17 November 2011
EMA/285264/2012
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Ariclaim, Cymbalta, Xeristar

duloxetine

Procedure No.: EMEA/H/C/xxxx/WS/0076

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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1. Scope of the variation and changes to the dossier

Scope of the variation:	Update of Summary of Product Characteristics and Package Leaflet Addition of the indication 'Treatment of chronic low back pain or chronic osteoarthritic pain of at least moderate severity in patients for whom the prolonged use of NSAIDs is not appropriate or is contraindicated' with subsequent changes to the SmPC sections 4.1, 4.2, 4.4, 4.8 and 5.1. The Package Leaflet would be amended accordingly. This application was submitted following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.
Rapporteur: Co-Rapporteur:	Arantxa Sancho-Lopez Tomas Salmonson
Product presentations affected:	See Annex A to the Opinion

2. Steps taken for the assessment

Step	Step date
Submission date:	13 October 2010
Start of procedure:	21 November 2010
Co-Rapporteur's preliminary assessment report circulated on:	17 January 2011
Rapporteur's preliminary assessment report circulated on:	17 January 2011
Rapporteur's updated assessment report circulated on:	11 February 2011
Request for supplementary information and extension of timetable adopted by the CHMP on :	17 February 2011
MAH's responses submitted to the CHMP on:	18 March 2011
Rapporteur's preliminary assessment report on the MAH's responses circulated on:	29 April 2011
Rapporteur's updated assessment report circulated on:	13 May 2011
Request for supplementary information and extension of timetable adopted by the CHMP on :	19 May 2011
MAH's responses submitted to the CHMP on:	28 June 2011

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Step	Step date
Rapporteur's and Co-Rapporteur's joint assessment report circulated on:	8 July 2011
An oral explanation to the CHMP took place on:	19 July 2001
CHMP opinion:	21 July 2011
Re-examination request letter received on:	2 August 2011
Grounds for re-examination received on:	23 September 2011
Rapporteur's preliminary assessment report circulated on:	25 October 2011
Co-Rapporteur's preliminary assessment report circulated on:	8 November 2011
Ad hoc expert group meeting held on:	8 November 2011
Rapporteur's and Co-Rapporteur's joint assessment report circulated on:	10 November 2011
An oral explanation to the CHMP took place on:	15 November 2011
CHMP Opinion:	17 November 2011

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3. Scientific discussion

3.1. Introduction

About the product

Duloxetine is a combined serotonin (5-HT) and noradrenaline (NA) reuptake inhibitor. It weakly inhibits dopamine reuptake with no significant affinity for histaminergic, dopaminergic, cholinergic and adrenergic receptors. Duloxetine dose-dependently increases extracellular levels of serotonin and noradrenaline in various brain areas of animals.

The duloxetine-containing products are approved for the following indications:

i. Ariclaim – treatment of diabetic peripheral neuropathic pain in adults; approved on 11 August 2004;

ii. Cymbalta and Xeristar – treatment of major depressive disorder, diabetic peripheral neuropathic pain in adults, generalised anxiety disorder; approved on 17 December 2004;

iii. Yentreve – treatment of moderate to severe Stress Urinary Incontinence (SUI) in women; approved on 11 August 2004.

The products concerned by this variation are listed below.

Medicinal product:	International non-proprietary name	Presentations:
Ariclaim	duloxetine	See Annex A
Cymbalta	duloxetine	See Annex A
Xeristar	duloxetine	See Annex A

About the disease

Chronic pain is defined as pain that is present on most days and persists for longer than the normal tissue healing time. It is a dynamic state in which different pathophysiological mechanisms play different roles at different times in individually different subjects. More than 37 million people worldwide suffer from chronic pain, with more than a third of the European Union population experiencing chronic pain at some point in their lives. CLBP and OA are 2 of the most prevalent types of chronic pain.

Treatment guidelines / recommendations

Three CHMP guidelines are particularly relevant for the development of products in the intended indication 'chronic somatic pain': Note for "Guidance on clinical investigation of medicinal products for treatment of nociceptive pain" (CPMP/EWP/612/00), "Guideline on clinical investigation of medicinal products used in the treatment of osteoarthritis" (CPMP/EWP/784/97 Rev. 1), and "Guideline on clinical medicinal products intended for the treatment of neuropathic pain" (CPMP/EWP/252/03).

Scientific advice was requested on two occasions by the MAH, in 2005 in relation to the development programme for the treatment of chronic low back pain (CLBP) (EMEA/H/SA/75/4/2005/II), and in 2006 in relation to the development programme for the treatment of moderate to moderately severe chronic pain (EMEA/H/SA/75/3/FU/1/2006/II).

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Information on Paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/268/2010 for the following condition:

- Treatment of chronic pain

on the granting of a product-specific waiver.

3.2. Clinical aspects

3.2.1. Introduction

- Tabular overview of clinical studies

The application is based on the data from the following trials:

Table 1. Tabular overview of clinical studies in chronic somatic pain.

Study ID	**Design Type**	**Number of Patients**	**Key Entry Criteria**	**Primary Endpoint(s)**
OA-FG	13 weeks; Dose escalation of non-responders[a] at Wk 7	DLX: 128 (60 mg QD first 7 wks; 60/120 mg QD last 6 wks) Placebo: 128	- ACR-classification: Idiopathic OA knee pain - ≥4 score on 24-hour average pain ratings from patient diaries - NSAID/PCM users: stable dose[c]	Reduction in 24-hour average pain rating of the BPI, all DLX patients
OA-EP	13 weeks; Dose Re-randomisation at Wk 7	DLX: 111 (60 mg QD first 7 wks; 60/120 mg QD last 6 wks) Placebo: 120	*Same as OA-FG*	Reduction in weekly mean of 24-hour average pain ratings from patient diaries; all DLX patients
CLBP-EN	13 weeks; Dose escalation of nonresponders[a] at Wk 7; 41-week extension	DLX: 115 (60 mg QD first 7 wks; 60/120 mg QD last 6 wks) Placebo: 121	- a clinical diagnosis of CLBP - pain present on most days ≥6 months. - Class 1 or Class 2 per QTF-SD - ≥4 score on weekly mean of 24-hour average pain ratings from patient diaries - NSAID/PCM users: stable dose[c]	Reduction in 24-hour average pain rating of the BPI; all DLX patients
CLBP-EO	13 weeks; Fixed-dose	DLX 20 mg QD: 59 DLX 60 mg QD: 116 DLX 120 mg QD: 112Placebo: 117	*Same as CLBP-EN*	Reduction in weekly mean of 24-hour average pain ratings from patient diaries: DLX 60mg QD
CLBP-GC	12 weeks; Fixed-dose	DLX 60 mg QD: 198 Placebo: 203	*Same as CLBP-EN* **except** - only episodic NSAID/PCM use (≤ 3 consecutive days)[e] - ≥4 score on BPI average pain	Reduction in 24-hour average pain rating of the BPI

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Abbreviations: BPI = Brief Pain Inventory; DLX = duloxetine; ID = identification; QD = once daily; PCM =paracetamol (acetaminophen); NSAID = nonsteroidal anti-inflammatory drug
Source:
a Non-responders were defined as those patients who experienced less than 30% reduction from baseline to endpoint in the 24-hour average pain score.
c An NSAID user is defined as a patient who takes an NSAID for ≥14 days per month for 3 months prior to study entry.
e Episodic use was defined as taking an NSAID or acetaminophen for no more than 3 consecutive days and not to exceed 20 total days during the Treatment Phase (Visits 2 through 6).

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

3.2.2. Clinical pharmacology

Pharmacokinetics

No new pharmacokinetic studies have been conducted in support of this application.

Pharmacodynamics

No new clinical pharmacology studies have been conducted in support of this application.

3.2.3. Clinical efficacy

Introduction

The application is supported by the safety and efficacy data from 839 patients exposed to duloxetine (representing 171.9 patient-years of exposure) from 2 clinical studies of osteoarthritis knee pain, 3 clinical studies of chronic low back pain (CLBP), and a long-term extension of study CLBP-EN.

All the studies submitted had a placebo controlled phase of 12 to 13 weeks; Study CLBP-EN (HMEN) had a long-term, uncontrolled, extension phase of 41 weeks to assess the maintenance of effect. Additionally, safety data from the approved indication for diabetic peripheral neuropathic pain, as well as from other studied indications, are included in this submission.

Dose response study

No formal dose finding studies have been performed.

The final doses used in the pivotal trials were chosen based on experience with the medicinal product in other pain disorders. The CHMP considered the dose selection acceptable.

Main studies

Methods

Study Participants

The table below presents baseline characteristics of all enrolled patients.

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Table 2. Baseline characteristics of study participants.

	OA-FG	OA-EP	CLBP-EN	CLBP-EO	CLBP-GC
Age in years (Mean)	**62.5**	**62.3**	**51.5**	**53.9**	**54.1**
Gender (%): **Female**	**76.6**	**65.4**	**61.0**	**57.43**	**61.3**
Ethnicity (%)					
African	**1.2**	**5.2**	**5.1**	**8.2**	**2.5**
Caucasian	**97.7**	**84.0**	**74.6**	**79.7**	**95.3**
East Asian	**0.4**	**1.3**	**0.9**	**0.7**	**-**
Hispanic	**0.8**	**8.2**	**18.6**	**10.2**	**2.0**
Native American	**0.0**	**1.3**	**0.9**	**0.3**	**0.2**
West Asian	**0.0**	**0.0**	**0.0**	**1.0**	
Average Pain Severity - 24-hour average pain rating (Mean)	**6.0**	**6.1**	**6.0**	**6.2**	**5.8**
NSAID Status (%)**: Yes**	**39.1**	**50.7**	**31.4**	**41.3**	**-**
Duration of Pain in Years (Mean)	**7.4**	**9.2**	**9.2**	**11.7**	**8.5**
WOMAC Physical Function Subscale Score[a]	**35.8**	**38.6**	**-**	**-**	**-**
WOMAC Total Score[a]	**49.6**	**53.4**	**-**	**-**	**-**
RMDQ-24 (Mean)[a]	**-**	**-**	**10.3**	**8.9**	**9.5**

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For all studies the following were required:

- the same level of baseline pain for entry into the study (24-hour average pain rating of 4 or greater based on an 11-point numerical rating scale, which is considered as moderate pain);

- patients with BMI below 40;

- excluded diagnoses of MDD (as determined by Mini International Neuropsyquiatric Interview (MINI));

- excluded concomitant use of anticonvulsants, antidepressants, antimanics, antipsychotics, capsaicin, cimetidine, lidocaine, monoamine oxidase (MAO) inhibitors, psychostimulants, quinolone class of antibiotics, triptans, tryptophan, and tramadol.

In all studies the treatment groups seemed to be fairly well balanced with respect to demographics as well as disease-related characteristics with the exception of study OA-FG in which there were more females in the placebo group. However, this imbalance was not likely to introduce any bias in favour of duloxetine since the effect tended to be more pronounced in females. Of note the average age of participants was 52-63 years.

Osteoarthritis studies

In the 2 OA studies male or female patients at least 40 years of age who meet the clinical and radiographic disease diagnosis criteria based upon American College of Rheumatology (ACR) classification of idiopathic OA of the knee (knee pain, radiographic evidence of osteophytes, and at least 1 of the following 3 conditions: age >50 years, morning stiffness <30 minutes, or crepitus) were included. Patients were required to have pain lasting for at least 14 days of each month for 3 months prior to the study.

