utilised in the management of moderately severe chronic somatic pain.

- Has a dose response been established?

  There is some indication of dose response effect with a definite proportion of patients failing to adequately benefit on 60 mg Duloxetine per day achieving appropriate therapeutic benefit at 120 mg per day. Further clarification of this dose response effect may be necessary with other studies.

- Withdrawal effects in patients with chronic pain.

  This matter will be addressed in the safety issues below.

Safety

This safety analysis will evaluate the safety assessments undertaken for the five pivotal studies including two for osteoarthritis of the knee, that is, HMEP (OA-EP) and HMFG (OA-FG) and the three studies for CLBP, namely HMEN (CLBP-EN), HMEO (CLBP-EO) and HMGC (CLBP-GC). In addition safety data for duloxetine treatment of patients with CLBP is available from the extension phase of study HMEN.

The primary placebo controlled analyses set, that is, the acute phase of the OA and CLBP studies where data from all duloxetine groups were pooled to form duloxetine group and data from all placebo groups pooled to form the placebo group. Also evaluated is the primary long-term analyses set containing data from the patients who have been randomised to duloxetine during the acute phase of study HMEN who continued to take duloxetine during the extension phase. All analyses involved are ITT analyses.

In the primary placebo controlled analyses set, 839 patients were exposed to duloxetine for a mean of 74.8 days and 689 patients were exposed to placebo for a mean of 81.2 days. Duloxetine treated patients had a significantly shorter mean duration; seven days shorter of exposure than placebo treated patients with a p value <0.001. Overall, study medication exposure in this analysis set represents 171.9 patient years of exposure to duloxetine and 153.2 patient years of exposure to placebo. Exposure provided by doses received is defined as the doses received at any time during the acute treatment phase. The majority of the DLX treated patients (664, 79.1%) received DLX 60 mg per day. Approximately one third of DLX treated patients (214, 25.5%) received DLX 120 mg per day at some point during the acute phase. For two studies (HMEO and HMEP) patients received 120 mg per day by randomisation or re-randomisation while in studies HMEN and HMFG the dose was increased to 120 mg per day in the event of lack of response to 60 mg per day.

In the primary long-term analyses set, that is, the HMEN extension, 83 patients were exposed to DLX for a mean of 243.37 days and 55.3 patient years of exposure. By the end of the extension phase, 67 (52.8%) of the 127 patients completing the study stayed on DLX 60 mg per day and 50 (39.4%) of these patients stayed on DLX 120 mg per day. However, of the 149 patients who entered the extension phase on DLX 60 mg, 50 (32.9%) of the them had their dose increased to DLX 120 mg per day by the end of the extension treatment phase. The remaining patients either discontinued treatment or were lost to follow up.

It is important to note that within the safety assessments, in the primary chronic pain studies except for study HMGC, randomisation of patients was stratified by whether they entered the study taking Acetaminophen (paracetamol) or a therapeutic analgesic dose of an NSAID. Paracetamol and NSAIDs related only if patients were on a stable dose prior to entering the study. A Stable dose was defined as taking the medication for at least 14 days per month for three months prior to study entry without dose change. In Study HMGC patients taking paracetamol or an NSAID had to stop their medication before entering the study. After study entry episodic use of short acting analgesics was allowed for management of breakthrough CLBP as rescue therapy or for unrelated acute conditions.

In relation to patient disposition in the primary placebo control analyses set, significantly more DLX treated patients discontinued due to any reason (30.2%) and due to adverse event (16.4%) than placebo treated patients (21.2% and 6.1%, respectively). Significantly more placebo treated patients discontinued due to lack of efficacy; 4.2% compared to 2.1% of DLX treated patients. Significantly more placebo treated patients completed this study; 78.8% compared to 69.8% for DLX treated patients. In the primary long term analysis set, 55/83 or 66.3% of patients completed the extension treatment phase. The remaining patients discontinued primarily due to patient decision (12%), adverse events (6%) and protocol violation (6%).

Ibuprofen was the only concomitant medication reported significantly more frequently by the DLX treatment group, being 15.4% compared with the placebo treatment group being 11.8%. No other significant differences in concomitant medication were observed between treatment groups. In the primary long term analyses set 81.9% of patients took at least one concomitant medication including paracetamol, Diclofenac and Ibuprofen were the most frequently reported concomitant medications in >10%.

In the reporting of adverse events, treatment emergent adverse events (TEAEs) were defined as events that first occurred and worsened in severity relative to baseline anytime during a clinical study. For the purposes of this evaluation, the phrase *common adverse events* refers to TEAEs in the primary placebo controlled analyses set with a frequency of at least 5% in the DLX treatment group and reported significantly more frequently with DLX than with placebo.

Table 17 summarises the incidences of common adverse events reported in the primary placebo controlled analyses set. Overall significantly more DLX treated patients (61.5%) than placebo treated patients (48%) experienced at least one TEAE. Specifically, patients treated with DLX experienced common adverse events significantly more frequently than placebo and these including nausea, dry mouth, constipation, insomnia, diarrhoea, dizziness, somnolence and fatigue. In the primary long term analysis set, 68.7% of patients reported one or more TEAEs. The individual TEAEs experienced with a frequency of >5% were headache (10.8%) and nausea (7.2%). It is noteworthy that as indicated Table 17, the TEAE profile of the primary placebo controlled analyses is similar to that of the all other placebo controlled analyses set from studies not evaluated in this submission. This is with the exception of a lower nausea rate for the current study group, being 13.9% compared with 24.2%.

Table 17. TEAEs by decreasing frequency reported in greater than or equal to 5% and significantly more frequently in DLX than placebo in the primary placebo-controlled analyses set. All randomised patients. All safety analyses sets.

	Primary Placebo-Controlled			All Placebo-Controlled (all indications excluding OA CLBP)			All DLX Exposures (all indications)
Event (a)	Placebo N=689 %	Duloxetine N=839 %	p-val(b)	Placebo N=7535 %	Duloxetine N=10466 %	p-val(b)	Duloxetine N=31268 %
ANY EVENT	48.0	61.5	<.001	59.0	73.7	<.001	76.5
Nausea	2.6	13.9	<.001	7.6	24.2	<.001	25.0
Dry mouth	1.7	7.0	<.001	4.2	13.1	<.001	12.9
Constipation	1.6	6.9	<.001	3.5	10.3	<.001	10.6
Insomnia	2.6	6.6	.007	4.1	8.5	<.001	10.1
Diarrhoea	3.2	5.7	.034	5.0	7.6	<.001	8.5
Dizziness	1.7	5.7	<.001	4.2	9.5	<.001	10.4
Somnolence	1.0	5.6	<.001	1.8	6.8	<.001	8.0
Fatigue	0.9	5.0	<.001	4.0	9.2	<.001	9.8

Abbreviations: DLX=duloxetine; N=number of patients; p-val=p-value.
(a) Event list comprises those TEAEs in the primary placebo-controlled analyses set for which the rate for duloxetine was >=5.0% and significantly higher than placebo.
(b) Cochran-Mantel-Haenszel test for general association, controlling for study.
MedDRA Version: 12.0

Review of the common adverse events by maximum severity being classified by patients to rate their adverse events as mild, moderate or severe, listed statistical comparisons being conducted compared with percentages of patients with severe TEAEs between treatment groups. Most patients reported common adverse events that were predominantly mild or moderate in severity indicating that their discomfort or interference with activity was not severe. However, significantly more DLX treated patients (11.1%) reported adverse events as severe compared with placebo treated patients (5.5%). For individual common events, DLX patients reported nausea, somnolence and fatigue as severe significantly more frequently (1.8%, 0.8% and 1.1%, respectively) than placebo patients (0.4%, 0% and 0%, respectively). In the primary long term analysis set most patients who experienced a TEAE reported their TEAEs as mild or moderate in severity with severe TEAEs being reported by 12% of patients. Generally, for DLX treated patients who experienced an event, the majority had an event onset during the first week of treatment. The majority of these events resolved between 15 and 30 days after onset. The time from onset to resolution for fatigue and dry mouth was significantly longer in patients who were assigned to DLX than in patients assigned to a placebo. No significant differences were observed for time from onset to resolution for the other frequently reported adverse events.

The common adverse events by demographic sub-groups were reviewed. With respect to age for patients reporting at least one TEAE, no significant treatment by strata interaction was observed although across all age groups the frequency was significantly greater in patients taking DLX compared to placebo. For nausea the DLX-placebo difference in patients <65 years was significantly greater than the DLX-placebo difference in patients >=65 years. No other significant treatment-by-age interactions were observed. With respect to gender, significant treatment by strata interaction was observed for the proportion of patients reporting at least one TEAE. The DLX-placebo difference in males was significantly greater than the DLX-placebo difference in females. However, for dry mouth the DLX-placebo difference in females was significantly greater than for males. These data suggest that males may have an increased risk of experiencing at least one TEAE and also experienced a decrease in libido more than females. In contrast, females may have an increased risk of dry mouth than males. Furthermore, younger patients may have an increased risk of nausea than older patients.

No deaths were reported during the primary chronic pain studies including the extension phase of study HMEN. One death occurred 11 days after the last drug dose of DLX due to a cardiopulmonary arrest in Study HMEO. The study investigator considered that the event was not related to study drug or protocol procedure. Reviewing serious adverse events (SAEs) from the primary placebo control analysis set, the proportion of patients who experienced at least one SAE was not significantly different with DLX (2.3%) compared to placebo (1.2%) as indicated in Table 18. Transient ischaemic attack, osteoarthritis and asthma were the most frequently reported SAEs with DLX (two DLX patients) and myocardial infarction was the most frequently reported SAEs with placebo (two placebo patients). No significant difference between treatment groups was observed for individual SAEs. In the primary long term analysis set, four patients experienced an SAE and no single SAE term was reported more than once. There was no evidence of the various sub-groups (including age, gender and race) experiencing a higher frequency of SAEs than the overall group.

Significant adverse events, defined as adverse events which resulted in discontinuation from study, are illustrated in Table 19. In the primary placebo control analyses set, significantly more DLX treated patients (16.4%) than placebo patients (6.1%) discontinued due to any adverse event. Nausea and somnolence were reported as reasons for discontinuation significantly more frequently with DLX than placebo, as indicated in Table 20.

Table 18a. SAES by decreasing frequency. MedDRA Preferred Term. All randomised patients. Primary Placebo controlled analysis set. Table continued across two pages.

MedDra Preferred Term	PLACEBO (N=689) n (%)	DULOXETINE (N=839) n (%)	TOTAL (N=1528) n (%)	CMH p-Value (a)	Fisher's Exact p-Value (b)
Bronchitis	0 (0.0)	1 (0.1)	1 (0.1)	.298	1.000
Dehydration	1 (0.1)	0 (0.0)	1 (0.1)	.336	.451
Diarrhoea	0 (0.0)	1 (0.1)	1 (0.1)	.523	1.000
Dizziness	0 (0.0)	1 (0.1)	1 (0.1)	.523	1.000
Drug intolerance	0 (0.0)	1 (0.1)	1 (0.1)	.317	1.000
Dyspnoea	0 (0.0)	1 (0.1)	1 (0.1)	.523	1.000
Gouty arthritis	1 (0.1)	0 (0.0)	1 (0.1)	.336	.451
Hypertensive encephalopathy	0 (0.0)	1 (0.1)	1 (0.1)	.305	1.000
Hypoaesthesia	0 (0.0)	1 (0.1)	1 (0.1)	.523	1.000
Hypoaesthesia oral	0 (0.0)	1 (0.1)	1 (0.1)	.523	1.000
Memory impairment	0 (0.0)	1 (0.1)	1 (0.1)	.317	1.000

N = Number of randomized patients.
n = Number of patients with serious adverse event.
postbaseline: VISSTD 100-199

(a) Frequencies are analyzed using Cochran-Mantel-Haenszel test for general association controlling for study.
(b) Fisher's Exact Test.

Table 18a continued.

MedDra Preferred Term	PLACEBO (N=689) n (%)	DULOXETINE (N=839) n (%)	TOTAL (N=1528) n (%)	CMH p-Value (a)	Fisher's Exact p-Value (b)
Muscular weakness	0 (0.0)	1 (0.1)	1 (0.1)	.523	1.000
Myopathy toxic	0 (0.0)	1 (0.1)	1 (0.1)	.311	1.000
Peritonsillar abscess	1 (0.1)	0 (0.0)	1 (0.1)	.117	.451
Pyelonephritis acute	1 (0.1)	0 (0.0)	1 (0.1)	.317	.451
Rhinitis allergic	0 (0.0)	1 (0.1)	1 (0.1)	.298	1.000
Supraventricular tachycardia	0 (0.0)	1 (0.1)	1 (0.1)	.317	1.000
Wrist fracture	0 (0.0)	1 (0.1)	1 (0.1)	.305	1.000

N = Number of randomized patients.
n = Number of patients with serious adverse event.
postbaseline: VISSTD 100-199

(a) Frequencies are analyzed using Cochran-Mantel-Haenszel test for general association controlling for study.
(b) Fisher's Exact Test.

Table 18b. Discontinuation due to the most common AEs. MedDRA Preferred Term.

All Randomised patients. Using the Different Safety Analyses sets.

	Primary Placebo-Controlled			All Placebo-Controlled (all indication excluding OA CLBP)			All DLX Exposures (all indications)
	Placebo N=689	Duloxetine N=839		Placebo N=7535	Duloxetine N=10466		Duloxetine N=31268
Event (a)	%	%	p-val(b)	%	%	p-val(b)	%
ANY EVENT	6.1	16.4	<.001	4.8	13.7	<.001	18.7
Nausea	0.7	3.0	<.001	0.5	3.0	<.001	3.3
Dry mouth	-	-		0.0	0.1	<.001	0.2
Constipation	0.1	0.5	.410	0.1	0.2	.041	0.5
Insomnia	0.4	0.8	.517	0.2	0.7	<.001	0.9
Diarrhoea	0.3	0.5	.607	0.1	0.3	<.001	0.5
Dizziness	0.4	0.5	.915	0.3	0.9	<.001	0.9
Somnolence	0.0	0.8	.015	0.0	0.6	<.001	0.8
Fatigue	0.0	0.4	.115	0.1	0.8	<.001	1.0

Abbreviations: DLX=duloxetine; N=number of patients; p-val=p-value.
(a) Event list comprises those TEAEs in the primary placebo-controlled analyses set for which the rate for duloxetine was >=5.0% and significantly higher than placebo.
(b) Cochran-Mantel-Haenszel test for general association, controlling for study.

Table 18c. AEs reported as Reason for Discontinuation. All Randomised patients.

Primary Placebo controlled Analyses set. Chronic pain.

MedDRA Preferred Term	PLACEBO (N=689) n (%)	DULOXETINE (N=839) n (%)	Total (N=1528) n (%)	CMH p-Value (a)	Fisher's Exact p-Value (b)
Patients Discontinued for any AE	42 (6.1)	138 (16.4)	180 (11.8)	<.001	<.001
Nausea	5 (0.7)	25 (3.0)	30 (2.0)	<.001	.001
Insomnia	3 (0.4)	7 (0.8)	10 (0.7)	.517	.526
Dizziness	3 (0.4)	4 (0.5)	7 (0.5)	.915	1.000
Somnolence	0 (0.0)	7 (0.8)	7 (0.5)	.015	.019
Diarrhoea	2 (0.3)	4 (0.5)	6 (0.4)	.607	.696
Vomiting	1 (0.1)	5 (0.6)	6 (0.4)	.307	.231
Anxiety	1 (0.1)	4 (0.5)	5 (0.3)	.400	.386
Constipation	1 (0.1)	4 (0.5)	5 (0.3)	.410	.386
Dyspepsia	2 (0.3)	3 (0.4)	5 (0.3)	.922	1.000
Erectile dysfunction	0 (0.0)	4 (0.5)	4 (0.3)	.095	.132

N = Number of randomized patients.
n = Number of patients with adverse event as reason for study discontinuation.
Visits included: VISSTD <=199

(a) Frequencies are analyzed using Cochran-Mantel-Haenszel test for general association controlling for study.
(b) Fisher's Exact Test.