Chronic low back pain studies

For the 3 CLBP studies male or female patients of at least 18 years of age, were required to have a clinical diagnosis of CLBP (as their primary painful condition) with pain present on most days for at

least 6 months. Pain was to be either restricted to the lower back or associated with radiation to the proximal portion of the lower limb only (corresponding with Class 1 and Class 2 according to the classification from Quebec Task Force on Spinal Disorders). In order to exclude neuropathic pain, patients could NOT have any of the following:

- neurological radicular signs;

- presumptive compression of a spinal nerve root on a simple radiogram;

- compression of a spinal nerve root confirmed by specific imaging techniques (for example, computerized tomography [CT]);

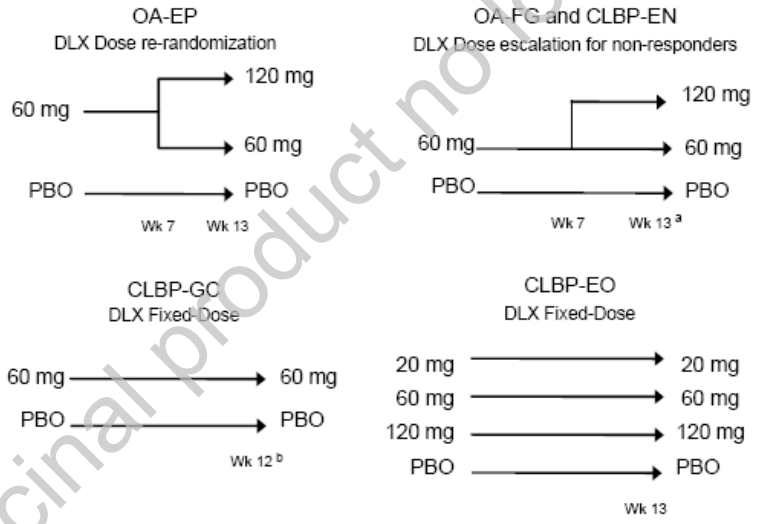
- spinal fracture, spondylolisthesis Grade 3 or 4, tumour, abscess or acute pathology in the low back/abdominal region, which were required to be confirmed by historical record of imaging studies (X-ray, CT, or magnetic resonance imaging [MRI]).

Treatments

All studies had a placebo controlled arm. All evaluated duloxetine doses of 60 mg to 120 mg daily (except study CLBP-GC which only included duloxetine 60 mg QD).

All studies consisted on three study periods:

- Study period I (screening): 5 to 9-day period where patients were screened for eligibility.
- Study period II was slightly different across studies



Abbreviations: DLX = duloxetine; PBO = placebo; V = visits, Wks = weeks.
a For Study CLBP-EN, after 13 weeks of treatment, patients were allowed to continue into the 41-week extension treatment.
b Study was 1 week shorter since it did not include a dose-titration step during the first weeks of treatment.

- Study period III (Taper Phase): patients who could not tolerate duloxetine 60 mg or 120 mg QD during the treatment phase were discontinued from the study and entered study period III to minimise discontinuation-emergent adverse events (DEAEs) if they have taken study treatment for at least 2 weeks or for at least 1 week in CLBP-EN and CLBP-GC. The taper phase was included to allow gradual reduction of study medication.

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Apart from study CLBP-GC, patients were allowed to remain on their regular dose of NSAIDs or acetaminophen, provided that they were using them at the time of enrolment. Patients were instructed to remain on the regular dose throughout the course of the study. NSAIDs or acetaminophen were also allowed as rescue therapy in all studies.

Randomisation was stratified by NSAID use in all studies (except for study CLBP-GC) allowing descriptive comparison of patients concomitantly using NSAIDs with duloxetine and those on duloxetine alone. An NSAID user was defined as a patient who takes an NSAID for ≥ 14 days per month for 3 months prior to study entry. Prior to randomisation, patients were required to wash out of all other analgesics, anticonvulsants, and antidepressants. Use of non-pharmacological therapy was allowed provided this was being used at the time of enrolment; the studies did not collect data on use of non-pharmacological therapies.

Objectives

The objective of the studies was to assess the duloxetine's efficacy in reducing pain in patients with osteoarthritic pain and chronic low back pain, and safety after 12 or 13 weeks of treatment.

Outcomes/endpoints

The primary outcome measure for all studies was change in pain severity, assessed using average pain ratings on an 11-point numerical rating scale (ranging from 0 for no pain to 10 for worst pain imaginable) from baseline to the end-of-treatment.

The weekly mean of 24-hour average pain rating (collected from electronic patient diaries) was originally specified as the primary efficacy outcome for all chronic somatic pain studies except for study CLBP-GC. However, the overall electronic diary compliance rate was low in the first two studies analysed (68% for Study OA-EP and 49% for Study CLBP-EO). Therefore, the 24-hour average pain item rating collected from Brief Pain Inventory (BPI) at study visits was specified as the primary efficacy outcome for all other studies (OA-FG, CLBP-EN, and CLBP-GC).

All studies employed a gatekeeper strategy for sequential testing of the following secondary objectives:

- effect of duloxetine versus placebo on patients' perceived improvement during the treatment phase as measured by the PGI-Improvement (PGI-I).

- effect of duloxetine versus placebo on the change in patients' physical function during the treatment phase as measured by the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) physical function subscale (studies OA-FG and OA-EP) or by the Roland-Morris Disability Questionnaire (RMDQ-24), a questionnaire addressing intensity of CLBP and its interference with activities of daily living (studies CLBP-EN, CLBP-EO, and CLBP-GC).

Response rates (using both ≥30% and ≥50% reduction from baseline at endpoint criteria) were included as a secondary endpoint in all studies.

Other (non-gatekeeper) secondary objectives were: 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.

To evaluate whether the reduction in pain was a direct analgesic effect and was independent of treatment effect on mood the Athens Insomnia Scale (studies CLBP-EN, CLBP-EO and CLBP-GC); Beck Depression Inventory II and Hospital Anxiety and Depression Scale (studies CLBP-EN, CLBP-EO, OA-EP, OA-FG) and the Profile of Mood States_ Brief Form (study CLBP-GC) were used.

To assess the impact of treatment with duloxetine versus placebo on patient-reported health outcomes the following tools were used: Euro-Quality of Life Questionnaire-5 Dimensions (CLBP-GC), 36-Item

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Short Form Health Survey and Work Productivity and Activity Impairment Instrument (studies CLBP-EN and CLBP-GC).

Randomisation and blinding (masking)

Patients were randomly assigned to duloxetine or placebo treatment in a 1:1 ratio using an interactive voice response system (IVRS). Randomisation was stratified by study site and NSAID use (yes/no). A 1:1 ratio was used in the re-randomisation in study OA-EP as well. All study drugs used were identical in colour, shape, smell, and taste, and all patients took the same number of capsules regardless of treatment group or dose.

Statistical methods

All analyses were conducted on an ITT basis, i.e. data were analysed by the treatment groups to which patients were randomly assigned even if the patient did not take the assigned treatment or did not comply with the protocol. To be included in the efficacy analyses patients had to have a baseline measurement and at least one non-missing post-baseline measurement.

A likelihood based mixed effects model repeated measures (MMRM) analysis was used to analyse the primary efficacy endpoint in all the studies.

The MAH predefined to use the best of the series of (co)variance matrix according to the Akaike's information criterion for the MMRM analyses. The analysis performed by the MAH included the fixed categorical effects of treatment, NSAID use (Yes/No), investigator, visit, and treatment-by-visit interaction, as well as the continuous fixed covariates of baseline score and baseline-by-visit interaction. In addition to MMRM, analyses of covariance (ANCOVA) using change from baseline to BOCF endpoint and change from baseline to LOCF endpoint were prespecified as sensitivity analyses methods for the primary efficacy objective.

For response rate (30% and 50% pain reduction) and the key secondary outcomes used to assess gatekeeper secondary objectives, analysis of LOCF endpoint (a priori specified analysis method), MMRM analysis (for outcomes collected at multiple post-baseline visits) and analysis of BOCF endpoint (for sensitivity analyses) were performed.

Three regression models were used to estimate the direct effect of treatment and the indirect effects though change in BDI-II and HADS-A on the change on 24-hour average pain score.

Interim Analyses

In Study CLBP-EN, when all subjects completed participation in the acute phase, the database was validated and locked to perform statistical analysis on all subjects (since the study continues with the extension phase, this analysis is referred to as an interim analysis). However, no adjustment to significance level was necessary since this was the only (final) analysis of the double-blind, placebo-controlled part of the study.

Results

Participants flow

The participants flow is presented in the table below.

Table 3. Participants flow in OA and CLBP studies.

Study ID	Dose	No of patients randomised	No of patients completed	No of patients discontinued

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OA-FG	Total DLX 60/120 mg PBO	256 128 128	204 93 111	52 35 17
OA-EP	Total DLX 120 mg DLX 60 mg PBO	231 43* 46* 120	173 38 39 96	36 5 7 24
CLBP-EN	Total DLX 60/120 mg PBO	236 115 121	182 84 98	54 31 23
CLBP-EO	Total DLX 120 mg DLX 60 mg DLX 20 mg PBO	404 112 116 59 117	267 62 80 43 82	137 50 36 16 35
CLBP-GC	Total DLX 60mg PBO	401** 197 200	302 146 156	95 51 44

*Following re-randomisation 22 patients discontinued from duloxetine group.

**Four patients discontinued following randomisation and before treatment.

Overall, the discontinuation rate was higher in the duloxetine arms as compared to placebo with the exception of the study OA-EP. The treatment-related adverse events were the main reason for the discontinuation in the duloxetine groups.

Conduct of the study

All studies included investigational sites from European countries except for the study CLBP-EO.

In studies OA-EP and CLBP-EO electronic patient diaries were used to record pain severity. As the overall electronic patient diary compliance over 13 weeks was low (68% and 49%, respectively), the primary endpoint of studies CLBP-EN and OA-FG was changed from the weekly mean score of 24-hour average pain severity ratings as collected from patient diaries to the BPI 24-hour average pain scores.

Based on the change in the primary efficacy measure, some secondary efficacy analyses were changed. Response rate analyses and subgroup analyses of the weekly mean of 24-hour average pain score from patient diaries were changed to the BPI average pain score. The BPI average pain score also replaced the weekly mean of 24-hour average pain score from diaries for the path analysis of direct analgesic effect. Statements regarding study power were also revised.

Numbers analysed

Patients who did not have either a baseline or post-baseline measurement were excluded from the efficacy analyses.

Study OA-FG: Of the 256 randomised patients, 248 were analysed for the primary efficacy measure; 8 patients were excluded from the efficacy analyses.

Study OA-EP: Data from 108 of the 111 patients assigned to duloxetine and 119 of the 120 patients randomly assigned to placebo were analysed for the primary efficacy measure; 4 patients were excluded from the efficacy analyses.

Study CLBP-EN: Of the 236 randomised patients only 182 completed and 224 were analysed for the primary efficacy measure; 12 patients were excluded from efficacy analyses.

Study CLBP-EO: Of the 404 randomised patients, 16 patients were excluded from the primary efficacy measure analysis. Data from 388 patients were used in the efficacy analyses.

Study CLBP-GC: Of the 401 randomised patients, 394 were analysed for the primary efficacy measure; 7 patients were excluded from the primary analysis.

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Outcomes and estimation

Main studies

Study OA-FG

Table 4. Analysis of the primary efficacy variable.

BPI 24-hour average pain (collected from study visits)				
Study	**Analysis**	**Treatment Group**	**LSMean Change (SE)**	**p-Value**
OA-FG	MMRM	DLX 60/120 QD	-2.72 (0.20)	<.001
		Placebo	-1.88 (0.18)	
	BOCF	DLX 60/120 QD	-2.23 (0.20)	.013
		Placebo	-1.63 (0.19)	
	LOCF	DLX 60/120 QD	-2.51 (0.20)	<.001
		Placebo	-1.72 (0.18)	

The MMRM, BOCF and LOCF analyses of the primary endpoint showed a statistically significant improvement in the BPI average pain score in the duloxetine treated-patients compared with the placebo-treated patients.

Table 5. Analysis of secondary efficacy variables.

Response Rates of Brief Pain Inventory 24-hour Average Pain Score						
Study	**Analysis**	**Treatment Group[a]**	**30% Response Rate (%)**	**p-Value**	**50% Response Rate (%)**	**p-Value**
OA-FG	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	

30% response rate was statistically significant in both BOCF and LOCF analyses, while inconsistent results were observed for the 50% response rate.

Subgroup analyses according to NSAIDs use

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 Trt.vs. Placebo
Use of NSAIDs	.233	.119	No	150	1)PLACEBO	74	6.05	1.28	-1.50	2.11	-1.34	0.25	
					2)DLX60/120QD	76	6.03	1.35	-2.49	1.94	-2.37	0.24	.001
			Yes	98	1)PLACEBO	53	6.30	1.22	-2.17	2.05	-2.08	0.32	
					2)DLX60/120QD	45	6.20	1.46	-2.62	2.09	-2.49	0.36	.291

Statistically significant result was observed in the subgroup of patients not taking the NSAIDs regularly.

Gatekeeper analysis

In the LOCF analysis of PGI-I a lower score was observed in duloxetine groups as compared to placebo, however the difference was not statistically significant.

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In the LOCF analysis a statically significant decrease in the mean WOMAC score change was observed in the duloxetine arm compared to placebo arm.

Path analysis for direct analgesic effect

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

Study CLBP-EN

Table 6. Analysis of the primary efficacy variable.

BPI 24-hour average pain (collected from study visits)				
Study	**Analysis**	**Treatment Group**	**LSMean Change (SE)**	**p-Value**
CLBP-EN	MMRM	DLX 60/120 QD	-2.32 (0.22)	.004
		Placebo	-1.50 (0.21)	
	BOCF	DLX 60/120 QD	-1.86 (0.20)	.019
		Placebo	-1.25 (0.20)	
	LOCF	DLX 60/120 QD	-2.09 (0.21)	.019
		Placebo	-1.45 (0.21)	

Results from the primary efficacy measure showed significant differences between the duloxetine group and the placebo group during the acute phase favouring the duloxetine arm. Additional analyses using the BOCF and LOCF approach showed also positive results in favour of duloxetine.

Table 7. Analysis of secondary efficacy variables.

Response Rate based on Brief Pain Inventory 24-hour Average Pain Score						
Study	**Analysis**	**Treatment Group[a]**	**30% Response Rate (%)**	**p-Value[b]**	**50% Response Rate (%)**	**p-Value[b]**
CLBP-EN	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	

The BOCF analysis of the 50% response rate was statistically significant. Results of other analyses showed a trend in favour of duloxetine.

Subgroup analyses according to NSAIDs use

Subgroup	Treatment by Subgroup p-Value	Sub-group p-Value	Strata	N	Treatment	Baseline n	Baseline Mean	Baseline SD	Change Mean	Change SD	Change LSMean	Change SE	p-Value Trt.vs. Placebo
Use of NSAIDs	.143	.841	No	156	1)PLACEBO	79	5.97	1.67	-1.24	2.26	-1.00	0.32	
					2)DLX60/120QD	77	5.73	1.67	-2.01	2.26	-1.94	0.30	.006
			Yes	68	1)PLACEBO	36	5.83	1.70	-1.86	2.21	-1.84	0.36	
					2)DLX60/120QD	32	6.34	1.38	-2.25	1.85	-1.65	0.39	.693

Statistically significant result was observed in the subgroup of patients not taking the NSAIDs regularly.

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Gatekeeper analyses

The analysis of patient's perceived improvement as measured by PGI-I with the LOCF approach demonstrated that patients in the duloxetine treatment group had a significantly greater improvement compared with patients in the placebo treatment group. The BOCF results were also significant in favour of duloxetine. Results were also significant for Roland-Morris Disability Questionnaire.

Path analysis for direct analgesic effect

The direct treatment effect of duloxetine (80.44% of the total effect) was statistically significant. The indirect effect of duloxetine on pain approached 20%.

Extension phase: Maintenance of effect

Maintenance of effect was evaluated in the 41 week uncontrolled extension phase of study CLBP-EN in 58 patients. The hypothesis of maintained effect was tested in a non-inferiority analysis including responders (>30% reduction of baseline pain score) on duloxetine treatment during the double-blind phase of the study. Non-inferiority would be concluded if the upper bound of a 97.5% one-sided confidence interval for the change from the last available pain score during the double-blind phase to the last available score during the extension phase was lower than 1.5. The observed upper bound was -0.45. The maintenance of effect was studied in a limited number of patients.

Study CLBP-GC

Table 8. Analysis of the primary efficacy variable.

BPI 24-hour average pain (collected from study visits)				
Study	**Analysis**	**Treatment Group**	**LSMean Change (SE)**	**p-Value**
CLBP-GC	MMRM	DLX 60 QD	-2.48 (0.16)	.001
		Placebo	-1.80 (0.15)	
	BOCF	DLX 60 QD	-1.92 (0.15)	.004
		Placebo	-1.37 (0.15)	
	LOCF	DLX 60 QD	-2.25 (0.15)	.002
		Placebo	-1.65 (0.15)	

Results from all three analyses of changes in the primary efficacy measure showed significant differences between the duloxetine group and the placebo group.

Table 9. Analysis of secondary efficacy variables.

Response Rate based on Brief Pain Inventory 24-hour Average Pain Score						
Study	**Analysis**	**Treatment Groupa**	**30% Response Rate (%)**	**p-Valueb**	**50% Response Rate (%)**	**p-Valueb**
CLBP-GC	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	

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Significantly more patients in the duloxetine group had at least 50% average pain reduction, compared with patients in the placebo group. Results for 30% response rate were not significant.

Gatekeeper analyses

The analysis of PGI-I with both LOCF and BOCF approach showed significant results. The results from RMDQ-24 were not statistically significant.

The path analysis was not performed in this study.

Ancillary analyses

In response to the CHMP's request to further justify the choice of sensitivity analyses presented initially, the MAH provided the results of two additional sensitivity analyses in all randomised patients from studies OA-EP (HMEP), OA-FG (HMFG), CLBP-EN (HMEN), CLBP-GC (HMGC).

Table 10. BPI 24-Hour Average Pain Score. MMRM Analysis and Requested Sensitivity Analyses*.

Study	Analysis	Treatment Group	LSMean Change (SE)	p-value[a]
HMEP	MMRM in CSR	DLX 60/120 QD	-3.01 (0.22)	<.001
		Placebo	-1.89 (0.20)	
	Sensitivity analysis I	DLX 60/120 QD	-2.88 (0.23)	<.001
		Placebo	-1.81 (0.22)	
	Sensitivity analysis II	DLX 60/120 QD	-3.01 (0.22)	<.001
		Placebo	-1.90 (0.20)	
HMFG	MMRM in CSR	DLX 60/120 QD	-2.72 (0.20)	<.001
		Placebo	-1.88 (0.18)	
	Sensitivity analysis I	DLX 60/120 QD	-2.69 (0.20)	.002
		Placebo	-1.85 (0.19)	
	Sensitivity analysis II	DLX 60/120 QD	-2.73 (0.20)	<.001
		Placebo	-1.88 (0.19)	
HMEN	MMRM in CSR	DLX 60/120 QD	-2.32 (0.22)	.004
		Placebo	-1.50 (0.21)	
	Sensitivity analysis I	DLX 60/120 QD	-2.29 (0.22)	.007
		Placebo	-1.48 (0.20)	
	Sensitivity analysis II	DLX 60/120 QD	-2.32 (0.21)	.003
		Placebo	-1.50 (0.20)	
HMGC	MMRM in CSR	DLX 60 QD	-2.48 (0.16)	.001
		Placebo	-1.80 (0.15)	
	Sensitivity analysis I	DLX 60 QD	-2.61 (0.15)	.001
		Placebo	-1.89 (0.15)	
	Sensitivity analysis II	DLX 60 QD	-2.49 (0.16)	.001
		Placebo	-1.79 (0.15)	

Abbreviations: DLX = duloxetine; LSMean = least-squares mean; MMRM = mixed-models repeated measures; QD = once daily; SE = standard error.

*sensitivity analysis I = model with only the treatment and treatment-by-visits factors as an adjusted analysis and sensitivity analysis II = with the same original model but without the baseline-by-visit interaction.

a p-value comparison with placebo.

Results from the MMRM analyses and both sensitivity analyses showed a similar trend.

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Furthermore, in the course of the procedure the MAH submitted additional analyses including primary efficacy outcome analysis and responder analyses in subgroups of patients defined as non-NSAID users (i.e., not taking NSAIDs regularly) performed on data from pooled OA and pooled CLBP studies. These data were submitted in support of the restricted indication.

Table 11. Mean change BPI average pain in NSAID non-users only (all randomised patients).

Study	N		difference (DLX-PBO)	p-value DLX vs. PBO[a]
	DLX	PBO		
OA Studies				
HMEP (DLX60/120)	53	60	-0.60	.147
HMFG (DLX60/120)	80	75	-0.67	.026
CLBP Studies				
HMGC (DLX60)[b]	198	203	-0.55	.004
HMEN (DLX60/120)	80	82	-0.54	.084
HMEO (DLX60)	65	73	-0.64	.087
HMEO (DLX120)	61	73	0.22	.540

Abbreviations: ANCOVA = analysis of covariance; BPI = Brief Pain Inventory; DLX = duloxetine; N = Number of randomised patients (NSAID nonusers) with a baseline value; OA = osteoarthritis of the knee; PBO = placebo. HMEP = OA-EP; HMFG = OA-FG; HMGC = CLBP-GC; HMEN = CLBP-EN; HMEO = CLBP-EO

a p-value is from ANCOVA including terms for Treatment, Pooled Investigator, and Baseline.

b Therapeutic NSAID use not allowed; therefore, all patients were NSAID nonusers.

Statistically significant differences were observed in two studies, study OA-FG and CLBP-GC, while trend in favour of duloxetine was seen in studies CLBP-EN and CLBP-EO.

Table 12. Response rates for the 24-Hour average pain score in NSAID non-users only (pooled data).

Indication	Treatment	30% response[a] n (%)	p-Value	50% response[a] n (%)	p-Value[b]
OA	DLX 60/120 mg QD (N=134)	71 (53.0)	.044	54 (40.3)	.008
	Placebo (n=136)	56 (41.2)		35 (25.7)	
CLBP	DLX 60/120 mg QD (N=404)	182 (45.0)	.018	155 (38.4)	<.001
	Placebo (n=359)	133 (37.0)		93 (25.9)	

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

a Response defined based on the percent change from baseline to endpoint of BPI average pain score.

b p-value is based on Cochran Mantel-Haenszel test.

In pooled data from all studies the BOCF analysis showed statistically significant results for both response rates in all randomised patients who were NSAID non-users (i.e., not taking NSAIDs regularly) at the end of treatment. When analysed individually studies OA-EP, CLBP-GC and CLBP-EN

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showed statistically significant results in favour of duloxetine in the 50% response rate group, while for 30% response rate a trend was observed in studies OA-FG, CLBP-EN, CLBP-EO.

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Summary of main studies

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections). The presented secondary analyses focus on data from gatekeeper analyses, responder analyses and quality of life analyses.

Table 13. Summary of Efficacy for trial OA-FG.