Table 18c. continued

MedDRA Preferred Term	PLACEBO (N=589) n (%)	DULOXETINE (N=839) n (%)	Total (N=1528) n (%)	CMH p-Value (a)	Fisher's Exact p-Value (b)
Headache	2 (0.3)	2 (0.2)	4 (0.3)	.855	1.000
Asthenia	0 (0.0)	3 (0.4)	3 (0.2)	.079	.257
Fatigue	0 (0.0)	3 (0.4)	3 (0.2)	.115	.257
Abdominal pain upper	1 (0.1)	1 (0.1)	2 (0.1)	.755	1.000
Arthralgia	0 (0.0)	2 (0.2)	2 (0.1)	.156	.504
Back pain	1 (0.1)	1 (0.1)	2 (0.1)	.971	1.000
Confusional state	0 (0.0)	2 (0.2)	2 (0.1)	.235	.504
Ejaculation disorder	0 (0.0)	2 (0.2)	2 (0.1)	.242	.504
Hepatic enzyme increased	0 (0.0)	2 (0.2)	2 (0.1)	.366	.504
Hot flush	0 (0.0)	2 (0.2)	2 (0.1)	.242	.504
Lethargy	1 (0.1)	1 (0.1)	2 (0.1)	.755	1.000

N = Number of randomized patients.
n = Number of patients with adverse event as reason for study discontinuation.
Visits included: VISITD <=199

(a) Frequencies are analyzed using Cochran-Mantel-Haenszel test for general association controlling for study.
(b) Fisher's Exact Test.

Table 18c. continued

MedDRA Preferred Term	PLACEBO (N=689) n (%)	DULOXETINE (N=839) n (%)	Total (N=1528) n (%)	CMH p-Value (a)	Fisher's Exact p-Value (b)
Loss of libido	1 (0.1)	1 (0.1)	2 (0.1)	.770	1.000
Migraine	0 (0.0)	2 (0.2)	2 (0.1)	.144	.504
Palpitations	0 (0.0)	2 (0.2)	2 (0.1)	.242	.504
Rash	0 (0.0)	2 (0.2)	2 (0.1)	.231	.504
Sedation	0 (0.0)	2 (0.2)	2 (0.1)	.238	.504
Vertigo	0 (0.0)	2 (0.2)	2 (0.1)	.152	.504
Abdominal distension	0 (0.0)	1 (0.1)	1 (0.1)	.305	1.000
Abdominal pain	0 (0.0)	1 (0.1)	1 (0.1)	.523	1.000
Abnormal dreams	0 (0.0)	1 (0.1)	1 (0.1)	.317	1.000
Acute myocardial infarction	0 (0.0)	1 (0.1)	1 (0.1)	.311	1.000
Aggression	0 (0.0)	1 (0.1)	1 (0.1)	.305	1.000

N = Number of randomized patients.
n = Number of patients with adverse event as reason for study discontinuation.
Visits included: VISSTD <=199

(a) Frequencies are analyzed using Cochran-Mantel-Haenszel test for general association controlling for study.
(b) Fisher's Exact Test.

Table 18c. continued

MedDRA Preferred Term	PLACEBO (N=689) n (%)	DULOXETINE (N=839) n (%)	Total (N=1528) n (%)	CMH p-Value (a)	Fisher's Exact p-Value (b)
Akathisia	0 (0.0)	1 (0.1)	1 (0.1)	.311	1.000
Apathy	0 (0.0)	1 (0.1)	1 (0.1)	.523	1.000
Asthma	0 (0.0)	1 (0.1)	1 (0.1)	.311	1.000
Ataxia	1 (0.1)	0 (0.0)	1 (0.1)	.117	.451
Atrial fibrillation	1 (0.1)	0 (0.0)	1 (0.1)	.317	.451
Blood creatine phosphokinase increased	1 (0.1)	0 (0.0)	1 (0.1)	.336	.451
Bronchitis	0 (0.0)	1 (0.1)	1 (0.1)	.298	1.000
Bursitis	0 (0.0)	1 (0.1)	1 (0.1)	.523	1.000
Condition aggravated	0 (0.0)	1 (0.1)	1 (0.1)	.298	1.000
Decreased appetite	0 (0.0)	1 (0.1)	1 (0.1)	.523	1.000
Dengue fever	1 (0.1)	0 (0.0)	1 (0.1)	.330	.451

N = Number of randomized patients.
n = Number of patients with adverse event as reason for study discontinuation.
Visits included: VISSTD <=199

(a) Frequencies are analyzed using Cochran-Mantel-Haenszel test for general association controlling for study.
(b) Fisher's Exact Test.

Table 18c. continued

MedDRA Preferred Term	PLACEBO (N=689) n (%)	DULOXETINE (N=839) n (%)	Total (N=1528) n (%)	CMH p-Value (a)	Fisher's Exact p-Value (b)
Diabetic neuropathy	1 (0.1)	0 (0.0)	1 (0.1)	.336	.451
Disturbance in attention	0 (0.0)	1 (0.1)	1 (0.1)	.523	1.000
Drug intolerance	0 (0.0)	1 (0.1)	1 (0.1)	.317	1.000
Dysgeusia	0 (0.0)	1 (0.1)	1 (0.1)	.305	1.000
Dysphoria	0 (0.0)	1 (0.1)	1 (0.1)	.523	1.000
Ejaculation failure	0 (0.0)	1 (0.1)	1 (0.1)	.311	1.000
Flatulence	0 (0.0)	1 (0.1)	1 (0.1)	.298	1.000
Frequent bowel movements	1 (0.1)	0 (0.0)	1 (0.1)	.330	.451
Gastroenteritis	0 (0.0)	1 (0.1)	1 (0.1)	.523	1.000
Glaucoma	1 (0.1)	0 (0.0)	1 (0.1)	.117	.451
Haemorrhoids	0 (0.0)	1 (0.1)	1 (0.1)	.317	1.000

N = Number of randomized patients.
n = Number of patients with adverse event as reason for study discontinuation.
Visits included: VISSTD <=199

(a) Frequencies are analyzed using Cochran-Mantel-Haenszel test for general association controlling for study.
(b) Fisher's Exact Test.

Table 18c. continued

MedDRA Preferred Term	PLACEBO (N=689) n (%)	DULOXETINE (N=839) n (%)	Total (N=1528) n (%)	CMH p-Value (a)	Fisher's Exact p-Value (b)
Helicobacter infection	1 (0.1)	0 (0.0)	1 (0.1)	.323	.451
Hepatitis	0 (0.0)	1 (0.1)	1 (0.1)	.523	1.000
Hypercreatininaemia	0 (0.0)	1 (0.1)	1 (0.1)	.298	1.000
Hyperhidrosis	0 (0.0)	1 (0.1)	1 (0.1)	.523	1.000
Hyperkalaemia	1 (0.1)	0 (0.0)	1 (0.1)	.323	.451
Hypersensitivity	0 (0.0)	1 (0.1)	1 (0.1)	.305	1.000
Hypertension	0 (0.0)	1 (0.1)	1 (0.1)	.523	1.000
Hypertensive crisis	1 (0.1)	0 (0.0)	1 (0.1)	.323	.451
Hypertensive encephalopathy	0 (0.0)	1 (0.1)	1 (0.1)	.305	1.000
Intervertebral disc protrusion	1 (0.1)	0 (0.0)	1 (0.1)	.330	.451
Irritability	0 (0.0)	1 (0.1)	1 (0.1)	.523	1.000

N = Number of randomized patients.
n = Number of patients with adverse event as reason for study discontinuation.
Visits included: VISSTD <=199

(a) Frequencies are analyzed using Cochran-Mantel-Haenszel test for general association controlling for study.
(b) Fisher's Exact Test.

Table 18c. continued

MedDRA Preferred Term	PLACEBO (N=689) n (%)	DULOXETINE (N=839) n (%)	Total (N=1528) n (%)	CMH p-Value (a)	Fisher's Exact p-Value (b)
Malaise	0 (0.0)	1 (0.1)	1 (0.1)	.311	1.000
Memory impairment	0 (0.0)	1 (0.1)	1 (0.1)	.317	1.000
Muscular weakness	0 (0.0)	1 (0.1)	1 (0.1)	.523	1.000
Myocardial infarction	0 (0.0)	1 (0.1)	1 (0.1)	.523	1.000
Myopathy toxic	0 (0.0)	1 (0.1)	1 (0.1)	.311	1.000
Non-cardiac chest pain	1 (0.1)	0 (0.0)	1 (0.1)	.330	.451
Peritonsillar abscess	1 (0.1)	0 (0.0)	1 (0.1)	.117	.451
Pregnancy	1 (0.1)	0 (0.0)	1 (0.1)	.117	.451
Pyelonephritis acute	1 (0.1)	0 (0.0)	1 (0.1)	.317	.451
Rash pruritic	1 (0.1)	0 (0.0)	1 (0.1)	.323	.451
Restless legs syndrome	0 (0.0)	1 (0.1)	1 (0.1)	.523	1.000

N = Number of randomized patients.
n = Number of patients with adverse event as reason for study discontinuation.
Visits included: VISSTD <=199

(a) Frequencies are analyzed using Cochran-Mantel-Haenszel test for general association controlling for study.
(b) Fisher's Exact Test.

Table 18c. continued

MedDRA Preferred Term	PLACEBO (N=589) n (%)	DULOXETINE (N=839) n (%)	Total (N=1528) n (%)	CMH p-Value (a)	Fisher's Exact p-Value (b)
Serotonin syndrome	1 (0.1)	0 (0.0)	1 (0.1)	.336	.451
Sleep disorder	0 (0.0)	1 (0.1)	1 (0.1)	.317	1.000
Supraventricular tachycardia	0 (0.0)	1 (0.1)	1 (0.1)	.317	1.000
Tachycardia	1 (0.1)	0 (0.0)	1 (0.1)	.323	.451
Testicular pain	0 (0.0)	1 (0.1)	1 (0.1)	.523	1.000
Trismus	0 (0.0)	1 (0.1)	1 (0.1)	.523	1.000
Urinary retention	0 (0.0)	1 (0.1)	1 (0.1)	.311	1.000
Vomiting projectile	0 (0.0)	1 (0.1)	1 (0.1)	.311	1.000

N = Number of randomized patients.
n = Number of patients with adverse event as reason for study discontinuation.
Visits included: VISSTD <=199

(a) Frequencies are analyzed using Cochran-Mantel-Haenszel test for general association controlling for study.
(b) Fisher's Exact Test.

Table 19. Discontinuation due to the most common adverse events. MedDRA Preferred Term. All randomised patients. Using the different safety analyse sets.

	Primary Placebo-Controlled			All Placebo-Controlled (all indication excluding OA CLBP)			All DLX Exposures (all indications)
	Placebo N=689	Duloxetine N=839		Placebo N=7535	Duloxetine N=10466		Duloxetine N=31268
Event (a)	%	%	p-val(b)	%	%	p-val(b)	%
ANY EVENT	6.1	16.4	<.001	4.8	13.7	<.001	18.7
Nausea	0.7	3.0	<.001	0.5	3.0	<.001	3.3
Dry mouth	-	-		0.0	0.1	<.001	0.2
Constipation	0.1	0.5	.410	0.1	0.2	.041	0.5
Insomnia	0.4	0.8	.517	0.2	0.7	<.001	0.9
Diarrhoea	0.3	0.5	.607	0.1	0.3	<.001	0.5
Dizziness	0.4	0.5	.915	0.3	0.9	<.001	0.9
Somnolence	0.0	0.8	.015	0.0	0.6	<.001	0.8
Fatigue	0.0	0.4	.115	0.1	0.8	<.001	1.0

Abbreviations: DLX=duloxetine; N=number of patients; p-val=p-value.
(a) Event list comprises those TEAEs in the primary placebo-controlled analyses set for which the rate for duloxetine was >=5.0% and significantly higher than placebo.
(b) Cochran-Mantel-Haenszel test for general association, controlling for study.
MedDRA Version: 12.0

Table 20. Adverse events reported as discontinuation. All randomised patients. Primary placebo controlled analyses set-Chronic pain. Abbreviated table.

MedDRA Preferred Term	PLACEBO (N=589) n (%)	DULOXETINE (N=839) n (%)	Total (N=1528) n (%)	CMH p-Value (a)	Fisher's Exact p-Value (b)
Patients Discontinued for any AE	42 (6.1)	138 (16.4)	180 (11.8)	<.001	<.001
Nausea	5 (0.7)	25 (3.0)	30 (2.0)	<.001	.001
Insomnia	3 (0.4)	7 (0.8)	10 (0.7)	.517	.526
Dizziness	3 (0.4)	4 (0.5)	7 (0.5)	.915	1.000
Somnolence	0 (0.0)	7 (0.8)	7 (0.5)	.015	.019
Diarrhoea	2 (0.3)	4 (0.5)	6 (0.4)	.607	.696
Vomiting	1 (0.1)	5 (0.6)	6 (0.4)	.307	.231
Anxiety	1 (0.1)	4 (0.5)	5 (0.3)	.400	.386
Constipation	1 (0.1)	4 (0.5)	5 (0.3)	.410	.386
Dyspepsia	2 (0.3)	3 (0.4)	5 (0.3)	.922	1.000
Erectile dysfunction	0 (0.0)	4 (0.5)	4 (0.3)	.095	.132

N = Number of randomized patients.
n = Number of patients with adverse event as reason for study discontinuation.
Visits included: VISITD <=199

(a) Frequencies are analyzed using Cochran-Mantel-Haenszel test for general association controlling for study.
(b) Fisher's Exact Test.

MedDRA Version: 12.0

All common events leading to discontinuation with the exception of dizziness were reported numerically more frequently with DLX than placebo. In the primary long term analysis set, five patients discontinued study due to an adverse event but no single adverse event which lead to discontinuation was reported more than once. No significant treatment by strata interactions for the various sub-groups was observed.

The fixed dose Study HMEO allowed for dose and adverse event comparisons across the completed acute treatment phase. However, for the other fixed dose Study HMGC was not used for dose comparison due to the single dose arm design. For the three remaining primary studies dose comparisons were only possible for the last six weeks of acute treatment. No TEAEs by dose analyses were performed for the primary long term analysis set.

Tables 21, 22, 23 and 24 presents the common adverse events, that is, the TEAEs for which the rate in the primary placebo controlled analysis set for DLX is at least 5% or greater and significantly higher than placebo by dose across all primary chronic pain studies.