Title: Duloxetine 60 to 120 mg versus Placebo in the Treatment of Patients with Osteoarthritis Knee Pain		
Study identifier	F1J-MC-HMFG(b)	
Design	A Phase 3, 13-week, multicentre, double-blind, randomised, placebo-controlled study	
	Duration of main phase:	13 weeks (including 1 week of titration for duloxetine patients at 30 mg per day)
	Duration of Run-in phase:	1-week screening for eligibility
	Duration of Extension phase:	2-week taper phase
Hypothesis	Superiority	
Treatments groups	Duloxetine	Duloxetine 30 mg QD (titration purposes only), 60 mg QD, or 120 mg QD given orally once daily as one or two 60 mg capsule(s) Planned: 115; Randomised: 128; Completed: 93
	Placebo	Matching dosing scheme Planned: 115; Randomised: 128; Completed: 111
Endpoints and definitions	Primary endpoint	Reduction of pain severity as measured by the BPI (Brief Pain Inventory) 24-hour average pain scores (referred to as the BPI average pain scores)
	Secondary gatekeeper analysis	• Evaluation of duloxetine 60/120 mg QD versus placebo on patients' perceived improvement during the 13-week treatment phase as measured by Patient Global Impressions of Improvement (PGI-Improvement) • Evaluation of duloxetine 60/120 mg QD versus placebo on the change in patients' functioning during the 13-week treatment phase as measured by the Western Ontario and McMaster Universities (WOMAC) physical function subscale
	Secondary endpoint	• Weekly mean of the 24-hour average pain score and worst pain score collected from diary • Clinical Global Impressions of Severity (CGI-S) • WOMAC pain and stiffness subscales • BPI - Severity and Interference • Response to treatment, as defined by a 30% and 50% reduction of BPI average pain score • Medical Outcomes Study Short Form-36 (SF-36) • EuroQoL Questionnaire - 5 Dimension (EQ-5D) • Beck Depression Inventory – II (BDI-II), and Hospital Anxiety and Depression Scale (HADS) anxiety subscale (HADS-A) (to evaluate direct analgesic effect of duloxetine and its independence of treatment effect on mood) • Safety evaluation • Assessment of effect of duloxetine 120 mg QD in patients who did not respond to duloxetine 60 mg for 6 weeks, as measured by reduction of BPI average pain, response to treatment, adverse events (AEs) reported as reasons for discontinuations
Database lock	04 May 2008	

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Analysis description	**Primary Analysis** *Reduction of pain severity from baseline to endpoint as measured by Brief Pain Inventory (BPI) 24-hour average pain*		
Analysis population and time point description	Intent to treat		
	Treatment group	Duloxetine 60/120 mg QD	Placebo
	Number of subject	MMRM N=100 BOCF N=121 LOCF N=121	MMRM N=116 BOCF N=127 LOCF N=127
	Statistical analysis	LS Mean Change/SE	LS Mean Change/SE
	MMRM BOCF LOCF	-2.72 / 0.20 -2.23 / 0.20 -2.51 / 0.20	-1.88 / 0.18 -1.63 / 0.19 -1.72 / 0.18
Effect estimate per comparison		Comparison groups	Duloxetine 60/120 mg QD vs. placebo
	MMRM	LSMean Change	-0.84
		95% CI	(-1.32, -0.36)
		P-value	0.001
	BOCF	LSMean Change	-0.59
		95% CI	(-1.06,-0.13)
		P-value	0.013
	LOCF	LSMean Change	-0.78
		95% CI	(-1.24,-0.32)
		P-value	0.001
Notes	Results from all three analyses of changes in the primary efficacy measure showed significant differences between the duloxetine group and the placebo group		
Analysis description	**Gatekeeper and Secondary analysis**		
Secondary endpoint	*Patient's Global Impressions of Improvement (PGI–Improvement)*		
Descriptive statistics and estimate variability	Treatment group	Duloxetine 60/120 mg QD	Placebo
	Number of subject	123	127
	LS Mean Change/SE	2.93 / 0.12	3.14 / 0.12
Effect estimate per comparison	Comparison groups	Duloxetine 60/120 mg QD vs. placebo	
		LS Mean Change	-0.20
		95% CI	(-0.49,-0.08)
		P-value	0.164
Secondary endpoint	*Western Ontario and McMaster Universities Physical Function Subscale Measurements*		
Descriptive statistics and estimate variability	Treatment group	Duloxetine 60/120 mg QD	Placebo
	Number of subject	118	126
	LS Mean Change/SE	-12.69 / 1.15	-9.43 / 1.08
Effect estimate per comparison	Comparison groups	Duloxetine 60/120 mg QD vs. placebo	
		LS Mean Change	-3.27
		95% CI	(-5.91,-0.62)
		P-value	0.016

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Secondary endpoint	*Response to treatment, defined as 50% reduction of the BPI average pain at endpoint*		
Descriptive statistics and estimate variability	Treatment group	Duloxetine 60/120 mg QD	Placebo
Effect estimate per comparison	Number of subject (LOCF)	121	127
	Responders (%) (LOCF)	53 (43.8)	41 (32.3)
	Duloxetine 60/120 mg QD vs. placebo (LOCF)	P-value	0.068
	Number of subject (BOCF)	121	127
	Responders (%) (BOCF)	46 (38.0)	40 (31.5)
	Duloxetine 60/120 mg QD vs. placebo (BOCF)	P-value	0.289
Secondary endpoint	*Response to treatment, defined as 30% reduction of the BPI average pain at endpoint*		
Descriptive statistics and estimate variability	Treatment group	Duloxetine 60/120 mg QD	Placebo
Effect estimate per comparison	Number of subject (LOCF)	121	127
	Responders (%) (LOCF)	79 (65.3)	56 (44.1)
	Duloxetine 60/120 mg QD vs. placebo (LOCF)	P-value	0.001
	Number of subject (BOCF)	121	127
	Responders (%) (BOCF)	69 (57.0)	54 (42.5)
	Duloxetine 60/120 mg QD vs. placebo (BOCF)	P-value	0.031
Secondary endpoint	*European Quality of Life Questionnaire – 5 Dimension (EQ–5D) (UK population)*		
Descriptive statistics and estimate variability	Treatment group	Duloxetine 60/120 mg QD	Placebo
	Number of subject	92	109
	LS Mean Change/SE	0.17 / 0.02	0.11 / 0.02
Effect estimate per comparison	Comparison groups	Duloxetine 60/120 mg QD vs. placebo	
		LS Mean Change	0.06
		95% CI	(0.01, 0.11)
		P-value	0.027

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Notes	Duloxetine 60/120 mg treated patients demonstrated statistically significant improvement over placebo-treated patients in weekly 24-hour average pain score, weekly 24-hour worst pain score, CGI-S, and most parameters of the BPI (worst pain, least pain, average pain, pain right now, general activity baseline, and normal work baseline). In the SF-36 Health Outcomes measure for all randomised patients, the duloxetine-treated patients showed significantly greater improvement on the SF-36 physical component summary as well as the subscales of bodily pain, physical functioning, and physical role. The path analysis revealed that improvements in pain scores were due to a direct analgesic effect independent of changes in depression as measured by BDI-II or anxiety as measured by the HADS-A subscale. Patients who did not respond to duloxetine 60 mg QD, and thus had their dose increased to 120 mg QD (nonresponders), experienced a statistically significant decrease (improvement) from baseline (Week 7) to endpoint (Week 13) in the BPI average pain score. Of this group, 27.3% met the 30% response criteria (≥30% reduction in BPI average pain score from baseline to endpoint).

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Table 14. Summary of Efficacy for trial CLBP-EN.

Title: Effect of Duloxetine 60 mg to 120 mg Once Daily in Patients with Chronic Low Back Pain		
Study identifier	F1J-MC-HMEN	
Design	A Phase 3, 13-week, multicentre, double-blind, randomised, placebo-controlled study followed by a 41-week open label extension phase	
	Duration of main phase:	13 weeks
	Duration of Run-in phase:	1-week screening phase for eligibility
	Duration of Extension phase:	41 weeks; 2-week taper phase
Hypothesis	Superiority	
Treatments groups	Duloxetine 60 / 120 mg Once Daily	Duloxetine hydrochloride 60 mg given QD as 1 x 60 mg capsules Duloxetine hydrochloride 120 mg/day, given QD as 2 x 60 mg capsules Planned: 115; Randomised: 115; Completed: 84
	Placebo	For DLX 60 mg QD: 2 placebo tablets with 1 x DLX 60 mg capsule; For DLX 120 mg QD: 1 placebo tablet with 2 x DLX 60 mg capsules Planned: 115; Randomised: 121; Completed: 98
	Primary endpoint	Reduction of pain severity from baseline to endpoint as measured by the Brief Pain Inventory (BPI) 24-hour average pain (for simplicity, it is referred hereafter as the BPI average pain)
	Secondary gatekeeper analysis	• Evaluation of duloxetine 60/120 mg QD versus placebo on patients' perceived improvement as measured by Patient's Global Impression of Improvement (PGI–Improvement) • Evaluation of duloxetine 60/120 mg QD versus placebo on the improvement of functioning as measured by the Roland Morris Disability Questionnaire (RMDQ–24)
	Secondary endpoint	• Weekly mean of 24-hour average pain, night pain, and worst pain scores (measured using 11-point Likert scale) computed from electronic diary scores • BPI – Severity and Interference • Clinical Global Impressions of Severity (CGI-Severity) • Response to treatment, as defined by a 30% reduction of BPI average pain scores and 50% reduction of BPI average pain scores • Athens Insomnia Scale (AIS) • 36-item Short-Form Health Survey (SF-36) • EuroQoL Questionnaire – 5 Dimension (EQ-5D) version of the instrument • Work Productivity and Activity Impairment Instrument (WPAI). • Treatment effect on mood (as measured by the total score of the Beck Depression Inventory [BDI-II] and anxiety (as measured by the Hospital Anxiety Depression Scale anxiety subscale [HADS-A]) • Safety evaluation
Database lock	19 December 2007	
<u>Results and Analysis</u>		
Analysis description	**Primary Analysis** *Reduction of pain severity from baseline to endpoint as measured by Brief Pain Inventory (BPI) 24-hour average pain (blinded phase)*	

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Analysis population and time point description	Intent to treat		
	Treatment group	Duloxetine 60/120 mg QD	Placebo
	Number of subject	MMRM N=90 BOCF N=109	MMRM N=102 BOCF N=115
	Statistical analysis	LS Mean Change/SE	LS Mean Change/SE
	MMRM BOCF	-2.32 / 0.22 -1.86 / 0.20	-1.50 / 0.21 -1.25 / 0.20
Effect estimate per comparison		Comparison groups	Duloxetine 60/120 mg QD vs. placebo
	MMRM	LSMean Change	-0.82
		95% CI	(-1.37, -0.27)
		P-value	0.004
	BOCF	LSMean Change	-0.61
		95% CI	(-1.11, -0.10)
		P-value	0.019
Notes	Results from all three analyses of changes in the primary efficacy measure showed significant differences between the duloxetine group and the placebo group		
Analysis description	**Gatekeeper and Secondary analysis**		
Secondary endpoint	*Patient's Global Impressions of Improvement (PGI–Improvement; blinded phase)*		
Descriptive statistics and estimate variability	Treatment group	Duloxetine 60/120 mg QD	Placebo
	Number of subject	107	115
	LS Mean Change/SE	2.82 / 0.13	3.23 / 0.13
Effect estimate per comparison	Comparison groups	Duloxetine 60/120 mg QD vs. placebo	
		LS Mean Change	-0.41
		95% CI	(-0.74,-0.08)
		P-value	0.014
Secondary endpoint	*Roland-Morris Disability Questionnaire-24 (blinded phase)*		
Descriptive statistics and estimate variability	Treatment group	Duloxetine 60/120 mg QD	Placebo
	Number of subject	99	105
	LS Mean Change/SE	-3.60 / 0.51	-1.93 / 0.50
Effect estimate per comparison	Comparison groups	Duloxetine 60/120 mg QD vs. placebo	
		LS Mean Change	-1.67
		95% CI	(-2.93,-0.42)
		P-value	0.009
Secondary endpoint	*Response to treatment, defined as 50% reduction of the BPI average pain at endpoint (blinded phase)*		
Descriptive statistics and estimate variability	Treatment group	Duloxetine 60/120 mg QD	Placebo
Effect estimate per comparison	Number of subject (LOCF)	109	115
	Responders (%) (LOCF)	42 (38.5)	31 (27.0)