In Study HMEO, except for nausea, all common adverse events occurred numerically more frequently and sometimes statistically more frequently with DLX 120 mg per day than 20 mg and 60 mg per day as indicated Table 21. When all six sexual dysfunction events were combined (but not when assessed individually) they were reported significantly more frequently by patients taking 120 mg per day DLX than patients taking DLX 60 mg per day (12.5% versus 4.3%, respectively) as indicated in Table 24. Table 22 summarises the common adverse events from the pooled analysis of Studies HMEP, HMFG and HMEN that first occurred or worsened during the last six weeks of acute treatment. For patients with at least one TEAE, a numerically high frequency of worsening or newly emerging TEAEs were observed in patients taking DLX 120 mg compared with patients taking 60 mg DLX. In addition, a majority of the individual common adverse events occurred more frequently in patients taking DLX 120 mg. A significantly higher proportion of patients (48.5%) experienced at least one TEAE during the first seven weeks of treatment compared with the second six weeks of treatment (25.2%; p value <0.001. This reinforces the previous observation that adverse events tend to occur early during treatment with DLX regardless of dose.

No clear pattern in the distribution of severe common adverse events across different DLX doses was observed in Study HMEO as indicated in Table 23. However, analyses of all combined TEAEs by dose and severity showed that patients taking DLX 120 mg reported any adverse event as severe significantly (statistically) more frequently than patients taking DLX 60 mg per day. This difference is partially driven by events related to sexual dysfunction, which tended to be significantly more severe in patients taking DLX 120 mg per day compared to 60 mg per day (5.4% versus 0%) as indicated Table 24.

Table 21. Incidence of the most common AEs by dose. All randomised patients. Study F1J-MC-HMEO.

	PBO N=117 %	DLX20QD N=59 %	DLX60QD N=116 %	DLX120QD N=112 %	p-Value 20QD vs. 60QD	p-Value 20QD vs. 120QD	p-Value 60QD vs. 120QD
Event a							
Patients with >1 TEAE	59	64.4	67.2	72.3	.737	.299	.417
Nausea	3.4	18.6	20.7	11.6	.843	.248	.073
Insomnia	2.6	8.5	8.6	18.8	1.000	.115	.033
Constipation	0.85	3.4	8.6	12.5	.342	.057	.392
Dry mouth	0.85	5.1	10.3	10.7	.392	.266	1.000
Dizziness	2.6	5.1	7.8	8.0	.753	.548	1.000
Somnolence	0.0	5.1	4.3	12.5	1.000	.179	.031
Fatigue	0.0	0.0	6.0	8.9	.097	.016	.457

Abbreviations: PBO = placebo; DLX = duloxetine; N = number of randomized patients in indicated treatment arm; QD = once daily; TEAE = treatment-emergent adverse event

[a] Event list comprises those TEAEs in **the primary placebo-controlled analyses set** for which the rate for duloxetine was ≥5.0% and significantly higher than placebo.

Table 22. Incidence of the most common AEs by dose. All randomised patients entering the last 6 weeks of acute treatment. Studies F1J-MC-HMEP, HMFG and HMEN.

	Placebo N = 329 %	DLX60QD N = 179 %	DLX120QD N = 103 %
Event [a]			
Patients with >1 TEAE	17.9	22.3	25.2
Nausea	0.6	1.1	1.9
Insomnia	1.5	1.1	1.9
Constipation	0.3	1.1	1.0
Dry mouth	0.9	1.1	0.0
Dizziness	0.6	1.7	2.9
Somnolence	0.3	1.1	0.0
Fatigue	0.3	0.0	1.9
Diarrhoea	0.6	0.0	1.9

DLX = duloxetine; N = number of patients in indicated treatment arm; QD = once daily; TEAE = treatment-emergent adverse event

[a] Event list comprises those TEAEs in the **primary placebo-controlled analyses set** for which the rate for duloxetine was ≥5% and significantly higher than placebo.

Table 23. Incidence of the most common adverse events by severity and by dose. All randomised patients. Study F1J-MC-HMEO.

		Study HMEO					
Event {a}	Severity	DLX20QD N=59 %	DLX60QD N=116 %	DLX120QD N=112 %	p-Value 20QD vs. 60QD	p-Value 20QD vs. 120QD	p-Value 60QD vs. 120QD
ANY EVENT	Mild	27.1	29.3	17.9	.762	.159	.042
	Moderate	20.3	27.6	33.9	.298	.064	.300
	Severe	16.9	10.3	20.5	.214	.573	.033
Nausea	Mild	10.2	12.9	6.3	.596	.359	.088
	Moderate	5.1	5.2	4.5	.980	.855	.803
	Severe	3.4	2.6	0.9	.764	.238	.331
Dry mouth	Mild	5.1	8.6	8.9	.400	.369	.935
	Moderate	0.0	0.9	1.8	.476	.303	.542
	Severe	0.0	0.9	0.0	.476		.326
Constipation	Mild	1.7	6.0	8.0	.195	.094	.555
	Moderate	0.0	1.7	3.6	.312	.143	.385
	Severe	1.7	0.9	0.9	.625	.644	.980
Insomnia	Mild	5.1	2.6	8.0	.392	.474	.066
	Moderate	3.4	5.2	8.0	.595	.240	.384
Event {a}	Severity	DLX20QD N=59 %	DLX60QD N=116 %	DLX120QD N=112 %	p-Value 20QD vs. 60QD	p-Value 20QD vs. 120QD	p-Value 60QD vs. 120QD
	Severe	0.0	0.9	2.7	.476	.206	.297
Diarrhoea	Mild	1.7	1.7	3.6	.989	.490	.385
	Moderate	1.7	6.9	1.8	.142	.966	.060
	Severe	0.0	0.0	1.8		.303	.149
Dizziness	Mild	1.7	6.0	4.5	.195	.351	.596
	Moderate	1.7	0.9	2.7	.625	.687	.297
	Severe	1.7	0.9	0.9	.625	.644	.980
Somnolence	Mild	3.4	2.6	8.0	.764	.240	.066
	Moderate	0.0	0.9	3.6	.476	.143	.163
	Severe	1.7	0.9	0.9	.625	.644	.980
Fatigue	Mild	0.0	1.7	5.4	.312	.071	.137
	Moderate	0.0	2.6	0.9	.214	.468	.331
	Severe	0.0	1.7	2.7	.312	.206	.624

Abbreviations: DLX=duloxetine; N=number of patients.
{a} Event list comprises those TEAEs in the primary placebo-controlled analyses set for which the rate for duloxetine was >=5.0% and significantly higher than placebo.
MedDRA Version: 12.0

Table 24. TEAEs by maximum severity sexual dysfunction events by dose. All randomised patients. Study F1J-MC-HMEO.

MedDRA Preferred Term	Maximum Severity	PLACEBO (N = 117) n (%)	DLX20QD (N = 59) n (%)	DLX60QD (N = 116) n (%)	DLX120QD (N = 112) n (%)	Total (N = 404) n (%)	p-Value* Overall	p-Value* DLX60QD vs DLX120QD
Any Sexual Dysfunction Event	Mild	0 (0.0)	1 (1.7)	3 (2.6)	5 (4.5)	9 (2.2)		
	Moderate	0 (0.0)	1 (1.7)	2 (1.7)	3 (2.7)	6 (1.5)		
	Severe	0 (0.0)	1 (1.7)	0 (0.0)	6 (5.4)	7 (1.7)	.003	.013
	Total	0 (0.0)	3 (5.1)	5 (4.3)	14 (12.5)	22 (5.4)	<.001	.031
Libido decreased	Mild	0 (0.0)	1 (1.7)	1 (0.9)	2 (1.8)	4 (1.0)		
	Moderate	0 (0.0)	0 (0.0)	1 (0.9)	1 (0.9)	2 (0.5)		
	Severe	0 (0.0)	1 (1.7)	0 (0.0)	1 (0.9)	2 (0.5)	.179	.491
	Total	0 (0.0)	2 (3.4)	2 (1.7)	4 (3.6)	8 (2.0)	.132	.440
Erectile dysfunction	Mild	0 (0.0)	0 (0.0)	2 (1.7)	1 (0.9)	3 (0.7)		
	Moderate	0 (0.0)	1 (1.7)	1 (0.9)	0 (0.0)	2 (0.5)		
	Severe	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.8)	2 (0.5)	.097	.240
	Total	0 (0.0)	1 (1.7)	3 (2.6)	3 (2.7)	7 (1.7)	.298	1.00
Anorgasmia	Mild	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)		
	Moderate	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.8)	2 (0.5)		
	Severe	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	1 (0.2)	.423	.491
	Total	0 (0.0)	0 (0.0)	0 (0.0)	3 (2.7)	3 (0.7)	.078	.117
Ejaculation delayed	Mild	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	1 (0.2)		
	Moderate	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	1 (0.2)		
	Severe	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)		
	Total	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.8)	2 (0.5)	.097	.240
Ejaculation disorder	Mild	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)		
	Moderate	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	1 (0.2)		
	Severe	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	1 (0.2)	.423	.491
	Total	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.8)	2 (0.5)	.097	.240
Loss of libido	Mild	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	1 (0.2)		
	Moderate	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)		
	Severe	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	1 (0.2)	.423	.491
	Total	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.8)	2 (0.5)	.097	.240
Sexual dysfunction	Mild	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)		
	Moderate	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)		
	Severe	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	1 (0.2)	.423	.491
	Total	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	1 (0.2)	.423	.491

Abbreviations: N = Number of randomized patients; n = Number of patients with treatment-emergent adverse event.
Sexual Dysfunction Event included: Ejaculation delayed; Libido decreased; Erectile dysfunction; Anorgasmia; Ejaculation disorder; Loss of libido; Sexual dysfunction.
*Frequencies are analyzed using Fisher's exact test.

The analysis of TEAEs by dose performed for the fixed dose studies in which patients were randomised to either DLX 60 mg per day or 120 mg per day (as indicated in Table 26) revealed no significant difference in the frequency of patients who experienced at least one TEAE between dose groups. For individual events, the following TEAEs occurred with a frequency of >2% and with a significantly greater frequency in patients taking DLX 120 mg per day: somnolence, dry mouth, constipation, decreased appetite, hyperhidrosis, tremor, erectile dysfunction, oropharyngeal pain, orgasm abnormal and vision blurred.

These data would suggest that a dose related adverse effect for DLX 120 mg is observed, in particular in relation to sexual dysfunction.

Review of the frequency of system organ class events demonstrated that the adverse events occurred with significantly more frequency among DLX than placebo patients in the primary placebo controlled analysis set (see and is illustrated in Table 26). When comparing the acute analyses set with the primary long term analyses set the frequency within the system organ classes tended to decrease. The exception was nervous system disorders, which appeared to be driven by an increasing frequency of headache in the long term analysis set (10.8%). These data tend to support the fact that the majority of adverse events were experienced within the initial weeks of treatment and then resolved in the presence of continued DLX treatment.

Table 25. Incidence of the most common adverse events by maximum severity and dose. All randomised patients entering the last 6 weeks of acute treatment. Studies F1J-MC-HMEP, F1J-MC-HMFG and F1J-MC-HMEN.

Preferred Term	Maximum Severity	PBO N=329 n (%)	DLX60QD N=179 n (%)	DLX120QD N=103 n (%)	TOTAL N=611 n (%)
Patients with ≥ 1 TEAE	Mild	26 (7.9)	19 (10.6)	13 (12.6)	58 (9.5)
	Moderate	29 (8.8)	20 (11.2)	10 (9.7)	59 (9.7)
	Severe	4 (1.2)	1 (0.6)	3 (2.9)	8 (1.3)
Nausea	Mild	2 (0.6)	1 (0.6)	1 (1.0)	4 (0.7)
	Moderate	0 (0.0)	1 (0.6)	1 (1.0)	2 (0.3)
	Severe	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Insomnia	Mild	2 (0.6)	1 (0.6)	1 (1.0)	4 (0.7)
	Moderate	2 (0.6)	1 (0.6)	0 (0.0)	3 (0.5)
	Severe	1 (0.3)	0 (0.0)	1 (1.0)	2 (0.3)
Constipation	Mild	0 (0.0)	2 (1.1)	0 (0.0)	2 (0.3)
	Moderate	1 (0.3)	0 (0.0)	1 (1.0)	2 (0.3)
	Severe	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Dry mouth	Mild	1 (0.3)	2 (1.1)	0 (0.0)	3 (0.5)
	Moderate	2 (0.6)	0 (0.0)	0 (0.0)	2 (0.3)
	Severe	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Dizziness	Mild	2 (0.6)	3 (1.7)	3 (2.9)	8 (1.3)
	Moderate	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Severe	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Somnolence	Mild	1 (0.3)	1 (0.6)	0 (0.0)	2 (0.3)
	Moderate	0 (0.0)	1 (0.6)	0 (0.0)	1 (0.2)
	Severe	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Fatigue	Mild	0 (0.0)	0 (0.0)	1 (1.0)	1 (0.2)
	Moderate	1 (0.3)	0 (0.0)	1 (1.0)	2 (0.3)
	Severe	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Diarrhoea	Mild	2 (0.6)	0 (0.0)	1 (1.0)	3 (0.5)
	Moderate	0 (0.0)	0 (0.0)	1 (1.0)	1 (0.2)
	Severe	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Abbreviations: DLX = duloxetine; N = total number of patients in treatment arm; n = number of patients reporting the event; PBO = placebo; QD = once daily.

Table 26. System Organ Classes most commonly reported in the primary placebo controlled analyses set. All randomised patients. Using the different safety analyses sets.

	Primary Placebo-Controlled			Primary Long-Term	All Other Placebo-Controlled (all indications)			All DLX Exposures (all indications)
	PBO N=689	DLX N=839		DLX60_ DLX60/120[a] N = 83	PBO N=7535	DLX N= 10466		DLX N=31268
SOC [b]	%	%	p-val[c]	%	%	%	p-val[c]	%
Gastrointestinal disorders	13.5	31.1	<.001	24.1	23.2	45.4	<.001	46.9
Nervous system disorders	13.2	21.2	<.001	21.7	19.2	31.9	<.001	34.8
Psychiatric disorders	5.7	13.6	<.001	8.4	11.1	19.7	<.001	23.4
General disorders and administration site conditions	3.8	10.5	<.001	3.6	10.9	18.3	<.001	19.7

Abbreviations: DLX = duloxetine; DLX60 = 60 mg duloxetine; DLX60/120 = duloxetine doses of 60 mg or 120 mg; N = number of randomized patients; PBO = placebo; p-val = p-value; SOC = system organ class.

[a] Treatment during the acute phase of Study F1J-MC-HMEN followed by treatment during the extension phase of Study HMEN with the baseline of the extension phase defined as the last value recorded from the acute-treatment phase.

[b] System organ class list comprises those in the primary placebo-controlled analyses set for which the rate for duloxetine was ≥10% and significantly higher than placebo.

[c] Cochran-Mantel-Haenszel test for general association, controlling for study.

Reviewing safety topics of special interest

In relation to *suicide and suicidal ideation*, there were no cases of suicidal ideation or suicidal behaviour in the primary chronic pain patient population. There was no evidence of a statistically significant increased risk of suicide related events including behaviour and/or ideation in patients treated with DLX compared with placebo across all the indications and combined across all ages.

With regards to assessment for *hepatic dysfunction,* the use of DLX in the primary chronic pain studies was associated with a mean hepatic enzyme elevation although bilirubin was not elevated. For patients who experienced an alanine aminotransferase (ALT) elevation of at least three times the upper limit of normal, greater than five times upper limit of normal, or greater than 10 times upper limit of normal and for whom follow up information was available, the ALT levels had returned to normal levels or decreased by the patient's last visit, regardless of whether they continued or discontinued study drug.