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	Duloxetine 60/120 mg QD vs. placebo (LOCF)	P-value	0.087
	Number of subject (BOCF)	109	115
	Responders (%) (BOCF)	39 (35.8)	26 (22.6)
	Duloxetine 60/120 mg QD vs. placebo (BOCF)	P-value	0.039
Secondary endpoint	*Response to treatment, defined as 30% reduction of the BPI average pain at endpoint (blinded phase)*		
Descriptive statistics and estimate variability	Treatment group	Duloxetine 60/120 mg QD	Placebo
Effect estimate per comparison	Number of subject (LOCF)	109	115
	Responders (%) (LOCF)	58 (53.2)	46 (40.0)
	Duloxetine 60/120 mg QD vs. placebo (LOCF)	P-value	0.060
	Number of subject (BOCF)	109	115
	Responders (%) (BOCF)	50 (45.9)	38 (33.0)
	Duloxetine 60/120 mg QD vs. placebo (BOCF)	P-value	0.056
Secondary endpoint	*European Quality of Life Questionnaire – 5 Dimension (EQ–5D) (UK population; blinded phase)*		
Descriptive statistics and estimate variability	Treatment group	Duloxetine 60/120 mg QD	Placebo
	Number of subject	101	102
	LS Mean Change/SE	0.16 / 0.03	0.11 / 0.03
Effect estimate per comparison	Comparison groups	Duloxetine 60/120 mg QD vs. placebo	
		LS Mean Change	0.05
		95% CI	(-0.01,0.12)
		P-value	0.117
Notes	In secondary analyses including 8 out of 10 BPI items, weekly 24-hour average pain score, weekly 24-hour worst pain, weekly 24-hour night pain the differences between duloxetine and placebo reached statistical significance. Clinical Global Impressions of Severity rating did not show significant difference in the mean change from baseline to endpoint between the treatment groups. No difference in the mean change of Athens Insomnia Scale (AIS) between the treatment groups was found. Overall, there was no significant difference between the treatment groups in the mean change in SF-36. There was a significantly greater improvement in the duloxetine treatment group on the work activity impairment score compared with the placebo treatment group using the WPAI. The path analysis indicated that the direct analgesic effect of duloxetine on pain was predominant.		
	For the results of extension phase please see the main text of the assessment report.		

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Table 15. Summary of Efficacy for trial CLBP-GC.

Title: Effect of Duloxetine 60 mg Once Daily versus Placebo in Patients with Chronic Low Back Pain		
Study identifier	F1J-MC-HMGC	
Design	A Phase 3, 12-week, multicentre, double-blind, randomised, placebo-controlled study	
	Duration of main phase:	12 weeks
	Duration of Run-in phase:	1-week screening phase for eligibility
	Duration of Extension phase:	not applicable; 1-week taper phase
Hypothesis	Superiority	
Treatments groups	Duloxetine 60 mg QD	Duloxetine 60 mg given orally once daily as 1 capsule during acute treatment phase; Planned: 200; Randomised: 198; Treated (at least 1 dose): 197; Completed: 147
	Placebo	Matching dosing scheme Planned: 200; Randomised: 203; Treated (at least 1 dose): 200; Completed : 156
Endpoints and definitions	Primary endpoint	Reduction of pain severity from baseline to endpoint as measured by the Brief Pain Inventory (BPI) 24-hour average pain (for simplicity, it is referred hereafter as the BPI average pain)
	Secondary gate keeper analysis	• Evaluation of duloxetine 60 mg QD versus placebo on patients' perceived improvement as measured by Patient's Global Impression of Improvement (PGI–Improvement)
	Secondary endpoints	• BPI–Severity and Interference ratings collected from patient responses at scheduled office visits (except for average pain stated as primary) • Weekly mean of 24-hour average pain, average pain at night, and worst daily pain ratings (measured using 11-point Likert scale) computed from daily electronic diary. • Response to treatment, defined as 30% reduction of the BPI average pain and 50% reduction of the BPI average pain • Sustained response to treatment, defined as BPI average pain of at least a 30% reduction from baseline to endpoint; a 30% reduction from baseline at an earlier visit than the last visit, and which remains at least at a 20% reduction from baseline in every visit in between (if there are any intervening visits) • Cumulative distribution of BPI average pain reduction, as measured by the percentage of patients who have reached each threshold of BPI average pain reduction from baseline endpoint (from >0% to 100% by 10% incremental increases) • Clinical Global Impressions of Severity (CGI–Severity) • Profile of Mood States – Brief Form (POMS–Brief Form) • 36-item Short-Form Health Survey (SF–36) • European Quality of Life Questionnaire – 5 Dimension (EQ–5D) version of the European Quality of Life instrument • Work Productivity and Activity Impairment Instrument (WPAI) • Safety evaluation
Database lock	6 July 2009	
<u>Results and Analysis</u>		
Analysis description	**Primary Analysis** *Reduction of pain severity from baseline to endpoint as measured by Brief Pain Inventory (BPI) 24-hour average pain*	

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Analysis population and time point description	Intent to treat		
	Treatment group	Duloxetine 60 mg QD	Placebo
		Number of subject	
	MMRM BOCF LOCF	152 198 195	162 203 199
	Statistical analysis	LS Mean Change/SE	LS Mean Change/SE
	MMRM BOCF LOCF	-2.48 (0.16) -1.92 (0.15) -2.25 (0.15)	-1.80 (0.15) -1.37 (0.15) -1.65 (0.15)
Effect estimate per comparison		Comparison groups	Duloxetine 60 mg QD vs. placebo
	MMRM	LSMean Change	-0.68
		95% CI	(-1.09, -0.26)
		P-value	0.001
	BOCF	LSMean Change	-0.55
		95% CI	(-0.93,-0.18)
		P-value	0.004
	LOCF	LSMean Change	-0.60
		95% CI	(-0.97,-0.22)
		P-value	0.002
Notes	Results from all three analyses of changes in the primary efficacy measure showed significant differences between the duloxetine group and the placebo group		
Analysis description	**Gatekeeper and Secondary analysis**		
Secondary endpoint	*Patient's Global Impressions of Improvement (PGI–Improvement)*		
Descriptive statistics and estimate variability	Treatment group	Duloxetine 60 mg QD	Placebo
	Number of subject	194	199
	LS Mean Change/SE	2.88 / 0.09	3.19 / 0.09
Effect estimate per comparison	Comparison groups	Duloxetine 60 mg QD vs. placebo	
		LS Mean Change	-0.31
		95% CI	(-0.56,-0.07)
		P-value	0.011
Secondary endpoint	*Response to treatment, defined as 50% reduction of the BPI average pain at Endpoint*		
Descriptive statistics and estimate variability	Treatment group	Duloxetine 60 mg QD	Placebo
Effect estimate per comparison	Number of subject (LOCF)	195	199
	Responders (%) (LOCF)	95 (48.7)	69 (34.7)
	Duloxetine 60 mg QD vs. placebo (LOCF)	P-value	0.006
	Number of subject (BOCF)	198	203

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	Responders (%) (BOCF)	85 (42.9)	57 (28.1)
	Duloxetine 60 mg QD vs. placebo (BOCF)	P-value	0.002
Secondary endpoint	*Response to treatment, defined as 30% reduction of the BPI average pain at Endpoint*		
Descriptive statistics and estimate variability	Treatment group	Duloxetine 60 mg QD	Placebo
Effect estimate per comparison	Number of subject (LOCF)	195	199
	Responders (%) (LOCF)	111 (56.9)	97 (48.7)
	Duloxetine 60 mg QD vs. placebo (LOCF)	P-value	0.108
	Number of subject (BOCF)	198	203
	Responders (%) (BOCF)	95 (48.0)	83 (40.9)
	Duloxetine 60 mg QD vs. placebo (BOCF)	P-value	0.161
Secondary endpoint	*European Quality of Life Questionnaire – 5 Dimension (EQ–5D) (UK population)*		
Descriptive statistics and estimate variability	Treatment group	Duloxetine 60 mg QD	Placebo
	Number of subject	190	192
	LS Mean Change/SE	0.15 / 0.02	0.07 / 0.02
Effect estimate per comparison	Comparison groups	Duloxetine 60 mg QD vs. placebo	
		LS Mean Change	0.07
		95% CI	(0.03,0.12)
		P-value	0.001
Notes	Other secondary outcome analyses showed significant difference between duloxetine 60 mg QD and placebo, including: BPI severity and interference; 50% response rate, weekly means of 24-hour average pain; worst pain and night pain ratings; and POMS. Improvements in physical function (RMDQ–24), CGI-S, and 30% pain response were numerically higher in patients treated with duloxetine, compared with placebo, but the differences were not significant.		

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Analysis performed across trials

Pooled subgroup analyses of the primary endpoint were performed separately for the OA and CLBP studies for the following factors:

- Age – <65, ≥65 (for both CLBP and OA studies); <55, ≥55 (for CLBP studies only since the overall CLBP population is younger compared to OA population)
- Gender – Male, Female
- Race – Caucasian, Other
- Baseline average pain severity – <=6, >6 (for pooled analysis); <median, >median

- Duration of CLBP or OA pain (for individual studies only)
- History of back surgery – Yes, No (for individual CLBP studies only)
- Quebec Task Force Class – Class I, Class II (for CLBP studies only)
- Non-Steroidal Anti-Inflammatory Drug (NSAID) use – Yes, No (not applicable in Study CLBP-GC).
- Geographic Region (North America, Europe, and others).

There was no statistically significant treatment-by-subgroup interaction for any of the subgroups analysed indicating that the effect was similar regardless of subgroup. Overall 88% of the patients were Caucasians. Although no significant treatment-by-subgroup interaction was observed it was noted that the magnitude of effect was considerably less in patients using NSAIDs and in European OA patients. As the difference was not statistically significant and the opposite phenomenon was observed in the CLBP studies it was concluded that no clinically meaningful regional differences were observed.

It was also noted that the effect was less pronounced in males (and not statistically significant for males in OA patients) and in patients with <1 year duration of CLBP. However, the limited patient numbers warranted caution in the interpretation of the results.

Pooled analyses of responder data have been performed for the studies in OA and CLBP separately.

Table 16. Pooled analyses of responder data in the OA studies.

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%)	

Table 17. Pooled analyses of responder data in the CLBP studies.

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%)	

Statistically significant effects in favour of duloxetine 60-120 mg in LOCF as well as in BOCF analyses of pooled data were found. As expected from the differential withdrawal pattern (especially in the OA studies) the effect was less pronounced in the BOCF analysis.

Supportive studies

Due to the inconsistent or negative results the below described studies were considered by the applicant as supportive for this procedure.

Study OA-EP

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Table 18. Analysis of the primary efficacy variable.

24-hour average pain from baseline to end of treatment (collected from patient diaries)				
Study	**Analysis**	**Treatment Group[a]**	**LSMean Change (SE)**	**p-Value**
OA-EP	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)	

The MMRM and LOCF analyses showed a significant reduction in the 24-hour average pain score from baseline to endpoint. In the BOCF analysis a positive trend in favour of duloxetine was observed without statistical significance.

Table 19. Analysis of secondary efficacy variables.