For DLX treated patients no significant differences were observed in the incidence of ALT elevations greater than three, five or 10 times the upper limit of normal between patients who took paracetamol before the ALT increase compared to those who did not.[9] No consistent evidence of relationship between dose and ALT elevations were observed. There were no statistically significant differences seen between the placebo and DLX treated groups in the percentage of patients who discontinued due to any specific hepatic related TEAE. The overall percentage of patients who discontinued due to a hepatic serious adverse event was low and no statistically significant differences were observed between the DLX and placebo treatment groups.

With respect to *cardiovascular related serious adverse events* the proportion of patients[10] who experienced at least one such event was 0.2% for DLX and 0.2% for placebo with a p value of 0.492. Myocardial infarction and palpitations were the most frequently reported SAEs with DLX (n=4) and myocardial infarction was also the most frequently reported SAE with placebo (n=3).

The analysis of cardiovascular related TEAEs by NSAID determine whether the concomitant use of DLX and NSAIDs increased the risk of adverse cardiovascular outcomes. The number of patients[10] experiencing at least one cardiovascular related TEAE was 3.9% for DLX and 3.22% for placebo with a p value 0.026 in non-NSAID users and 4.69% for DLX and 4.23% for placebo with a p value 0.493 for NSAID users. As indicated, there was no evidence of a synergistic effect between DLX and NSAIDs in regards to cardiovascular related TEAEs. However, consistent with the known cardiovascular effects of NSAIDs, a significantly higher rate of events were observed in patients who took NSAIDs compared with those who did not (p value of 0.009). It is also important to note that within the patient population identified as non-NSAID users, DLX treated patients reported a significantly higher frequency of cardiovascular related TEAEs compared with placebo, with a p value of 0.026.

A review of bleeding related adverse events[10] revealed that the percentage of patients in the placebo controlled studies reporting at least one bleeding related SAE was 0.1% for DLX treated patients and <0.1% for placebo patients (p value 0.550). Of the 11 bleeding related SAEs, one case of upper GI bleeding was reported by one placebo treated patient. Analysis of all bleeding related TEAEs for all randomised patients[10] revealed that the percentage of patients in the placebo controlled studies reporting at least one bleeding related TEAE was statistically significantly greater for DLX treated patients compared with

[9] Sponsor comment: Compared to those who did not use paracetamol at all, or to those who took paracetamol after ALT increase.

[10] Sponsor comment: Across all indications, including OA/CLBP.

placebo subjects, being 1.76 versus 1.22% with a p value of 0.006. Looking specifically at GI related bleeding TEAEs, the percentage of patients reporting at least one GI related TEAE was 0.23% for DLX patients and 0.15% for placebo patients (p value of 0.198). Review of this in relation to NSAID use revealed that the percentage reports of an GI bleeding event were numerically higher among both DLX and placebo treated patients who used NSAIDs or aspirin; DLX 0.33% and placebo 0.23% compared to DLX 0.19% and placebo 0.11% for patients who did not take NSAIDs or aspirin. Overall these data do not suggest a synergistic effect of DLX and NSAID or aspirin use in regards to GI bleeding.

A review of *laboratory assessments* revealed that in relation to chemical changes the data obtained in primary chronic pain studies were generally consistent with data from all other placebo controlled studies with few differences emerging. Although there were greater changes in the DLX treated patients than the primary placebo controlled analyses compared to all other placebo controlled analyses for mean albumin, mean creatinine and mean total protein decreased at endpoint. Overall the majority of these changes do not appear to be clinically meaningful. A discussion regarding changes in hepatic enzymes has been outlined above. Results from the primary long term analyses set demonstrated that mean change from baseline to endpoint for albumin, alkaline phosphatase, bicarbonate, calcium, cholesterol and creatinine were statistically significantly different from zero but data for both placebo and DLX groups were combined. However, overall these findings were not considered likely to be clinically relevant.

Changes in *vital signs and weight* were analysed for change from baseline to endpoint and at any time and at endpoint. In the primary placebo controlled analyses set, patients experienced a significantly greater mean increase from baseline to endpoint in pulse rate and diastolic blood pressure with DLX than placebo as indicated in Table 27. Patients taking DLX experienced a significantly greater mean decrease (from baseline to endpoint) in weight (-0.53 kg) than patients on placebo, who experienced an increase of 0.10 kg. No significant difference between DLX and placebo was observed with regards to mean change (from baseline to endpoint) in systolic blood pressure.

In the primary long term analyses set patients experienced a significantly greater mean change (from baseline to endpoint) in weight compared with patients initially treated with placebo who subsequently received DLX treatment during the HMEN extension phase (1.42 kg and -0.38 kg, respectively, with a p value of < 0.001). This is consistent with previously observed changes in weight with long term DLX exposure. No other significant differences for weight, pulse or blood pressure were observed within treatment groups or overall.

In the primary placebo controlled analyses set, patients experienced potentially clinically significant weight loss of at least 7% of baseline weight significantly more frequently with DLX (being 3.2% than placebo 0.4% at any time) and at endpoint (DLX 2.7% and placebo 0.4%). There were no other significant findings. In the primary long term analyses set the most frequently reported potentially clinically significant value was weight gain of at least 7%, at any time of 6.2% and at endpoint on 3.7%.

Sustained elevation of blood pressure (BP) was defined as a diastolic blood pressure of at least 90 mmHg, increased from baseline by at least 10 mmHg for three consecutive visits, or systolic blood pressure >=140 mmHg, increased from baseline of at least 10 mmHg for three consecutive visits. No significant treatment group differences in the incidences of sustained elevation of BP were observed in either placebo controlled analyses set. In the primary placebo controlled analyses set a lower frequency of sustained elevation in systolic BP was observed in DLX treated patients (0.6% versus 1.5% for placebo). In the primary long term analyses set three patients experienced sustained elevation of systolic BP.

Table 27. Vital signs and weight. Mean change from baseline to endpoint. All randomised patients. Primary placebo controlled analyses set.

			Baseline		Change to Endpoint		
Vital	Therapy	N	Mean	SD	Mean	SD	p-Value*
Pulse	Placebo	664	71.34	9.11	0.08	8.84	.004
	Duloxetine	802	71.99	9.00	1.61	9.32	
Systolic BP	Placebo	665	128.68	14.44	-0.76	12.59	.436
	Duloxetine	802	127.99	14.28	-0.26	12.77	
Diastolic BP	Placebo	665	79.55	9.18	-0.64	8.43	.037
	Duloxetine	802	79.17	9.02	0.29	8.70	
Weight(Kg)	Placebo	674	80.55	14.98	0.10	2.07	<.001
	Duloxetine	809	80.87	15.86	-0.53	2.30	

Note: N = Number of patients with a baseline and at least one non-missing post-baseline measurement.
baseline: VISSTD 1-99, postbaseline: VISSTD 100-199.

Pulse: sitting pulse.
Diastolic BP: sitting diastolic blood pressure.
Systolic BP: sitting systolic blood pressure.

*Type III Sums of Squares from an analysis of variance (ANOVA) Model=Study and Treatment.

There was no significant differences between the treatment groups in orthostatic hypotension (defined as a standing diastolic BP of at least 10 mmHg less than the supine diastolic BP or standing systolic BP of at least 20 mmHg less than supine systolic BP); the incidence of orthostatic hypotension across the primary placebo controlled analyses set was 6.9% for DLX treated patients and 5.3% for placebo patients with a p value of 0.169.

In relation to data regarding withdrawal and rebound adverse events, studies in the primary placebo controlled analyses set employed a two week double-blind taper phase for DLX. Overall, significantly more patients experienced at least one taper emergent adverse event with DLX being 12.1% and placebo being 4.3%. Dizziness was the only taper emergent adverse event that was reported significantly more frequently in the DLX treatment group compared to the placebo group.

Evaluator comment

The data from these five chronic pain studies have essentially revealed a safety profile compatible with that observed in earlier controlled clinical trials for other indications of DLX use.

The most common TEAEs reported included nausea, dry mouth, constipation, insomnia, diarrhoea, dizziness, somnolence and fatigue. There was certainly a significantly higher incidence of TEAEs among patients receiving DLX compared to placebo with an associated increase in patient discontinuing therapy. Nevertheless, the overall incidence of TEAEs and SAEs were in line with that previously observed in other studies. There were no deaths reported in relation to DLX in the chronic pain trials. It is also noteworthy that the incidence of adverse events in the long term analysis set was lower than those observed during the acute treatment phase. There were no cases of suicidal ideation or suicidal behaviour in this study and no new safety information defined in relation to hepatic enzyme disturbances. The concomitant use of DLX and paracetamol was not associated with significantly greater incidence of hepatic enzyme disturbances. There was no evidence of synergistic effect of DLX and NSAIDs on bleeding or cardiovascular related outcomes. Overall, the safety profile observed in the primary chronic pain studies were consistent with that observed in all other placebo controlled analyses sets previously assessed.

Clinical summary and conclusions

Clinical aspects

This report evaluated duloxetine for the proposed indication of chronic somatic pain. Nonclinical studies have shown that duloxetine effectively reduced pain across a range of persistent neuropathic and inflammatory chronic pain models. The serotonin norepinephrine re-uptake inhibitor duloxetine is believed to have a central analgesic effect via the potentiation of activity in the descending pain inhibitory pathways. Thus, the mechanism of action of this agent differs from currently used analgesic drugs including paracetamol, NSAIDs and opioids. To assess this hypothesis, this application investigates duloxetine in prevalent disease states representing the main types of chronic pain including inflammatory pain as evidenced by osteoarthritis of the knee and non-inflammatory/non-neuropathic pain as evidenced by idiopathic CLBP.

A total of five placebo controlled studies support the application in osteoarthritis of the knee, Studies HMEP or OA-EP and Study HMFG or OA-FG and three in chronic lower back pain (Studies HMEN or CLBP-EN; HMEO or CLBP-EO and HMGC or CLBP-GC). The first of these studies CLBP-EN contained a 41 week dose blinded uncontrolled duloxetine treatment extension period to assess maintenance of effect and tolerance. All studies include investigational sites from Europe except for Study CLBP-EO. All studies were conducted and adherent to the Principles of Good Clinical Practice.

The five studies comprised a total of 839 patients treated with duloxetine at doses of 20, 60 and 120 mg once daily and 689 patients treated with placebo. All five studies had a placebo controlled phase of at least 12 weeks. In addition, Study CLBP-EN had an uncontrolled extension phase of 41 weeks.

All studies had a 12-13 week double-blind randomised placebo controlled treatment phase. The primary outcome measure for all studies was pain severity assessed using an average pain rating on an 11 point numerical rating scale. The data were collected daily using patients' diaries and expressed as weekly mean in two studies (Study OA-EP and CLBP-EO) and at study visits using the brief pain inventory (BPI) in the remaining studies (Studies OA-FG, CLBP-EN and CLBP-GC). While the primary efficacy endpoint was a change from baseline to Week 13 in pain severity it is also recognised that the difference in response rates between treatment groups with response to find at least 30% reduction in pain severity from baseline as a key outcome of interest. Thus, response rates using both at least 30% and at least 50% reduction from baseline and endpoint criteria were included as a secondary endpoint in all studies, with 80% power to detect the treatment difference between duloxetine and placebo.

Two key secondary outcome measures were tested sequentially, namely PGI-I and a disease specific function scale (WOMAC for OA patients and RMDQ-24 for CLBP).

Apart from Study CLBP-GC, patients were allowed to remain on their regular dose of NSAIDs or paracetamol provided they were using them at the time of enrolment. Patients were instructed to remain on their regular dose regimen throughout the course of the study. Randomisation was stratified by NSAID use. Prior to randomisation patients were required to washout all other analgesics, anticonvulsants and antidepressants.

The studies assessed daily doses of 20, 60 and 120 mg DLX. A fixed dose multiple dose study (Study CLPB-EO) which included a DLX 20 mg treatment group was included in the program. In all studies except CLBP-GC, patients were randomly assigned to DLX 60 mg or 120 mg, initiated DLX treatment at 30 mg for one week before titration of 60 mg to minimise nausea. Two of the five studies had a fixed dose design (Studies CLBP-EO and CLBP-GC). The remaining three studies had a flexible dose design (60 mg per day to 120 mg per day) and the primary analyses were based on the combined 60/120 mg DLX arm versus placebo. For these three studies a seven week time point for dose escalation was chosen due to previously observed (in previous fixed dose chronic pain studies) absence of any clinically significant change in therapeutic response beyond this time point.

Disease specific diagnostic and inclusion criteria were based upon well known clinically relevant measures. A baseline pain severity of at least 4/10 on a 24 hour average pain rating consistent with moderate pain severity was the criterion for entry into all of the studies. Subjects were required to have had chronic pain for at least three months for OA or six months for CLBP prior to entry into the study.

In order to specifically assess the effects of DLX on pain, patients with major depressive disorder (and assessed using appropriate evaluation scales) were excluded from all OA and CLBP studies. Except for Study CLBP-GC, depression and anxiety symptoms were monitored using BDI-II and HADS sub-group analyses to assess whether pain reduction was affected by the level of baseline depressive and anxiety symptoms. Study CLBP-GC utilised a profile of mood states/grief states scale.

Based on baseline demographics and disease characteristics, patients enrolled in the different chronic pain studies were representative of patients who seek and obtain treatment in clinical practice. Patients in all the studies were experiencing chronic pain with a median baseline pain severity across studies of at least 6, indicating moderately severe pain. Across the OA and CLBP studies patient characteristics were similar between the two treatment groups.

In both the OA studies and two out of the 3 CLBP studies (Studies CLBP-EN and CLBP-GC) patients experienced a statistically significant greater reduction in pain with DLX than with placebo. For all studies the 24 hour average pain reduction with DLX ranged from 1.9 to 2.9, which is in line with other therapeutic treatment options. In addition the mean average pain rating at endpoint in all five studies for DLX treated patients is below 4, which is considered the cut-off point for mild pain.

Statistically significant pain reduction was observed as early as the first or second week on DLX. Ongoing DLX treatment was associated with a gradual increase in analgesic effect measured by BPI up until about Week 7, with no of significant change thereafter.

In relation to response rates using the 30% response criterion, statistically significant more DLX treated patients than placebo treated patients met the response criteria in three of the studies (Studies OA-EP, OA-FG and CLBP-EO). Similarly, using the most conservative criteria (the 50% response rate), significantly (statistically) more DLX treated patients than placebo treated patients met the response criteria in the other two studies (CLBP-EN and CLBP-GC).

Sub-group analysis of pain reduction by NSAID use revealed no statistically significant interaction between treatment groups, indicating that DLX provides an analgesic effect either as a monotherapy or in combination with NSAID.

In an analysis of analgesic effect independent of the effect on depression and anxiety scores with regards to depression symptoms, there was no statistically significant treatment by sub-group interaction observed. Thus, indicating that the effect of DLX in the reduction of BPI average pain is similar in patients regardless of their HADS-D score at baseline. Similarly, with regards to anxiety no statistically significant treatment by sub-group interaction was observed in the pooled CLBP studies. However, one was observed for the pooled OA studies, where the magnitude of improvement was greater in patients without an anxiety disorder compared with those with an anxiety disorder.

All secondary efficacy endpoints also demonstrated a significant improvement for DLX treated patients vs those receiving placebo.

The totality of data from the OA and CLBP studies demonstrated that a daily dose of DLX 60 mg is the lowest consistently effective dose. Data from the fixed dose study indicated a sub-optimal response of 20 mg and data from the flexible dose studies suggested an increase to 120 mg on the basis of clinical response and tolerability maybe suitable for some patients who do not achieve adequate response with DLX 60 mg. In relation to maintenance of effect as determined by evaluation of the 41 week extension phase of Study CLBP-EN, a total of 58 or 53% of patients who were initial DLX 60-120 mg responders experienced a group mean pain reduction of -0.97 with an upper bound of the one-sided 97.5% CI -0.45 at the end of the extension study, demonstrating that the treatment effect of DLX was maintained during the extension phase. Similarly a statistically significant pain reduction was observed in the sub-group of DLX 60 mg responders who remained on DLX 60 mg during the extension phase. In both analyses the decreases in pain severity were statistically significant ($p<0.001$) relative to the beginning of the extension phase.

The safety data base[11] for evaluation involved 839 patients who were treated with DLX and the placebo controlled clinical studies for OA and CLBP using doses of 20, 60 and 120 mg DLX per day. Safety data from these studies were pooled to form the primary placebo controlled analyses set for this submission. Additionally, 181 patients who had completed the acute phase of Study HMEN were exposed to DLX for long term treatment up to 41 weeks during which patients were blinded to treatment dose.

Results of safety analysis revealed that no new safety signals were detected in the chronic pain studies, including short and long term treatment. There were no deaths reported among the 839 DLX treated and 689 placebo treated patients during the acute phase of evaluation or in the 181 patients who completed the maintenance phase of Study HMEN. A total of 19 or 2.3% of DLX treated and 8 or 1.2% of placebo treated patients experienced a serious adverse event. The proportion of patients experiencing at least SAE was not significantly different between treatment groups and no significant difference of the incidence of individual SAEs was observed. No single event was predominant. Also, significantly more DLX treated patients discontinued due to adverse events (16.4% compared to 6.1% of placebo). Overall the AEs given as reasons for discontinuation in the primary chronic pain studies are consistent with those reported in all other placebo controlled analyses sets.

Significantly more DLX treated patients (62%) than placebo treated patients (48%) experienced at least one treatment emergent adverse event. As would be expected from a compound with this known mechanism of action, the common TEAEs reported involved the gastrointestinal tract and the CNS.

[11] Sponsor comment: The Primary Placebo-controlled analyses set.

These included nausea, dry mouth, constipation, insomnia, diarrhoea, dizziness, somnolence and fatigue. The majority of these were transient which is consistent with previous experience with DLX.

In relation to dose effect, the most common adverse events were reported more frequently with 120 mg per day than 60 mg per day. In particular, this was related to an increased incidence of sexual dysfunction which was noted to be more frequent and more severe with DLX 120 mg per day than 60 mg per day.

The reported frequency of adverse events and discontinuations due to adverse events in the primary long term analysis set was lower than that observed with the acute treatment. There were no cases of suicidal ideation or suicidal behaviour reported in the primary placebo controlled analyses set.

No new safety information related to hepatic laboratory analyses or hepatic related adverse events was identified in the primary chronic pain study. The incidence of TEAEs were added to the cardiovascular system was 0.5% for DLX and 0.3% for placebo, which was low and not significantly different between treatment groups. There was no significant treatment differences observed in the incidence of sustained elevation of blood pressure.

Concomitant use of DLX and paracetamol was not associated with a significantly greater incidence of clinically significant hepatic enzyme elevation compared with DLX alone. Furthermore, there was no evidence of a synergistic effect of DLX and NSAIDs on bleeding or cardiovascular related outcomes compared with DLX alone in clinical trials.

Benefit risk assessment

The five pivotal chronic pain studies have clearly demonstrated an analgesic effect for DLX in these conditions, which was significant and maintained. The studies were carefully designed and stringently monitored. Influence of the effect of ongoing NSAIDs and possible influence of psychological states including depression and anxiety have been accounted for. The data supports an independent analgesic effect for DLX.

The lack of a randomised trial directly comparing DLX with other analgesics including NSAIDs for this treatment indication was a little disappointing as it reduces the opportunity to have a precise understanding of the position in which DLX may be considered for the management of chronic somatic pain. Nevertheless, the evidence is such that it supports an independent analgesic effect for DLX and based on its differing mechanism of action from other established analgesics for the treatment of somatic pain it would seem reasonable to accept the introduction of DLX as an added component of the armamentaria available for the treatment of moderately severe chronic somatic pain.

While adverse effects were clearly documented in these studies and obviously represent a fact to be taken into account when considering the use of DLX in patients with chronic somatic pain, the overall safety profile is in line with that previously observed in other clinical trials and taking into account the recognised approved indication for the treatment of diabetic peripheral neuropathic pain, it would seem appropriate to also approve duloxetine for the proposed indication of chronic somatic pain.

In view of the fact that all five pivotal studies evaluated the role of DLX as analgesia in the management of moderately severe chronic somatic pain as defined by the appropriate criteria, it would seem that the proposed indication should read for the treatment of moderately severe chronic somatic pain rather than the all encompassing proposal of just chronic somatic pain.

Apart from this proposed amendment, the evaluator considered that the data was sufficient to support the proposal for duloxetine to be indicated for the treatment of moderately severe chronic somatic pain.

Recommended conditions for registration

The only changes proposed for the Product Information in relation to the submitted data and the proposed new indication are in relation to the clinical trial evidence in support of the proposed

indication of *chronic somatic pain*. Summary data is in line with that presented in the submission and representative of the results obtained across the five studies.

The sponsor has proposed that Cymbalta be indicated for

The treatment of chronic somatic pain.

The evaluator proposed that this should be altered to:

Cymbalta is indicated for the treatment of moderately severe chronic somatic pain.

V. Pharmacovigilance findings

Risk management plan

The sponsor submitted a Risk Management Plan which was reviewed by the TGA's Office of Product Review (OPR).

Safety specification

The sponsor provided a summary of Ongoing Safety Concerns which are shown at Table 28.

Table 28. Summary of Ongoing Safety Concerns

Important identified risks	• Hepatic risks • Suicidality • Hyperglycemia • Stevens-Johnson Syndrome • GIT Bleeding
Important potential risks	• Cardiovascular events (including myocardial infarction and ventricular arrhythmia) • UGIT bleeding events with concomitant use of NSAIDs • Renal Failure
Important missing information	• Characterization of the safety and tolerability of duloxetine in paediatric patients • Prospective data about potential risks of exposure to duloxetine during pregnancy • Characterisation of drug utilisation in unapproved indications and populations.

OPR reviewer comment

The above summary of the Ongoing Safety Concerns was considered acceptable.

Pharmacovigilance (PhV) plan

In addition to routine PhV, targeted questionnaires will continue to be used for enhanced follow-up of AE reports with regards to the following:

- Hepatic risks
- Suicidality
- Hyperglycemia
- Stevens-Johnson Syndrome
- GIT bleeding
- Cardiovascular events (including myocardial infarction and ventricular arrhythmia)

There are additional proposed or ongoing PhV activities identified by the sponsor with the aim of further characterising and monitoring specified safety concerns as outlined below:

1. Identified risk - Hepatic risks

- As a requirement of the US FDA, the sponsor is undertaking quarterly analysis of the FDA Adverse Event Reporting System (AERS) of hepatic adverse events for all cases and fatal case series, both in the overall database and against antidepressant-only background. AERS fatal case series followed by individual case expert review to evaluate causality. This reporting will be incorporated within the Periodic Safety Update Reports (PSURs).
- A follow on study, B037 '*Hepatic outcomes among adults taking duloxetine in a US Health Insurance Database',* with methodological enhancements and a larger number of participants based on Study F1J-MC-B021 (B021: '*Hepatic and cardiovascular events in adults taking duloxetine compared with depressed treated, depressed not pharmacologically treated and non-depressed patients in a large U.S. Health Insurance Database*') was proposed in the RMP. The duloxetine co-exposur*e study is a retrospective cohort study based on a large external US-based insuranc*e claims database and is conducted in patients who have a diagnosis of MDD, GAD, DPNP or fibromyalgia a*nd also chronic pain. The sponsor states that a biannual analysis of the health-claims database will be conducted to assess the potential risk of negative hepatic outcomes when duloxetine is administered* concomitantly with analgesics. After an additional 2 years a decision will be made by a safety surveillance team on whether continuation is warranted. The results will be summarised in the annual PSUR. It was noted that other outcomes to be measured and analysed are medical claims codes for GI bleeding and cardiovascular events (acute myocardial infarction and stroke). A study outcome is assigned to a certain type of treatment exposure if the claims of the outcome were recorded during the period of available drug supply plus 15 days. Patient and prescription drug exposure-specific periods are determined at the individual patient level, summed up, and used as the drug exposure-specific denominator in the estimation of incidence of each outcome of interest. An 'as treated' approach is employed to analyse the data, whereby only events occurring during time under a treatment-specific exposure category are considered. The outcome measure is the unadjusted incidence of insurance claims for a specific outcome.

2. Identified risk – Suicidality

- A European general practice research database analysis of suicidality among duloxetine exposed and unexposed women diagnosed with urinary stress incontinence (approved indication for duloxetine in the UK). The study was ongoing at the time of the RMP submission and a final report was estimated for December 2010.
- Active monitoring of suicidality in clinical trials for psychiatric and non-psychiatric indications. Monitoring utilises the Beck Depression Inventory - Suicidality Item - or the Columbia Suicide Severity Rating Scale.

3. Potential risk – Cardiovascular events

- As a requirement of the US FDA, the sponsor is undertaking quarterly analysis of the FDA AERS of cardiovascular (CV) AEs, singly and by clinical clusters, for all cases and fatal case series, both in the

overall database and against antidepressant-only background. This reporting will be incorporated within the PSUR.

- Biannual analysis of the US based insurance claims database (as described above under hepatic risk) to assess the risk of negative CV outcomes when duloxetine is administered concomitantly with analgesics (including NSAIDs and cyclooxygenase 2 (COX-2) inhibitors).

4. Potential risk –UGIT bleeding

- As a requirement of the US FDA, the sponsor is undertaking quarterly analysis of the UGIT bleeding events from the FDA AERS. This reporting will be incorporated within the PSUR.
- A postmarketing population based case control study comparing a group of patients with GI bleeding leading to hospitalisation with a control group of patients hospitalised for reasons other than GI bleeding is proposed to investigate whether duloxetine alone or in combination with NSAIDs is associated with an increased risk of UGIT bleeding leading to hospitalisation. A letter from the sponsor dated 9 February 2011 was received following a request for the study protocol at the submission phase. In this communication the sponsor stated that since the submission of the RMP it was concluded that it would not be feasible to conduct a scientifically rigorous observational study that could produce reliable results in a reasonable timeframe. This conclusion was based on a rare study outcome and the long period required to complete a large observational study. The sponsor has confirmed that an agreement has since been made with the European Union (EU) authorities to conduct a modified version of this study, based on the understanding that such a study would be unable to control for the potentially confounding effects of non-prescription medicine use. It was considered that the misclassification of use of non-prescription medicines may be non-differential between study groups. Protocol development was to begin in the first quarter of 2012.
- Biannual analysis of the US based insurance claims database (as described above under hepatic risk) to assess the potential risk of increased UGIT bleeding when duloxetine is administered concomitantly with analgesics (including NSAIDs and COX-2 inhibitors)

5. Important missing information – Safety and tolerability in paediatric patients

- Two placebo controlled trials in children and adolescents with MDD are being conducted.
- Duloxetine is not approved for any paediatric indication in Australia.

6. Important missing information – Exposure during pregnancy

- A Cymbalta pregnancy registry has been implemented in the US in 2009. The registry will collect prospective data on pregnancy exposure, pregnancy outcomes and birth outcomes up to 1 year. As of April 2010, there were 5 patients entered in the registry. Annual study reports will be submitted by the sponsor until 2016.

7. Important missing information – Use in unapproved indications

- The sponsor plans to conduct a drug-utilisation study (Study F1J-MC-B038) to estimate off-label use with a focus on age strata. The protocol for this study was requested at the submission phase and in their letter of 9 February 2011, the sponsor stated that due to unforseen circumstances regarding the availability of the principal investigator, there have been delays in finalisation of the study protocol (SUDULOX: Study on the Utilization of Duloxetine). The sponsor proposes to submit the protocol with the next PSUR.

Reporting of interim analyses and final results from these additional PhV activities will be incorporated into the PSURs.

OPR reviewer's comments in regard to the pharmacovigilance plan (PP) and the appropriateness of milestones

Regarding the duloxetine co-exposure study, there are limitations to surveillance by the use of the health insurance claims database described. These include the variability in the positive predictive value of insurance codes relative to the disease, the lack of medical record confirmation, unmeasured confounders and lack of controlling for potential confounders. An inherent limitation of these types of studies is the lack of data for non-prescription medications, such as over the counter NSAIDs. Nevertheless, this design allows for the descriptive analysis of health related data (diagnostic code, medication, medical history, demographics) from large numbers of patients over a period of time and at this stage is considered acceptable for the surveillance of hepatic, cardiovascular and GIT bleeding outcomes when duloxetine is co-administered with analgesics.

Despite the apparent limitations due to unmeasured confounding, Study B037 has the advantage of a large source population potentially providing statistical power to investigate liver injury in association with antidepressant drugs and the ability to validate potential outcomes identified on the basis of the insurance claim via medical records review. It is possible that this study will further characterise hepatic outcomes in conjunction with the other PhV activities identified to monitor this risk. These additional PhV activities are considered acceptable, at this stage, to monitor the risk of hepatic injury.

The annual incidence of acute UGIT bleeding in the United Kingdom (UK) is approximately 1 per 1000 adults/year with a crude mortality for patients presenting to emergency departments of about 10%, rising to 33% among inpatients who develop GIT bleeding while hospitalised for other reasons.[12] NSAIDs are associated with serious GIT (peptic ulcer haemorrhage and perforation) events in the range of 0.3% to 2.5% per year[13] The 5 chronic pain clinical trials comprised total of 839 patients treated with duloxetine and 689 patients treated with placebo with patients being allowed to remain on their regular dose of NSAID, apart from in one of the studies. Although the reports of GIT bleeding from these trials did not suggest a synergistic effect from duloxetine on NSAID/aspirin with regards to GIT bleeding, the trials may not have been able to detect increases above the background rates.

As chronic somatic pain is a common feature of a number of highly prevalent chronic conditions, the proposed extension of indication would likely significantly increase the population exposure to duloxetine. A proportion of this population is likely to be taking NSAIDs concomitantly. The sponsor informed the TGA that they will not be proceeding with the planned population based case control study due to a negative feasibility analysis. However, following an agreement with the EU authorities, the sponsor plans to develop a protocol (beginning in the first quarter of 2012) for a modified version of this study to further investigate UGIT bleeding in patients taking NSAIDs concomitantly with duloxetine.

Although there were concerns about the potential confounding effects of non-prescription medicine use, it was considered that the misclassification of use of non-prescription medicines may be non-differential between study groups. This appears to be a reasonable proposition. It was recommended that the sponsor provide the TGA with a copy of the draft protocol when it becomes available. The twice yearly analysis of the ongoing co-exposure insurance claim database study and the analysis of UGIT bleeding events from the FDA AERS will be reported in the PSUR. These enhanced PhV activities are considered acceptable, at this stage, to monitor the risk of UGIT bleeding.