Response Rate of the Weekly 24-Hour Average Pain Score						
Study	**Analysis**	**Treatment Group**	**30% Response Rate (%)**	**p-Value**	**50% Response Rate (%)**	**p-Value**
OA-EP	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	

Response rates analysis did not show statistically significant results when the BOCF analysis was applied.

Subgroup analyses according to NSAIDs use

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*
NSAID use	.453	.028	No	111	1) PLACEBO	60	6.05	1.35	-1.99	1.72	-2.12	0.31	.024
					2) DLX60/120QD	51	6.28	1.40	-3.00	2.28	-3.01	0.32	
			Yes	116	1) PLACEBO	59	6.30	1.31	-1.85	1.84	-1.76	0.27	.199
					2) DLX60/120QD	57	5.98	1.28	-2.27	1.89	-2.22	0.29	

Statistically significant result was observed in the subgroup of patients not taking the NSAIDs regularly.

Gatekeeper analysis

The duloxetine group demonstrated a statistically significant improvement in both gatekeeper assessments (PGI-I and the WOMAC physical function subscale analysis) compared to the placebo group.

Path analysis for direct analgesic effect

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

Study CLBP-EO

Table 20. Analysis of the primary efficacy variable.

24-hour average pain from baseline to the end of treatment (collected from patient diaries)				
Study	**Analysis**	**Treatment Group[a]**	**LSMean Change (SE)**	**p-Value[b]**
CLBP-EO	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)	

Results from the primary efficacy measure showed no significant differences between the 60 mg QD duloxetine group and the placebo group. Additional analyses using the LOCF and BOCF did not reach statistical significance.

Table 21. Analysis of secondary efficacy variables.

Response Rate of the Weekly 24-Hour Average Pain Score						
Study	**Analysis**	**Treatment Group**	**30% Response Rate (%)**	**p-Value**	**50% Response Rate (%)**	**p-Value**
CLBP-EO	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	

Although a numerical trend could be noted in favour of duloxetine in the responder analysis no statistically significant effects were observed.

<u>Subgroup analyses according to NSAIDs use</u>

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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
Use of NSAIDs	.241	.772	No	225	1) PLACEBO	70	6.27	1.28	-1.69	2.13	-1.68	0.25	
					2) DLX20QD	35	6.25	1.24	-1.85	1.99	-1.73	0.35	.902
					3) DLX60QD	62	6.08	1.41	-2.35	2.07	-2.45	0.28	.030
					4) DLX120QD	58	6.08	1.39	-2.01	1.85	-1.95	0.29	.453
			Yes	163	1) PLACEBO	43	6.17	1.03	-1.94	2.15	-2.03	0.35	
					2) DLX20QD	21	6.58	1.50	-1.14	1.76	-1.21	0.50	.154
					3) DLX60QD	48	6.18	1.44	-1.96	2.06	-2.11	0.33	.862
					4) DLX120QD	51	6.04	1.54	-2.28	1.97	-2.38	0.32	.442

The subgroup analysis showed significant effects of duloxetine 60 mg QD when given to patients not taking NSAIDs.

Gate keeper analyses

In the study protocol a gatekeeper analyses was predefined for the sequential testing of the secondary hypotheses. As no significant results were observed in the primary efficacy analysis subsequent analysis of secondary endpoints would not be taken into account.

Path analysis for direct analgesic effect

Results of the path analysis demonstrated that the treatment difference between 60 mg QD duloxetine and placebo for depression and anxiety accounted for 17.7% of the total treatment difference for pain reduction.

Discussion of clinical efficacy

Design and conduct of clinical studies

The Applicant has submitted 5 clinical studies in order to support the application for use of duloxetine in chronic somatic pain: 2 in osteoarthritis of the knee (OA) (OA-EP; and OA-FG) and 3 in chronic low back pain (CLBP) (CLBP-EN; CLBP-EO; and CLBP-GC).

All OA and CLBP studies had a 12- to 13-week, double-blind, randomised, placebo-controlled treatment phase. The OA studies allowed the inclusion of patients diagnosed with idiopathic OA knee pain according to the American College of Rheumatology criteria. In the CLBP studies, subjects were required to have a clinical diagnosis of CLBP (as their primary pain condition) with pain present on most days for at least 6 months.

Regarding the basal characteristics, the patients' mean age was 50+ years in all the studies. The mean duration of chronic pain was between 7 and 12 years. The median baseline pain value was 6.0, which is referred to as a moderate-severe pain. The CHMP noted that the elderly population was underrepresented in the submitted clinical trials.

The lack of an active comparator in all of the studies was considered as an important weakness of the clinical development program in the intended indication.

The backbone treatment of patients with chronic pain disorders are non steroidal anti-inflammatory drugs (NSAIDs). In fact, in all the studies but one (CLBP-GC), patients were allowed to remain on their regular dose of NSAIDs or acetaminophen, provided they were using them at the time of enrolment. This is a key feature of the clinical development for the current application. Undoubtedly, patients with OA of knee or CLBP are treated with analgesics and an overall basal pain rate of 6 could automatically imply that these patients are being undertreated or that they have an inadequate response to NSAIDs and may require an add-on medication, although due to the lack of criteria to properly define the population, this fact cannot be confirmed. Patients with moderate pain who were not receiving NSAIDs

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were also included in the studies at a different proportion. The fact that both groups of patients were included in the studies is considered an important drawback of the clinical development program in chronic somatic pain. These scenarios are considered as completely different, the expected contribution of each population to the overall benefit is different and the overall benefit not necessarily applicable to each of them. The broader indication initially sought by the applicant namely 'treatment of moderately severe chronic somatic pain' cannot be supported by the current clinical development program. In other words, the target patient population should have been properly defined. Consequently, the inclusion of analgesics in the study can be seen as a methodological flaw which renders difficult the interpretation of the outcomes.

The CHMP also expressed concerns regarding the handling of missing data and its impact on the estimated treatment effects due to the differences in results observed with different analytical approaches, i.e. BOCF versus MMRM or LOCF. The MAH carried out additional exploratory analyses to further characterise the drop-outs with the focus on non-NSAID users (i.e., not taking NSAIDs regularly) as this population was the only one showing some benefit from the duloxetine treatment. The results demonstrated that in three of the studies (OA-EP, OA-FG and CLBP-EN) time to discontinuation was in favour of duloxetine thus substantiating, in view of the applicant, the treatment effect. Most of the discontinuations were due to the adverse events in the active treatment group. The CHMP agreed that handling of the missing data would not change the conclusions from the studies.

The adequacy of blinding of the studies and their external validity was also questioned by the CHMP. It was not clear to the committee whether study participants or investigators could have identified the treatment assignment based on AE-related discontinuation from studies as the data on clinical characteristics of trials non-completers was missing. In response the applicant provided data on baseline characteristics of patients who did not complete the studies. From the data submitted it transpired that there were only slight differences between patients who discontinued and those who completed the studies, hence the CHMP concluded that the integrity of blinding was adequately preserved. Furthermore, the CHMP expressed reservations as to how the potential participants were identified and recruited. In their response the MAH clarified how the recruitment process was organised and why some patients were excluded prior to randomisation. It was concluded that given the modalities of the recruitment process (e.g. advertising campaigns) the 30% screen failures were acceptable.

Additionally, the MAH was requested to clarify the impact of low patients' compliance with electronic diaries on validity and integrity of the studies OA-EP and CLBP-EO. The applicant explained that other data collected within these studies which were not reliant on the compliance with diaries, e.g. data collected using BPI demonstrated changes in favour of duloxetine. Nonetheless, the applicant considered these studies as supportive for the procedure due to inconsistent or negative results. The CHMP acknowledged the applicant's response that albeit valid the studies do not provide information supporting the applied for indication.

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Efficacy data and additional analyses

With regards to the outcomes, the primary endpoints results were statistically significant in four out of five studies. The 24-hour average pain reduction with duloxetine ranged from -1.9 to -2.9, whereas for placebo it ranged from -1.25 to -2.1. These results are positive in statistical terms, nevertheless their clinical relevance is highly questionable. In fact, the absolute difference between placebo and duloxetine ranged between 0.40 and 0.84, which raises the question as to whether such difference would be perceived by patients. Interestingly, the estimated minimal perceptible clinical improvement, in a 100 mm normalised VAS, has been observed to be in the range of 8 to 12 mm (Ehrich et al. 2000 J Rheumatol). The minimal clinically important improvement was also determined by F. Tubach et al. in

the 2005 publication 'Evaluation of clinically relevant changes in patient reported outcomes in knee and hip osteoarthritis: the minimal clinical important improvement'. The authors concluded that at best patients could perceive 1.08 points of pain decrease from baseline score, a change that could be considered the minimal clinical important improvement. It could be reasonable to think that differences between control and duloxetine group should be at least of 1 point to be deemed clinically relevant.

In this context it is also worth highlighting the importance of performing studies where the substance under investigation is tested against both placebo and an active control. In the publication 'Efficacy and safety of etoricoxib 30 mg and celecoxib 200 mg in the treatment of osteoarthritis in two identically designed, randomized, placebo-controlled, non-inferiority studies' (Bingham et al, 2007) the non-inferiority margin was predefined as ±10 mm on a 100 mm VAS. In addition, differences between tested products (etoricoxib and celecoxib) and placebo were always greater than 11 points (100 mm VAS). In 'Efficacy of etoricoxib 60 mg/day and diclofenac 150 mg/day in reduction of pain and disability in patients with chronic low back pain: results of a 4-week, multinational, randomized, double-blind study' (Zerbini et al, 2005) the non-inferiority margin was set at the same level (±10 mm on a 100mm).

This further evidences the lack of a clinically relevant effect of duloxetine on pain relief as differences between duloxetine and placebo were not greater than 1 point on a 10 mm scale in any of the studies (which falls within the generally accepted non-inferiority margin in chronic pain studies).

In response to the CHMP request the MAH performed two additional sensitivity analyses using the LOCF and a modified BOCF. The observed results were pointing in the same direction, i.e. positive statistical result and absence of clinical relevance when duloxetine was compared to placebo. Of note, although initially not fully supported by the CHMP the statistical methods were considered acceptable as MMRM constitutes a recognised tool in the assessment of pain. However, the difference between the results of BOCF and MMRM analyses provided an excellent case study of why MMRM may not be suitably conservative in this indication. In this regard it should be highlighted that when designing studies there should be sufficient evidence that the primary variable selected can provide a valid and reliable measure of a clinically relevant and important treatment benefit in the patient population described by the inclusion and exclusion criteria.

The "Guideline on clinical medicinal products intended for the treatment of neuropathic pain" (CPMP/EWP/252/03) recommends defining responders as subjects with a 30 to 50% reduction in the assessment scale as compared to baseline. Response rate comparison was recommended as primary endpoint for CLBP studies in the scientific advice received in 2005. Thus, response rates (using both ≥ 30% and ≥50% reduction from baseline at endpoint criteria) were included as a secondary endpoint in all studies, with 80% power to detect a treatment difference between duloxetine and placebo. It should be emphasised that demonstrating a numeric decrease even though statistically significant would not be sufficient to demonstrate a clinically relevant response.

In the 30% response rate analysis, according to the LOCF, the difference between duloxetine 60 mg and placebo ranged from 8.2% to 21.2%. Based on the BOCF method the results showed a difference from 7.1% to 14.5%. In the 50% response rate analysis, the difference between duloxetine and placebo was from 5.3% to 17.8% (LOCF) and 4.3% to 14.8% (BOCF). In summary, at best 20% of difference between placebo and duloxetine could be observed using the 30% response rate. Even though somebody could wonder whether these results (response rate) may be deemed as relevant for a subset of patients, no criteria have been proposed to select a subgroup of subjects in whom some clinical benefit could be reached.