While renal failure is identified by the sponsor as an important potential risk in the, it has not been included in the PhV plan or in the summary of the RMP. The sponsor states that no signal for renal failure has been identified from clinical trial data, 2 cumulative reviews of renal failure in the PSURs and a disproportionality analysis of the FDA AERS data. There have been reports in spontaneous postmarketing data which are consistent with renal failure/impairment although the sponsor states

[12] Rockall TA, Dowson HMP. Gastrointestinal bleeding. In: Warrell DA, Cox TA, Firth JD, Ogg GS, editors. Oxford Textbook of Medicine. 5th edition. Oxford University Press; 2010.
[13] Schaffer D, Florin T, Eagle C, Marschner I, Singh G, Gerobler M, Fenn C, *et al.* Risk of serious NSAID-related gastrointestinal events during long-term exposure: a systematic review. MJA 2006;185:501-506.

that all of the reported cases were confounded by pre existing medical history, concomitant medication use or other disease states. Nevertheless, the sponsor has retained renal failure as a potential risk at the request of other regulators. To augment the ongoing surveillance, the sponsor will add renal failure to the twice yearly analysis of the ongoing co-exposure insurance claim database study. The sponsor states that this commitment will be reflected in the updated RMP revision 9, scheduled for October 2011, with results of the recurrent analyses summarised in the PSUR. This is considered acceptable, at this stage.

For the remaining identified and potential risks, routine PhV with enhanced follow-up by way of the targeted questionnaires is acceptable.

Risk minimisation activities

The sponsor concludes that routine risk minimisation by way of labelling information is sufficient to mitigate the risks. For the Identified risks this justification is based on there being no recent safety concerns detected or increased trends identified that warrant additional risk minimisation. For the Potential risks of CV events (myocardial infarction; ventricular arrhythmias) and UGIT bleeding the sponsor's justification is based on the lack of any established association.

OPR evaluator comment

The sponsor's justification for routine risk minimisation was considered acceptable at this stage.

Summary of recommendations

The OPR provides the following recommendations in the context that the submitted RMP is supportive to the application:

1. The Cymbalta Risk Management Plan, that identified as revision 8 and dated September 2010, and any subsequent versions, is implemented as a condition of registration.
2. The next version of the RMP should include:
    2.1 Reference in the pharmacovigilance plan to the proposed modified version of the observational case control study to investigate the interaction of duloxetine with NSAIDs for the risk of UGIT bleeding. The study is that identified in the sponsor's response requests dated 29 September.
    2.2 Reference in the pharmacovigilance plan of the twice yearly analysis of the ongoing co-exposure insurance claim database study as an additional activity to further characterise the potential risk of renal failure.
3. As the study identified in 2.1 above is a proposed pharmacovigilance activity, the draft study protocol should be submitted to the TGAs Office of Product Review when it becomes available.
4. As the drug utilisation study identified as Study F1J-MC-B038 is a proposed pharmacovigilance activity, the study protocol should be submitted to the TGAs Office of Product Review when it becomes available.

VI. Overall conclusion and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations:

Quality

There was no requirement for a quality evaluation in a submission of this type.

Nonclinical

There was no requirement for a nonclinical evaluation in a submission of this type.

Clinical

Efficacy

The data package consisted of 5 randomised, double-blind, placebo-controlled efficacy/ safety studies in chronic pain conditions: three in patients with chronic low back pain (CLBP) and two in patients with knee pain due to osteoarthritis (OA). The studies enrolled 839 patients treated with duloxetine at doses of 20, 60 and 120 mg once daily and 689 patients treated with placebo. All five studies had a placebo controlled phase of 12-13 weeks and Study CLBP-EN had a long term uncontrolled extension phase of 41 weeks to assess maintenance of effect. Two studies were fixed dose, two had dose escalation of non-responders at Week 7 and one study had re-randomisation at Week 7. All studies required patients to start on duloxetine 30 mg once daily before increasing the dose during a 1week titration period except for Study CLBP-GC, where duloxetine patients directly started on 60 mg once daily.

All studies used a 24 hour average pain rating (either collected in patient daily diary or through Brief Pain Inventory (BPI) at scheduled office visits) as primary efficacy outcomes. The primary efficacy analysis in all studies was to test the null hypothesis that the difference in the BPI 24-hour average pain score between the duloxetine and placebo treatment groups at the last visit of the treatment phase was zero (clinical summary).

The 24 hour average pain score were derived using an 11 point scale where 0 = no pain and 10 = worst possible pain. The 24-hour average pain score was a weekly mean, gathered from electronic patient diaries in Studies OA-EP and CLBP-EO and was from the BPI instrument at study visits in Studies CLBP-EN, CLBP-GC and OA-FG. The change in method collection occurred after low diary completion rates in the initial studies.

Secondary endpoints included the proportion of patients with 30% and 50% reductions in 24 hour average pain scores (30% and 50% response rates) and changes from baseline in measures of function (WOMAC and RMDQ-24). The primary analysis was Mix-Models Repeated Measures (MMRM) for all randomised patients with Last Observation Carried Forward (LOCF) and Baseline Observation Carried Forward (BOCF) analyses also performed.

Combined analyses of all CLBP studies and all OA studies were performed for differences between duloxetine and placebo in the change from baseline in BPI 24 hour average pain score and 30% and 50% response rates for all subjects. Subgroups including: use versus non-use of NSAIDs; pain severity at baseline; age; gender; depression score at baseline; and location (Europe vs. N. America) were examined for the primary endpoint only in the combined analyses.

Subjects were required to have a baseline 24 hour average pain score of at least 4, equating to moderate pain. Subjects were required to have had chronic pain for at least 3 months (OA) or 6 months (CLBP) prior to entry into the studies. To limit the inclusion of subjects with neuropathic pain in the CLBP studies, pain was to be either restricted to lower back or associated with radiation to a proximal portion of the lower limb only. Subjects could not have neurological radicular pain; presumptive compression of the spinal nerve root on simple radiogram; compression of a spinal nerve root confirmed by imaging; spinal fracture; spondylolisthesis Grade III or IV; tumour; abscess; or other acute pathology in the lower back/ abdominal region.

All studies excluded subjects who, in the opinion of the investigator, were likely to require medication which was not permitted on study (clinical summary). These included: opioids (episodic use for up to 3 days permitted), antidepressants, antiepileptics; anti-manics; antipsychotics; capsaicin; cimetidine; lignocaine; MAOIs; psychostimulants; quinoline antibiotics; triptans; tryptophan; and tramadol. Subjects with a diagnosis of MDD were excluded from the studies.

Mean 24-hour average pain scores at baseline were from 5.75 to 6.34 across study groups. In the clinical summary it was reported that 188 (40%) subjects in the OA studies and 340 (36%) in the CLBP studies had baseline mean 24 hour average pain scores of ≥7, consistent with moderate to severe pain. Completion rates for the 12/13 week double-blind period ranged from 86.7% to 55.4% across groups in the 5 studies with generally higher completion rates in the placebo groups. Differences in completion rates were mostly due to higher withdrawals due to adverse events in the active treatment groups.

Table 6 above shows the differences between placebo and each dose of duloxetine for least-squares mean changes from baseline to endpoint in 24 hour average pain scores for the 4 studies in which this endpoint was statistically significant for the MMRM analysis. The largest difference between placebo and any dose of duloxetine in least-squares mean change from baseline to endpoint in 24 hour average pain scores (MMRM analysis) was 1.12, reported in Study OA-EP. Between group differences were generally < 1 on the 11-point pain rating scale. Results for Study CLBP-EO for this parameter were not statistically significant for the primary comparison. Statistical comparisons for measures of physical function that were secondary endpoints are shown in the clinical evaluation report CER above.

Results for 30% and 50% response rates were provided for each study for the 13 week period and are presented in the CER. Statistically significant differences in the 30% response rate were seen for the LOCF analysis for Studies OA-FG and OA-EP and for the 120 mg versus placebo comparison in CLBP-EO. Statistically significant differences in 50% response rate (LOCF) occurred in OA-EP and CLBP-GC only. Other secondary endpoint results are in the CER above.

For the combined CLBP and combined OA datasets, the 30% and 50% response rates are presented in the CER. All these comparisons (LOCF and BOCF) between duloxetine and placebo were statistically significant. For the CLBP studies (LOCF analysis) 56.0% subjects given duloxetine and 45.3% of subjects given placebo had at least a 30% reduction from baseline in pain severity ($p = 0.002$; Number Needed to Treat (NNT) 9.3). The percentage of subjects with at least a 50% reduction in pain intensity from baseline was 46.2% versus 32.7% for duloxetine and placebo respectively ($p < 0.001$; NNT 7.4). Results for the BOCF were also statistically significant but the absolute differences between duloxetine and placebo were generally smaller. For the pooled OA studies 64.6% of subjects given duloxetine versus 44.7% of subjects given placebo had at least a 30% reduction in pain severity ($p<0.001$;NNT 10.1) and 47.2% given duloxetine versus 30.7% given placebo had at least a 50% reduction in pain severity ($p<0.001$; NNT 6.1). Other secondary analyses were generally supportive of efficacy. There were no clear differences in efficacy based on age, sex, use of NSAIDS, depression/ anxiety measures, or pain severity at baseline (≥7 versus ≤ 6).

Mean changes in weekly 24 hour average pain scores by week in each study are shown in the CER. Separation of duloxetine from placebo was apparent within a week and generally increased during the first 4 - 7 weeks of each study and then stabilised, suggesting that for subjects given duloxetine little or no further pain reduction occurs beyond 7 weeks of commencement of treatment. This also suggests if clinically significant pain reduction has not occurred within 7 weeks, treatment should be discontinued.

To assess whether there was additional pain relief from the 120 mg dose compared to the 60 mg dose of duloxetine a post hoc analysis of the flexible dose studies (CLBP-EN, OA-EP and OA-FG) was performed. This showed there was an increase in the proportion of responders with the 120 mg dose.

Maintenance of effect was assessed over 41 weeks in the extension phase of Study CLBP-EN. All subjects received either 60 mg or 120 mg duloxetine during this phase. In general, there was a continuous reduction in pain during the extension phase with lower mean BPI average pain ratings at each subsequent visit with the lowest ratings reported after 54 weeks of duloxetine treatment as shown in the CER.

As this was not placebo controlled the effect of fluctuations in pain severity could not be separated from the effect of duloxetine.

The CER shows data for the concomitant therapy used by ≥ 5% of patients in the pooled clinical trials. These included paracetamol, ibuprofen, acetylsalicylic acid, naproxen and diclofenac. Differences in the proportions of subjects given duloxetine versus placebo for each of these medicines were similar, with

the largest difference for ibuprofen (15.4% duloxetine versus 11.8% placebo). This was the only comparison that was statistically significant (p= 0.44).

Safety

A total of 839 subjects were exposed to duloxetine for a mean of 74.8 days in the double-blind studies. Of these 79.1% received 60 mg daily and 214 (25.5%) received 120 mg daily at some point during the double-blind treatment phase. In the long term extension phase of Study CLBP-EN 83 subjects received duloxetine for a mean of 243.37 days.

Discontinuation rates are shown in the CER. These were lower for subjects given placebo than duloxetine (21.2% versus 30.2%) with the difference mostly due to higher discontinuation due to AEs in the duloxetine group. TEAEs occurring more frequently with duloxetine than placebo included: nausea, dry mouth, constipation, insomnia, diarrhoea, dizziness, somnolence and fatigue. No deaths were reported on study, including in the extension phase of Study CLBP-EN. One death, due to cardiopulmonary arrest occurred 11 days after the last dose of duloxetine in Study CLBP-EO. SAE were reported for 2.3% of subjects given duloxetine versus 1.2% of subjects given placebo. The most frequently reported SAEs were transient ischaemic attack (TIA), osteoarthritis and asthma.

There was a 2 week double blind taper phase in the placebo-controlled studies. TEAEs were more frequent during this phase in subjects given duloxetine (12.1%) compared to placebo (4.3%). Dizziness was the most frequently reported event (2.4% given duloxetine).

Overall the safety profile was consistent with that shown in subjects given duloxetine for its current indications.

Risk management plan

The RMP evaluator has noted the following safety issues with respect to the chronic pain trials:

- The data from the five chronic pain studies has essentially revealed a safety profile compatible with that observed in earlier controlled clinical trials for other indications of Cymbalta.
- The incidence of adverse events in the long term analysis set was lower than those observed during acute treatment.
- There were no deaths reported in relation to Cymbalta.
- There were no cases of suicidal ideation or suicidal behaviour reported.
- No new safety information was defined in relation to hepatic enzyme disturbances.
- The concomitant use of Cymbalta and paracetamol was not associated with a significantly greater incidence of hepatic enzyme disturbances.
- There was no evidence of synergistic effect of Cymbalta and NSAIDs combined on bleeding or cardiovascular related outcomes.
- In relation to dose effect, the most common adverse events were reported more frequently with Cymbalta 120 mg per day compared with 60 mg per day. Sexual dysfunction was noted to be more frequent and more severe with 120 mg per day than 60 mg per day.

Ongoing safety concerns identified by the sponsor are tabulated above (under *Pharmacovigilance Findings*).

The evaluator has recommended that the RMP version 8, dated September 2010 and any subsequent versions be implemented as a condition of registration. The RMP includes an observational case control study to investigate the interaction of duloxetine with NSAIDS for the risk of UGIT bleeding and a twice yearly analysis of the ongoing co-exposure insurance claim database study as an additional activity to further characterise the potential risk of renal failure. Further pharmacovigilance activities as described

in the RMP evaluation are also planned and the TGA has requested submission of the protocols for 2 postmarket studies when available.

Risk-benefit analysis

Extent of efficacy: The differences between duloxetine and placebo in reduction from baseline to Week 13 in mean 24 hour average pain scores were statistically significant favouring duloxetine for 2 of the 3 CLBP studies and in both OA studies. However, the extent of difference was ~1 on an 11-point scale and is not clinically meaningful. The majority of patients with chronic pain given duloxetine will not derive a clinically significant benefit.

The 30% and 50% responder analyses showed that for a minority of individuals duloxetine does result in clinically meaningful pain relief. The NNT for an additional subject with 30% reduction in pain severity is ~ 10 and for an additional subject with 50% reduction in pain severity the NNT is 6-7. This difference in NNT may seem paradoxical but is due to the difference between duloxetine and placebo being larger for the ≥50% reduction in pain intensity than for the 30% reduction in pain intensity.

Dose and timing of effect: The proposed dose regimen has been justified by the data presented. Given the maximal effect is apparent within 7 weeks and most patients will not obtain a clinically significant benefit from treatment patients who do not respond initially should not be continued beyond 7 weeks.

Maintenance of effect was assessed without a placebo or other active control so the extent of apparent benefit attributable to treatment with duloxetine cannot be determined as placebo effects and the natural fluctuations in pain severity that may occur in subjects with chronic pain are likely to have contributed to the maintenance outcome. However no reduction in benefit was seen.

Active comparator: The main concern with the study program is the lack of any active comparator. The relative efficacy in comparison with other available treatments has not been examined and it is not clear if duloxetine has similar efficacy to an opioid, an NSAID or to paracetamol. The exclusion of most other analgesics from the clinical studies prevents an assessment of any adjuvant effect of duloxetine with established treatments for pain, other than NSAIDs where it appears to add to the effect of the NSAID.

Subject selection: Subjects who, in the opinion of the investigator, required excluded medications were not enrolled in any of the studies. These medications included opioids. However, nearly 40% of subjects in the study program reported pain of ≥7 at baseline, this corresponds to moderate to severe pain. The Delegate was not satisfied that the efficacy of duloxetine in severe pain has been adequately assessed due to the absence of patients with malignancy and of patients considered to require opioids for analgesia in the study program.

CLBP is not due only to nociceptive pain however the majority of subjects in this study program had CLBP. It is not an ideal model for somatic pain, though attempts were made to exclude individuals with neurologic components to their pain it is unlikely this was wholly successful. The conditions assessed do not, in the Delegate's opinion support an indication for somatic pain and it would be more accurate to describe the type of conditions treated in the limited program submitted, rather than permit the broader indication of somatic pain. An amended indication could reflect the absence of assessment of efficacy in the treatment of severe pain and more accurately describe the type of pain studied in clinical trials. The US PI describes this as "musculoskeletal pain" rather than somatic pain.

The safety profile of duloxetine is such that it would be unsuitable to use in the treatment of mild pain. There are patients who are unable to tolerate, or who do not significantly benefit from current treatments for moderate to severe chronic pain. Duloxetine has been shown to be effective for a significant minority of patients with moderate to severe musculoskeletal pain. Use of duloxetine for treatment of moderate to severe musculoskeletal pain should be limited to adults because efficacy and safety for this indication has been examined only in adults.

Conclusion and recommendation

The Delegate proposed to approve Cymbalta (duloxetine) for treatment of moderate to severe chronic musculoskeletal pain in adults.

The Australian PI requires revision to make it clear that the majority of individuals given duloxetine for chronic musculoskeletal pain will not derive a clinically meaningful benefit and that the effects of adjuvant treatment with other treatments for pain other than NSAIDs have not been assessed.

The advice of the ACPM was requested on the following:

- Is it appropriate to restrict the indication to musculoskeletal pain rather than allow somatic pain as requested by the sponsor, given the pain conditions assessed in clinical trials?
- Is it appropriate to approve a treatment for chronic pain when duloxetine has not been compared with an active comparator? Could this be addressed by limiting the indication to treatment in individuals who are unresponsive or intolerant to alternative registered treatments for chronic pain and/or to those not considered to require regular opioids as was the case in the clinical trial program?

Response from sponsor

Eli Lilly acknowledge receipt of the Delegate's Overview and thanked the TGA for the opportunity to provide comments at this time. The sponsor's response focused on the key areas of:

(1) Proposed indication, particularly with respect to alignment with the trial population;

(2) Comparative efficacy data and proportion of response;

(3) Requested PI amendments;

(4) Other minor matters of clarification for the benefit of committee deliberations.

1. Proposed indication and trial population

Lilly accepted the Delegate's proposed indication statement revision to replace "somatic pain" with "musculoskeletal pain". As noted by the Delegate there can be a neuropathic component to CLBP, however, every clinically reasonable effort has been made to exclude patients who experienced a neuropathic component since duloxetine's efficacy has already be established in neuropathic pain (DPNP approved in Australia July 2009), although such an exclusion is challenging due to the complexity of the condition. In particular, the inclusion of non radiculopathic and/or non neuropathic low back pain was maximised by specifying the enrolment of patients assessed with a Class 1 or 2 CLBP per the Quebec Task Force on Spinal Disorders. In fact, the substantial majority of enrolled patients (722, 79%) were assessed in the Class 1 category (restricted to the lower back with no radiation of pain). On this basis, Lilly concluded that the assessment of duloxetine was primarily in non radiculopathic and/or non neuropathic CLBP which are, as suggested by the Delegate, appropriately described as musculoskeletal.

The patients enrolled in the OA and CLBP studies included those with a pain severity rated as at least moderate pain (4 to 6 on the BPI scale) and a substantial proportion (37%) rated their pain as more severe (greater than 6 on BPI scale). Thus, even exclusion of opioid use did not prevent patients with more severe pain entering the trial. Opioid use was indeed excluded so that a statement to this point in the proposed label is accurate although patients were allowed to enter the study irrespective of prior opioid use. Other analgesics were excluded for safety reasons or restricted in frequency and duration to avoid confounding.

2. Comparative efficacy data

Choice of comparator

Since the Delegate raised a concern regarding the lack of an active comparator in duloxetine studies, Lilly offered additional rationale regarding the choice of comparator in the OA and CLBP studies.

Approved pharmacological treatment options for chronic pain, including OA and CLBP, primarily include non-steroidal anti-inflammatory drugs (NSAIDs) and opioids[14] . Though inclusion of one of these treatment options as an active comparator was considered very seriously, placebo was selected as the sole comparator for all studies for the following reasons:

1. Study protocols allowed patients to enter the trial on a stable dose of NSAID as background therapy but did not require NSAID use in order to enter the trials. In this instance, the decision regarding NSAID use was made by the patient's physician as part of standard care. If the use of a NSAID as an active comparator had been mandated by the study protocols, criteria would had to have been incorporated into the protocol to exclude patients with established CV, GI or renal disease consistent with the Warnings and Precautions contained within NSAID labeling. Exclusion of these patients would have been required even if the protocol mandated only short term use of NSAIDs. Since patients with the above diseases constitute a sizable portion of patients with CLBP and, particularly OA, their exclusion would have resulted in studies of at least questionable generalisability.
2. While paracetamol may be used for the first line treatment of low back pain such a comparator would not be appropriate for the studied patient population who, after at least 3 months (that is, established chronic pain), still experience pain severity of ≥4 on the BPI average pain scale.
3. Administration of any non-selective NSAID would need to be associated with concomitant use of a proton-pump inhibitor, which poses a significant challenge with blinding the trial.
4. Use of a selective COX2 inhibitor did not appear an acceptable choice since our studies were launched at the time of public disclosure of the VIGOR trial results, subsequent withdrawal of rofecoxib from the market and mounting concerns about safety of COX2 inhibitors as a class.
5. Use of any opioid as an active comparator was not seen as an option. Apart from many medical reasons for not using an opioid (such as narrow therapeutic index, abuse potential and diversion) the difference in adverse event profile and tolerability between duloxetine and any opioid would likely lead to an unblinding of the study.

Given the above rationale, the sponsor concluded that the choice of placebo control only is scientifically valid. In order to aid the TGA's interpretation of the clinical relevance of duloxetine's effect in the context of other available treatments, further supportive evidence from historical comparisons (benchmarking data) was provided as part of the submission (reproduced in Figures 8 and 9 below) and is further supported by more recent publications and product approval referenced below.

Magnitude of treatment effect

A concern noted in the Delegate's Overview is the clinical relevance of a approximately 1 point drug-placebo difference (on a scale of 1-10) in mean change by study endpoint. The sponsor agreed that the observed group **mean** treatment effect is moderate. However, as also noted by the Delegate, a significant minority of patients achieve a clinically meaningful benefit (that is, decrease in average pain by at least 30%) and the sponsor wished to take this opportunity to illustrate that this is the same magnitude of treatment effect as observed with other currently used analgesics.

Figures 8 and 9 summarise data from 2 meta-analyses published by[15, 16], respectively, for the comparison of commonly used analgesics for the treatment of chronic OA and CLBP, respectively. The average treatment effect of duloxetine (drug-placebo difference), calculated from the pooled OA or pooled CLBP studies, is included in each of these comparisons, which demonstrate that the treatment

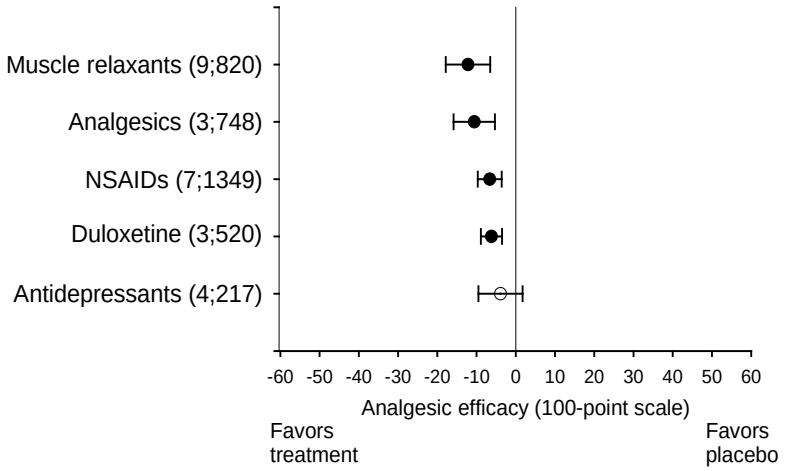
[14] [DASSA] Drug and Alcohol Services South Australia. Opioid prescription in chronic pain conditions. Guidelines for South Australian General Practitioners (GPs). 2008. Available at: http://www.dassa.sa.gov.au/webdata/resources/files/Opioid_prescription_chronic_pain_guidelines_for_SA_GPs.pdf. Accessed 21 September 2011.

[15] Machado LAC, Kamper SJ, Herbert RD, Maher CG, and McAuley JH. Analgesic effects of treatments for non-specific low back pain: a meta-analysis of placebo-controlled randomized trials. Rheumatol. 2009;48:520–527

[16] Bjordal JM, Klovning A, Ljunggren AE, Slørdal L. Short-term efficacy of pharmacotherapeutic interventions in osteoarthritic knee pain: A meta-analysis of randomized placebo-controlled trials. Eur J Pain. 2007;11:125-138.

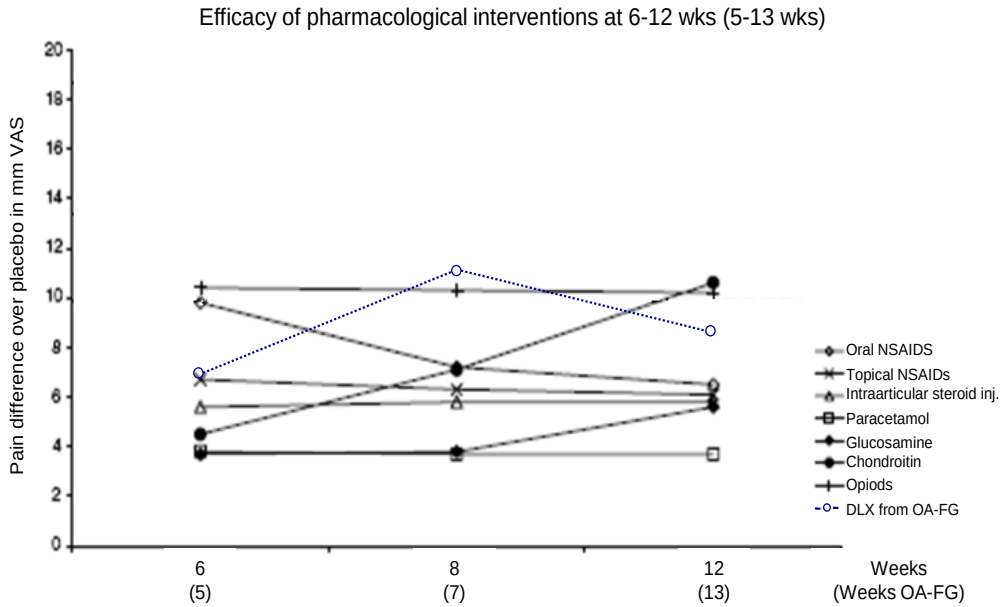
effect of duloxetine lies within the range of currently available analgesics; all with a group mean drug-placebo difference of <1.

Figure 8. Analgesic effect of pharmacological treatments for low back pain.



Abbreviations: NSAID = non-steroidal anti-inflammatory drugs; in parenthesis=number trials; total participants.
Adapted figure from Machado *et al*. 2009

Figure 9. Effect over placebo for pharmacological interventions and duloxetine.



Adapted from the meta-analysis by Bjordal *et al* 2007

This conclusion is further supported by study results from the recently approved opioid, Palexia SR (tapentadol, average treatment effect range -0.3 to -0.8), which has been studied in similar disease states as duloxetine (OA, CLBP, and DPNP) over similar treatment periods, demographics and end-points (that is, mean change in average pain)[17, 18].

[17] Lange B, Kuperwasser B, Okamoto A, Steup A, Häufel T, Ashworth J, Etropolski M. Efficacy and safety of tapentadol prolonged release for chronic osteoarthritis pain and low back pain. Adv Ther. 2010;27:381-399.
[18] Australian Public Assessment Report for Tapentadol. http://www.tga.gov.au/pdf/auspar/auspar-palexia-sr.pdf

Proportion of response

The drug-placebo difference of clinically relevant pain relief (at least 30% reduction in pain) as represented by NNT for historical comparator data are presented in Table 29. Overall, although these data need to be interpreted with caution due to different study designs (such as flare, which favours the comparator analgesics) and data collection methods, the proportion of patients responding to duloxetine consistently lies within the range of commonly used treatment options for chronic pain.

Table 29. Comparison of Number Needed to Treat across Analgesic Monotherapy (BOCF) based on at Least 30% Response

Drug and Daily Dose	Pain Condition	Percentage with Outcome		NNT[a] (95% CI)
		Active	Placebo	
Etoricoxib 60 mg	Osteoarthritis	59	35	4.0 (2.9 to 6.7)
Celecoxib 200 mg	Osteoarthritis	53	31	4.7 (3.5 to 7.1)
Naproxen 1000 mg	Osteoarthritis	55	35	4.8 (3.2 to 9.2)
Ibuprofen 2400 mg	Osteoarthritis	49	41	12 (6.8 to infinity)
Duloxetine 60/120 mg	Osteoarthritis	52	41	8.5 (4.8 to 37)
Etoricoxib 60 mg	CLBP	55	40	7.5 (NR)
Etoricoxib 90 mg	CLBP	55	40	7.0 (NR)
Duloxetine 60/120 mg	CLBP	44	37	13 (7.0 to 63)

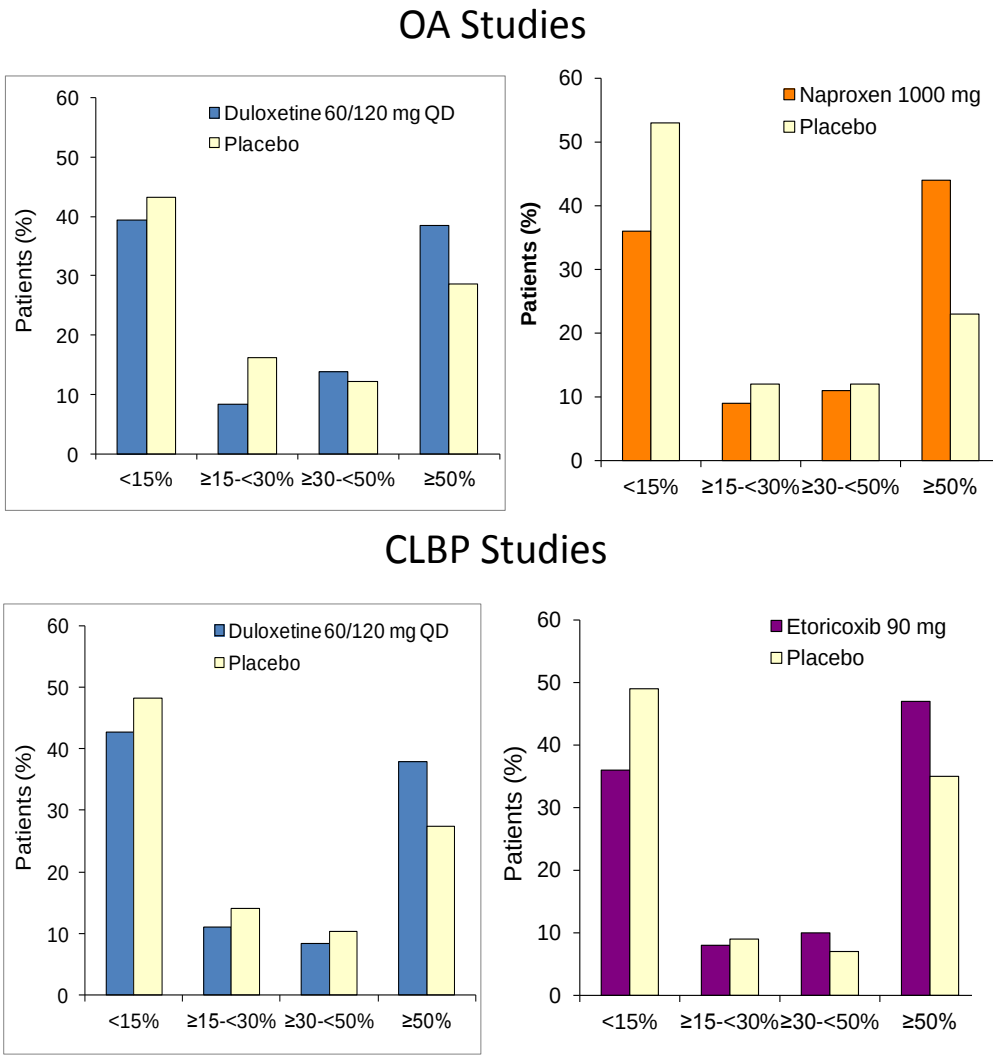
Abbreviations: BOCF = baseline observation carried forward; CI = confidence interval; CLBP = chronic low back pain; mg = milligrams; NNT = number needed to treat; NNR = not reported.