Interestingly, when the primary analysis was carried out in the subgroup of patients treated with NSAIDs during the course of the study, the statistical significance disappeared. On the contrary, only

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the patients without NSAIDs intake (i.e., not taking NSAIDs regularly) demonstrated a positive result. Consequently, the applicant provided additional analyses, including primary efficacy outcome analysis and responder analyses, in subgroups of patients defined as non-NSAID users (i.e., not taking NSAIDs regularly).

Regarding studies in CLBP differences in favour of duloxetine were of -0.54 in CLBP-EN, -0.64 in CLBP-EO (60 mg strength) and -0.55 CLBP-GC, the latter can be considered as the study which better shows the use of duloxetine alone as no NSAIDs were allowed. Therefore in terms of the primary endpoint, results showed mean differences in favour of duloxetine of about 0.55 points on an 11-point scale, which can hardly be considered as clinically relevant.

Differences in 30% response rates were of 13.3 % in study CLBP-EN, 15.4% in study CLBP-EO, and 7.1% in CLBP-GC. Differences in 50% response rates were 15.5 % in study CLBP-EN, 10.1% in study CLBP-EO, and 14.8% in CLBP-GC.

In the OA studies pain reduction measured by the primary endpoint was -0.60 in OA-EP and -0.67 in OA-FG both in favour of duloxetine. When assessing BPI 30% response rates in OA studies results showed differences in favour of duloxetine of 9.1% and 14.6% in study OA-EP and OA-FG respectively. These differences were of 23% and 9.3% for 50% response rate respectively, suggesting high variability between OA studies. Interestingly, when looking at the primary endpoint results seemed to be more favourable, however when looking at response rates they showed the same magnitude. Once again, these analyses of subsets cannot be considered as confirmatory.

In the scientific advice held on 2005 the CHMP concluded that 'the choice of only placebo as the control arm in studies of CLBP with duloxetine as add-on therapy to a well-established analgesic regimen would be acceptable as long as utilisation of all concomitant treatments was recorded, analysed and reported'. Regarding the OA CHMP answer followed the same trend (SA held on 2006): if duloxetine was intended as a first line therapy a three arm study was recommended including one arm with any available NSAID indicated for the symptomatic treatment of OA. On the other hand, if duloxetine was intended as a rescue therapy, the pain threshold for non responders should have been properly defined. The use of analgesics was not thoroughly recorded in the studies. No active comparator was included in the trials nor was proper definition of non-responder to NSAIDs pre-specified. Taking into account deviations from the above advices it is difficult to identify the target population for duloxetine in the current application. In the absence of an accepted comparator and in order to put findings into perspective the applicant provided several analyses with the use of historical comparators; however given the limitations of such approach these data are unlikely to be sufficient.

The fact that a noteworthy therapeutic effect (30% response rate) needs more than 20 days to be reached by the vast majority of patients makes duloxetine less suitable for being considered as monotherapy in chronic pain.

Finally, the use of rescue medication has not been reported in all the studies. Moreover, the secondary variables did not include this important endpoint. This issue is a matter of concern, since the recording of pain severity could have been modified if the patient had taken rescue medication in previous hours/days before the study's visit. According to "Note for guidance on clinical investigation of medicinal products used in the treatment of OA" for all trials 'rescue treatment (including physical therapy) should be standardised, monitored carefully and recorded for each individual patient. Time points of endpoint assessment should be appropriately chosen to avoid confounding effects of the rescue medication'. Additionally in "Note for guidance on clinical investigation of medicinal products for treatment of nociceptive pain" it is stated that 'special attention should be given to concomitant medications or nonpharmacological pain management techniques. If unavoidable, any treatment that can modulate the perception on pain should be comparable across study groups'.

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The pre-specified definition of episodic use would be acceptable and would not have constituted a potential bias if the use of rescue medication had been properly recorded. Only data on days of concomitant rescue therapy have been provided. Total number of days of rescue analgesic use ranged from 1 to 16 for duloxetine-treated patients and 1 to 35 for placebo-treated patients. This is reassuring, albeit information on actual days of rescue therapy consumption is lacking. To what extent the use of rescue therapies could have affected the effects of duloxetine is still unknown. Taking into account these unknowns and the complete lack of data on non-pharmacological interventions the possible role of duloxetine alone in pain relief is still uncertain.

The results supporting maintenance of effect were considered to have a very limited value as only 58 patients completed the open-label extension part of the study CLBP-EN, and the statistical approach used (LOCF) was likely to overestimate the effect. An updated analysis including 61 patients, a more conservative delta margin and using the BOCF method for missing data imputation showed that in up to 64% of the patients the response was maintained. Despite that, these results were considered to provide a very limited evidence to support the use of duloxetine for the treatment of this chronic condition.

The CHMP noted that numbers of elderly patients participating in duloxetine OA/CLBP clinical trials were limited (181 duloxetine-treated patients were 65-75 years old; 21.6%) especially in the subset of the very elderly (56 duloxetine-treated patients were ≥75 years old; 6.7%).

Having considered all the above stated the applicant restricted the indication to patients in whom duloxetine showed to have the most noticeable effect, i.e. patients receiving duloxetine in 'monotherapy' (patients not taking NSAIDs regularly). Results for this subset were submitted as per the BOCF approach showing differences between placebo and duloxetine of 0.55 and 0.67. It should be noted that only 2 out of 5 studies (study CLBP-GC and OA-FG) turned out to be statistically significant. Even if considering the most favourable analysis for duloxetine, i.e. subgroup analyses with LOCF approach, duloxetine-placebo differences ranged from 0.60 (study CLBP-GC) to 1.03 (study OA-FG). The latter could be deemed as a result of borderline clinical relevance. However the following should be highlighted: firstly the BOCF approach (0.67) differs substantially from the LOCF approach; secondly, this can be considered an isolated result as no other study showed clinical relevance; thirdly, all the concerns already raised and not resolved as well as concerns regarding the heterogeneity of the target population, i.e. the population included in trials was not adequately defined, as patients not taking NSAIDs were included in trials irrespective of the reason for not using them, play down the importance of this isolated result. Furthermore, in the clinical studies presented, patients taking NSAIDs for less than 15 days per month during at least 3 consecutive months, were considered as 'non-NSAIDs users' and were allowed to continue this regimen during clinical trial, which questions the definition of a monotherapy setting and adds further uncertainties to the contribution of duloxetine to the observed effect.

Considering the marginal differences between duloxetine and placebo in pain intensity reduction, the applicant was requested to clarify the contribution of the effect of duloxetine on depression/anxiety to the analgesic effect. The MAH submitted new analyses in addition to the initial path analysis performed to test the direct effect of duloxetine treatment on pain reduction. Although the method was accepted results showed rates around 20% for studies CLBP-EN and CLBP-EO which were considered as non negligible. Logistic regression of 30% response rate has been performed including HADS-D and BDI-II total scores as covariates (based on the fact that path analyses showed that depression status contributed to the majority of the indirect effect rather that anxiety). Based on the results of this post-hoc analysis, the CHMP agreed that the effect of duloxetine was mainly due to its analgesic properties rather than its effects on mood or anxiety.

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Although no new information was submitted that could change the CHMP's opinion regarding the marginal clinical efficacy of duloxetine, the submitted subgroup analysis results enabled the committee to state the following:

- The modest clinical effects observed in the overall population are mostly driven by patients receiving duloxetine alone.

- OA population receiving duloxetine monotherapy (patients not taking NSAIDs regularly) can be considered the most favoured population, however the observed effect is still considered of scarce clinical relevance.

Conclusion on the clinical efficacy

The proposed restricted indication 'Treatment of chronic somatic pain (as established in chronic low back pain and osteoarthritis) of at least moderate severity in patients not taking NSAIDs regularly' is not supported for the following reasons:

- The clinical relevance of the effect observed of duloxetine as 'monotherapy' is still considered negligible.

- The unknown contribution of the rescue medication to the overall effect adds further uncertainties to the efficacy assessment.

- In the absence of an active comparator, it is difficult to reach any conclusion on the benefit/risk of duloxetine as an alternative to the well established treatment in the studied conditions. The delay in reaching a therapeutic effect makes this drug less suitable as an optimal alternative for treating this condition in monotherapy.

- The heterogeneity of the studied population makes it difficult to elucidate the potential effect of duloxetine in the intended target population.

- The maintenance of the effect has not been adequately demonstrated as a very limited number of patients were evaluated in the long-term extension study.

- The efficacy in the elderly, in particular the very elderly, was studied in a very limited number of patients.

3.2.4. Clinical safety

Patient exposure

The integrated safety database for duloxetine hydrochloride currently consists of more than 31,000 patients exposed to duloxetine in the entire clinical program as of 23 April 2010. These exposures include 4039 additional patients exposed to duloxetine since the datalock of May 2007 for the fibromyalgia submission in the US. Of these additional exposures, 1860 duloxetine-treated patients participated in placebo-controlled studies. The database includes safety data for individual patient exposures over 5 years (that is, a maximum duration of patient exposure of 2115 days), with similar safety results observed between acute treatment (12 weeks) and long-term treatment. In addition to clinical trials, more than 31 million patients have been exposed to duloxetine based on postmarketing experience (through 02 August 2010). Patients ≥65 years of age comprise 13.8% of the clinical trial population and 18.1% of the postmarketing population.

In this submission, 839 patients were treated with duloxetine in placebo-controlled clinical studies for osteoarthritis (OA) and chronic low back pain (CLBP) using doses of 20, 60, and 120 mg once daily

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(QD). Among these patients 829 (98.8%) had >0 days of exposure, 708 (84.4%) patients had ≥30 days of exposure, 449 (59.5%) had ≥90 days of exposure to duloxetine. Safety data from these studies were pooled to form the primary placebo-controlled analyses set for this submission. Safety analyses included all patients with baseline data.

Additionally, 83 (55.3 patient-years) patients who completed the acute phase from study CLBP-EN (HMEN) were exposed to duloxetine for long-term treatment (up to 41 weeks), the remaining patients discontinued primarily due to subject decision (12%), AE (6%), and protocol violation (6%).

Adverse events

Of the 839 enrolled patients in the primary placebo-controlled chronic pain studies, 61.5% reported at least one TEAE. Nausea (13.9%), dry mouth (7.0%), constipation (6.9%, insomnia (6.6%), diarrhoea (5.7%), dizziness (5.7%), somnolence (5.6%), and fatigue (5.0%), all were reported at a significantly greater level compared to placebo and by more than 5% of patients.

The profile of AE observed in this application was similar, although numerically lower than that seen in other placebo controlled studies or in all duloxetine exposures. The lower frequency of nausea could be explained by the use of 30 mg as lead-in dose as well as by the recommendation of duloxetine being administered with food.

- Common AEs by severity

Another measure of tolerability apart from the discontinuation rate was the severity of the events as reported by patients. Patients were asked to rate AEs as mild, moderate, or severe based upon the discomfort, health risk, interference with activity, or any combination of the 3. No TEAE-by-severity analysis was performed for the all duloxetine exposures analyses set. For all AEs, statistical comparison was conducted to compare percentages of patients with severe TEAEs between treatment groups. All common adverse events graded as severe were more frequent in the duloxetine groups and the differences were statistically significant.

Overall, the TEAE profile by severity of the primary placebo-controlled analyses set was similar to the all other placebo-controlled analyses set and the primary long-term analyses set. This consistency provides reassurance that chronic pain indication does not differ substantially from other indications in terms of severity of the common AEs.

- Common AEs over the time

The analysis of the most common adverse events over the time showed that nausea, constipation, insomnia, diarrhoea, dizziness, and somnolence appeared early in duloxetine treatment and subsided quickly, whereas fatigue and dry mouth seemed to persist significantly longer in patients assigned to duloxetine than in patients assigned to placebo.