Finally, when considering that the point decrease (>3 point decrease in baseline pain at endpoint) required to attain substantial pain relief (50% response status by BOCF) is far greater than the effect observed on a group mean level (<1 point decrease), it is clear that response to duloxetine is not normally distributed, thus skewing the magnitude of effect on a group mean level. In fact, this skewed distribution of response is common among analgesics[19,20] , as demonstrated in Figure 10. This skewed distribution highlights the difficulties in establishing a threshold of clinical relevance on a group mean level.

[19] Moore RA, Moore OA, Derry S, Peloso PM, Gammaitoni AR, Wang H. Responder analysis for pain relief and numbers needed to treat in a meta-analysis of etoricoxib osteoarthritis trials: bridging a gap between clinical trials and clinical practice. Ann Rheum Dis. 2010a;69:374–379

[20] Moore RA, Smugar SS, Wang H, Peloso PM, Gammaitoni A. Numbers-needed-to-treat analyses-do timing, dropouts, and outcome matter? Pooled analysis of two randomized, placebo-controlled chronic low back pain trials. Pain. 2010b;151(3):592-597

Figure 10.The distribution of response and the proportion of patients attaining 50% response with duloxetine, naproxen, and etoricoxib.



Consensus View of Clinical Relevance for New Analgesics

Every determination of clinical significance is by nature a somewhat subjective process and particularly challenging when performed at the group level. In fact, within the chronic pain field there is no consensus on what constitutes a clinically relevant difference on a group mean level. There is agreement, however, that one cannot extrapolate a change on an individual level (that is, what amount of decrease an individual needs to experience for it to be meaningful) to those on a group mean level (for example, mean change from baseline to endpoint). The importance of this distinction was expanded upon in the scholarly article by the IMMPACT group, which consists of prominent pain experts from academia, industry and regulatory agencies[21]:

> *'It is crucial to recognize that criteria for clinically important changes in individuals cannot be extrapolated to the evaluation of group differences."* It was also noted that "*group mean differences can obscure meaningful individual patient improvements and other benefits and risks*".

With this in mind, a consensus statement was developed by IMMPACT, consisting of a list of 14 recommendations on how to appropriately interpret group mean differences. In order to place duloxetine's magnitude of effect into perspective, a detailed assessment of duloxetine clinical data

[21] Dworkin RH, Turk DC, McDermott MP, Peirce-Sandner S, Burke LB, Cowan P, Farrar JT, Hertz S, Raja SN, Rappaport BA, Rauschkolb C, Sampaio C. Interpreting the clinical importance of group differences in chronic pain clinical trials: IMMPACT recommendations. Pain. 2009;146:238–244.

against each of these recommendations is summarised in Table 30 below. Based on all applicable IMMPACT criteria, the magnitude of effect for duloxetine is demonstrated as consistently clinically meaningful across these wide ranging criteria.

3. Requested Product Information amendments

The Product information revisions requested by the Delegate were incorporated as requested.

4. Other minor matters of clarification

Regarding the lack of a control in the maintenance of effect CLBP study (extension phase of Study HMEN), Lilly agreed that pain severity fluctuates over time. However, even in the presence of this expected fluctuation, the impact on pain severity was below the threshold of improvement as seen by both a lack of an increase in average pain and a continuous decrease (improvement) in the mean pain calculated at each visit (MMRM analysis). Further, when considering those who entered the extension treatment as duloxetine responders (defined as at least a 30% decrease in average pain from baseline to endpoint), 95% maintained their response through their last visit. By using patients as their own control, as it were, the fact that nearly all responders after 12 weeks of treatment maintained their response through extension treatment provides reassurance that, even in the midst of natural pain severity fluctuations, duloxetine remains effective in managing pain over the long term.

5. Conclusion

The sponsor believed that the information provided confirms the agreement with the Delegate's proposed revision to the stated indication: *Cymbalta is indicated for the treatment of chronic musculoskeletal pain in adults.* The sponsor considered that it was reflective of both the pain state and the population studied. The sponsor noted that the alternative suggestion of a second line indication (restricted to those unresponsive or intolerant to alternative treatments) would not be representative of the trial population.

Table 30. Assessing Clinical Relevance of Duloxetine Effect using IMMPACT Recommendations. Continued across two pages.

IMMPACT Criteria (Dworkin et al. 2009)		Results of Duloxetine Assessment
1. Statistical difference of the primary efficacy analysis (typically necessary but not sufficient to determine clinical meaningfulness).	✓	A statistically significant greater improvement with DLX vs. PBO achieved in 4 out of 5 DLX trials using primary analysis method (MMRM). (Also in 3 out of 5 DLX trials using sensitivity analysis [BOCF].)
2. Magnitude of improvement in the primary efficacy outcome	✓	DLX-PBO difference (LSM average pain): LOCF -0.60 to -0.97; BOCF -0.45 to -0.79.
3. Results of the responder analysis	✓	50% response rate [LOCF] was 47% and 46% for OA and CLBP , respectively; DLX-PBO difference was 17% and 13%, respectively.
4. Treatment effect size compared to available treatments	✓	30% and 50% response rates were comparable to established analgesics for both CLBP and OA (see Table 1 and Figure 1).
5. Rapidity of onset of treatment benefit	✓	Significant pain reduction achieved within 1 week (at least a 30% reduction in baseline average pain); statistically significantly more with DLX (15%) than PBO (8%).
6. Durability of treatment benefit	✓	In CLBP model 95% (LOCF) of patients maintained pain reduction of at least 30% over 9 months.
7. Results for secondary efficacy endpoints	✓	Statistically significantly more DLX patients than PBO attained response based on PGI ≤2 (DLX-PBO difference) in all 5 studies (13%-21%) and based on Physical Function definition[a] (DLX-PBO difference) in 3/5 studies (8%-17%).
8. Safety and tolerability	✓	Well-established safety profile in 31,000 patients in trials and more than 42 million patients postmarketing across multiple indications, including pain. Differs from opioids, in that it does not include abuse potential or addiction. All the identified and potential risks (with the exception of renal failure, for which there is no evidence of a casual association) are described appropriately in the label.

Table 30. continued		Results of Duloxetine Assessment
9. Safety and tolerability	✓	Potential risks (CV, GI bleeding) with concomitant NSAID use does not appear increased, compared with NSAIDs alone; risk mitigation plan in place and no risk minimization beyond labelling required for use in target population: • Labelling, to highlight the potential risk of co-administration; • New twice yearly active surveillance of a large health claims database; • New hepatic and GI bleeding pharmacoepidemiology studies and new drug utilization study.
10. Convenience	✓	Once daily oral medication (improved convenience to most NSAIDs and opioids); simpler dose adjustments compared with opioids dose-titration; no co medication with PPI or laxatives; suitable for long-term use (as opposed to NSAIDs); non-controlled substance (as opposed to opioids).
11. Patient adherence	✓	46% adhered to 6 month treatment in MDD/comorbid pain study, generally a low compliance population[b].
12. Cost	-	Not applicable for this review.
13. Different mechanism of action vs. existing treatments	✓	Non-NSAID, non-opioid; first SNRI with wide spectrum analgesic efficacy with a different MOA (a well-recognized need in chronic pain field); can be used for long-term treatment.
14. Limitations of available treatments	✓	Regular NSAID use: appreciable risks of GI bleeding and congestive heart failure that increase with age, duration of treatment, and daily dose; guidelines caution against prolonged use[c]. Opioids: diversion/drug abuse, addiction, development of tolerance; death due to overdose[d].
15. Other benefit	✓	Efficacy in MDD and GAD, common comorbidities in patients with chronic pain[e]; relatively low potential for drug-drug interactions; no evidence of abuse potential, simpler dose adjustments.

Abbreviations: BOCF = baseline-observation carried forward; CLBP = chronic low back pain; CV = cardiovascular; DLX = duloxetine; GAD = generalised anxiety disorder; GI = gastrointestinal; IMMPACT = Initiative on Methods, Measurements, and Pain Assessment in Clinical Trials; LOCF = last observation carried forward; LSM = least square mean; MDD = major depressive disorder; MMRM = mixed model repeated measure; MOA = monoamine oxidase inhibitor; NSAID = nonsteroidal anti-inflammatory drug; OA = osteoarthritis; PBO = placebo; PGI = Patient Global Impression; PPI = proton pump inhibitor; RMDQ-24 = Roland Morris Disability Questionnaire; SNRI = serotonin noradrenaline inhibitor; WOMAC = Western Ontario and McMaster Universities Arthritis Index. [A] For OA, a decrease of at least 26% on the WOMAC physical function scale; for CLBP, a decrease of at least 5 points on the RMDQ-24 total. [b] Wang et al. *Curr Med Res Opin* 2011, 27(7):1303-1313. [c] EMEA/CHMP/410051/2006. [d]Okie et al. *N Engl J Med.* 2010, 363(21):1981-1984; Bohnert et al. *JAMA* 2011, 305(13):1315-1321; Gomes et al. *Open Med* 2011, 5(1):E13-E22. [e]Ritzwoller et al. *BMC Musculoskeletal Disord* 2006, 7(1):72; Bair et al. *Arch Intern Med* 2003, 163:2433-2445.

Advisory Committee considerations

The Advisory Committee on Prescription Medicines (ACPM), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following:

The ACPM considered this product to have a negative benefit-risk profile for the proposed indication, for the following reasons:

- The term 'somatic pain' is not well defined, nor used consistently in clinical practice. It is therefore inappropriate for use in studies to determine efficacy.
- The study design and data collection processes have limited the development of clear evidence of efficacy in a well defined population group. While clinically significant efficacy was demonstrated for a small minority of patients with chronic musculoskeletal pain, the difference compared to placebo was not clinically significant for the majority of patients.
- Clinical efficacy of duloxetine in severe pain has not been adequately assessed due to the absence of patients with malignancy and of patients considered to require opioids or similar analgesia in the study program.
- The ACPM noted that while the guidelines do permit clinical trials without an active comparator, the submitted studies have not adequately addressed the clinical context. The exclusion of patients using most other analgesics from the clinical studies prevents an assessment of relative efficacy of this product compared with available treatments.
- The side effect profile for this product is significant, and while the safety issues identified in the studies matched those identified in controlled clinical trials for other indications of this product, on balance, the clinical benefit has not been sufficiently demonstrated to justify safe patient exposure in the proposed population group.

Outcome

Based on a review of quality, safety and efficacy, TGA rejected the current application to extend the indications of Cymbalta 30 mg and 60 mg capsules to include

The treatment of chronic somatic pain.

The alternative indication of

The treatment of chronic musculoskeletal pain

that had been proposed during the evaluation process was also rejected. This decision has been taken on the grounds that on balance, the clinical benefit has not been sufficiently demonstrated to justify the risks from patient exposure in the proposed population group.

This decision was based on the evaluation of information and data provided with the original submission letter and with any subsequent correspondence and submissions relating to the original submission. In making this decision, the Delegate also considered the advice provided by the Prescription Medicines Advisory Committee (ACPM) at its 281st meeting that Cymbalta had a negative benefit-risk profile for the proposed indication.

Reasons for decision

Firstly, the term "somatic pain" is not well defined, nor used consistently in clinical practice. It is therefore an inappropriate term for identification of subjects to be assessed in clinical trials to determine efficacy, or for inclusion as an indication for use.

The alternative proposed indication of "musculoskeletal pain", while more accurately describing the conditions causing pain that were assessed in the clinical trial program, is also rejected due to an insufficient demonstration of clinical benefit to justify the risks from exposure to duloxetine in the proposed population group.

Secondly, clear evidence of efficacy in a well defined population group was not provided in the submission. Individuals enrolled in clinical trials must represent the demographic and clinical characteristics of the target population. The pivotal studies included only individuals with chronic pain due to osteoarthritis of the knee or with chronic low back pain who did not consistently require regular analgesia.

The Delegate was satisfied that some degree of efficacy of duloxetine in selected individuals with chronic musculoskeletal pain has been demonstrated. The Delegate noted that for individuals with chronic low back pain assessed in the clinical trial program (LOCF analysis) 56.0% given duloxetine and 45.3% given placebo had at least a 30% reduction from baseline in pain severity ($p = 0.002$; NNT 9.3). Thus one person in 9 to 10 with chronic low back pain who did not require regular analgesia is anticipated to gain clinically significant benefit from the use of duloxetine. The benefits for other patients with chronic musculoskeletal pain, other than a similar patient group with osteoarthritis of the knee, have not been assessed. The Delegate was not satisfied that the efficacy demonstrated by duloxetine in the clinical trial program can be extrapolated to other patients with chronic musculoskeletal pain including patients with chronic low back pain who require regular analgesia.

Thirdly, EU guideline *Note for Guidance on Clinical Investigation of Medicinal Products for Treatment of Nociceptive Pain*[1] has been adopted by the TGA. In this guideline, pain due to osteoarthritis and low back pain are provided as examples of conditions suitable for assessment of chronic mild to moderate pain. The clinical trial program explored efficacy only in individuals with osteoarthritis of the knee or low back pain. The Delegate did not consider that efficacy of duloxetine in individuals with severe pain of musculoskeletal origin, or any other origin, has been adequately demonstrated.

Fourthly, the submitted clinical trials have not adequately addressed the clinical context in which duloxetine is proposed to be administered. The clinical trials were placebo-controlled and had no active comparator. In addition there were no studies assessing concurrent use of duloxetine with other treatments for chronic pain. The Delegate did not consider that the circumstances in which duloxetine may be of clinically significant benefit have been sufficiently elucidated. The side effect profile for this product is significant, and while the safety issues identified in the studies matched those identified in controlled clinical trials for other indications of this product, on balance, the clinical benefit has not been sufficiently demonstrated to justify exposure of the proposed population to duloxetine.

Fifthly, there was inadequate investigation into dosing in patients with reduced hepatic capacity in view of the 70% change in clearance in patients with moderate hepatic impairment. This presents significant risk for the proposed patient population.

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Reference/Publication #