- Common adverse events by demographic subgroups and dose

The frequency of adverse events was examined as function of age, gender and origin for the primary placebo-controlled analyses set. A statistically significant difference for the treatment-by-strata analyses was defined as p<.10. Males may have an increased risk of experiencing at least one AE, as well as decreased libido compared to females, while an increased risk of dry mouth is indicated for females compared to males, and younger patients may have an increased risk of nausea as compared to older patients.

Adverse events by dose were analysed in the fixed-dose study CLBP-EO and across 3 studies which included a one-time duloxetine dose increase (CLBP-EN, OA-EP and OA-FG). Due to the fact that AEs tended to appear early in duloxetine treatment and subside quickly (with the exception of fatigue and

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dry mouth which seemed to persist longer during treatment with duloxetine) it was felt that study CLBP-EO best represented the actual exposure to duloxetine 120 QD (as studies CLBP-EN, OA-EP and OA-FG introduced 120 mg dose by dose escalation or re-randomisation at visit 4). Except for nausea all common AEs occurred numerically more frequently with duloxetine 120 mg than 60 or 20 mg QD. All sexual-dysfunction effects combined were reported significantly more frequently by patients taking duloxetine 120 mg QD than patients taking duloxetine 60 mg QD.

Serious adverse events and deaths

Deaths

No deaths were reported during the primary chronic pain studies, including the extension phase of study CLBP-EN. One death occurred 11 days after last drug dose (duloxetine) due to cardiopulmonary arrest (study CLBP-EO). The investigator considered the event as not related to study drug or protocol procedure. A total of 9 deaths (5 patients treated with duloxetine and 4 patients treated with placebo) were reported in the controlled phases of the all other placebo-controlled analyses set. A total of 43 deaths were reported in the all duloxetine analyses set. The cause of death in these patients did not form a meaningful pattern and did not suggest a particular effect on any specific body system or evidence of systemic drug toxicity.

Other serious adverse events

In the primary long-term analyses set, 4 (4.8%) patients experienced an SAE including acute tonsillitis, ostheoarthritis, syncope and tonsillitis, all of them were reported with the same frequency (1; 1.2%). The most frequently reported SAEs were myocardial infarction, asthma, non-cardiac chest pain and transient ischemic attack.

Safety Topics of Special Interest

Suicidality Analyses

There were no cases of suicidal ideation or suicidal behaviour in the primary placebo-controlled analysis set, while one patient experienced suicidal ideation during the extension phase of study CLBP-EN.

Hepatic Analyses

The use of duloxetine in the chronic pain studies was associated with mean hepatic enzyme elevation but not bilirubin elevation. There were 4 cases (0.55%) of ALT values >3X ULN in duloxetine-treated patients compared with 1 case (0.17%) in placebo-treated patients. Two of these duloxetine-treated cases (0.28%) also had ALT values of >5X ULN and >10X ULN compared with no cases in the placebo-treated patients. Given the small number of cases, there were no statistically significant differences between the duloxetine and placebo treatment groups.

In addition to the evaluation of liver-related events in the overall duloxetine-treated population, the subset of patients taking acetaminophen is of special interest, since acetaminophen is a known hepatotoxin and would be a likely concomitant medication in patients with chronic pain conditions. Data from the analysis by acetaminofen use from all placebo-controlled studies did not show significant differences in the incidence of ALT elevations (categories >3X ULN, >5X ULN, 10X ULN) between patients with and without concomitant intake of acetaminophen, however the number of patients who reported ALT abnormalities was considerably higher in the duloxetine/acetaminophen subset (n=33/1928; 2%) when compared to the placebo/acetaminophen subset (n=7/1466; 0.4%).

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Cardiovascular-Related Events

Given the known effects of duloxetine on blood pressure, and the increased risk of cardiovascular morbidity associated with NSAIDs, this is an area of particular interest in the chronic pain population, who will be receiving NSAIDs concomitantly with duloxetine.

The proportion of patients within the indication of OA/CLBP experiencing at least 1 cardiovascular-related SAE was 4 (0.5%) for duloxetine and 2 (0.3%) for placebo (p=.452).

Analyses of cardiovascular-related TEAEs by NSAID use were performed to determine whether concomitant use of duloxetine and NSAIDs increased the risk of adverse cardiovascular outcomes. This analysis was undertaken in patients from all placebo-controlled trials (i.e., with any indication including OA/CLBP). The following tables show the frequency of cardiovascular-related SAEs between treatment groups by NSAIDs use across all indications (OA/CLBP, DPNP, FMS, GAD, MDD, SUI/LUTD).

Tables 22 a) and b). Cardio-related Treatment Emergent Adverse Events by NSAID Uses.

SMQs: All cardio-related term

MedDRA Preferred Term	--- p-Value* --- Treatment by Strata	Strata (NSAID)	PLA N	PLA n	PLA (%)	DLX N	DLX n	DLX (%)	Fisher's Exact p-Value** Chi-Sq(c)
PATIENTS WITH >=1 TEAE	.607	.009 No	6427	207	(3.22)	9044	353	(3.90)	.026
		Yes	1797	76	(4.23)	2261	106	(4.69)	.493
Acute myocardial infarction		No	6427	0	(0)	9044	2	(0.02)	.514
		Yes	1797	0	(0)	2261	0	(0)	
Angina pectoris		No	6427	4	(0.06)	9044	4	(0.04)	.726
		Yes	1797	3	(0.17)	2261	0	(0)	.087
Angina unstable		No	6427	0	(0)	9044	0	(0)	
		Yes	1797	1	(0.06)	2261	0	(0)	.443
Arrhythmia		No	6427	1	(0.02)	9044	3	(0.03)	.646
		Yes	1797	2	(0.11)	2261	0	(0)	.196
Arteriosclerosis coronary artery		No	6427	1	(0.02)	9044	0	(0)	.415
		Yes	1797	0	(0)	2261	0	(0)	
Arteriospasm coronary		No	6427	0	(0)	9044	0	(0)	
		Yes	1797	1	(0.06)	2261	0	(0)	.443
Blood creatine phosphokinase MB increased		No	6427	0	(0)	9044	1	(0.01)	1.000
		Yes	1797	0	(0)	2261	0	(0)	
Blood creatine phosphokinase increased		No	6427	10	(0.16)	9044	27	(0.30)	.094
		Yes	1797	6	(0.33)	2261	3	(0.13)	.197
Bradycardia		No	6427	5	(0.08)	9044	3	(0.03)	.290
		Yes	1797	1	(0.06)	2261	2	(0.09)	1.000
Cardiac failure acute		No	6427	1	(0.02)	9044	0	(0)	.415
		Yes	1797	0	(0)	2261	0	(0)	
Cardiac failure congestive		No	6427	1	(0.02)	9044	2	(0.02)	1.000
		Yes	1797	3	(0.17)	2261	1	(0.04)	.328

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When analysing the non-NSAIDs users strata the frequency of cardiovascular adverse events was slightly higher in the duloxetine arm (4.69%) as compared to placebo (4.23%). However according to data on patients experiencing at least 1 TEAE no statistically significant interaction between NSAIDs and duloxetine could be observed. Albeit reassuring the lack of information on dose, duration, and frequency of concomitant NSAID/ acetylsalicylic acid make the interpretation of these results difficult.

Bleeding-Related Adverse Events

Looking specifically at bleeding TEAEs related to gastrointestinal track (GIT) in this population, the percentage of patients in the placebo-controlled studies reporting at least 1 GIT-related bleeding TEAE

was higher in the duloxetine (0.23%) than in the placebo group (0.15%). The most frequently reported treatment emergent GIT-bleeding events in duloxetine-treated patients were rectal haemorrhage and haematochezia, followed by melaena.

In order to determine whether concomitant use of an NSAID with duloxetine would lead to a synergistic effect on bleeding, the incidence of GIT-bleeding events in patients taking duloxetine with concomitant NSAID / acetylsalicylic acid was compared with that of patients taking duloxetine without concomitant NSAIDs / acetylsalicylic acid. The percentage of reports of any GIT-bleeding event was numerically higher among both duloxetine and placebo-treated patients who used NSAIDs/ acetylsalicylic acid (duloxetine 0.33%, placebo 0.23%) than those who did not (duloxetine 0.19%, placebo 0.11%). The lack of information on dose, duration, and frequency of concomitant NSAID/ acetylsalicylic acid make the interpretation of the results difficult.

Severe Cutaneous Adverse Reaction Analyses

No significant differences were observed between treatment groups of the primary placebo-controlled analyses set, patients taking duloxetine experienced at least 1 'severe cutaneous adverse reaction' with a similar frequency (5; 0.6%) to patients taking placebo (2; 0.3%).

Laboratory findings

Overall no new laboratory findings of clinical significance were seen in the chronic pain placebo-controlled studies compared to placebo-controlled studies in other indications.

Safety in special populations

Patients with clinically significant renal or hepatic dysfunction were excluded from primary chronic pain studies, and thus no new information was obtained from these studies.

No new population pharmacokinetic (Pop PK) analyses have been conducted in support of this application.

Safety related to drug-drug interactions and other interactions

No new interaction studies have been conducted in support of this application. Drug interactions with duloxetine have been well characterised in previous studies showing that duloxetine is metabolised by cytochrome P450 1A2 (CYP1A2) and cytochrome P450 2D6 (CYP2D6) and that duloxetine is a moderate inhibitor of CYP2D6.

Discontinuation due to adverse events

In the primary placebo-controlled analyses set discontinuation rate was higher in the duloxetine-treated groups. Discontinuation due to any reason was 30.2% and due to AE 16.4% in the duloxetine groups whereas it was 21.2% and 6.1% for placebo respectively. Nausea was the main reason for withdrawals seen in the active treatment arms (3%). Significantly more placebo-treated patients discontinued due to lack of efficacy (4.2%) than duloxetine-treated patients (2.1%). Significantly more placebo-treated patients completed the studies (78.8%) than duloxetine-treated patients (69.8%).

Post marketing experience

Postmarketing data has not been reviewed specifically for this application. However, duloxetine postmarketing data is regularly reviewed in a series of yearly Postmarketing Safety Update Reports (PSURs), the latest of which, PSUR 10, was submitted 01 October 2010.

For the purpose of active surveillance (signal detection), a retrospective cohort analysis based on a large external US-based insurance claims database is being conducted in patients who had a diagnosis

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of MDD, GAD, DPNP, or fibromyalgia (the approved indications for duloxetine in the US) and also had chronic pain diagnoses.

Discussion of clinical safety

The primary placebo-controlled analysis set comprises a total of 839 patients who were exposed to duloxetine over the course of both acute and long-term treatment in the current development programme. 16.4% of duloxetine patients discontinued due to AE, in the placebo arm discontinuation rates were 6.1%. In the primary long-term analyses set, 55 of the 83 (66.3%) patients completed the extension treatment phase. A brief summary of discontinuations due to the most common adverse events has been provided, which shows that nausea was the most reported adverse event as the reason for discontinuation. Discontinuation rates, although lower for the chronic pain studies are consistent with other duloxetine exposures.

Overall, statistically significantly more duloxetine-treated patients experienced TEAEs compared with placebo-treated patients. Of the 839 patients who were treated with duloxetine in the placebo-controlled chronic pain studies 61.5% experienced any AE. Nausea, dry mouth, constipation, insomnia, diarrhoea, dizziness, somnolence and fatigue were reported at significantly greater level and by more than 5% of patients. The profile of TEAEs of duloxetine in the chronic pain studies is similar to that seen in all other placebo controlled studies, with the exception of the frequency of nausea. The applicant argues that lower rate of nauseas seen in chronic pain studies could be explained by the fact that the majority of the studies required a lead-in dose of 30-mg QD and patients were encouraged to take duloxetine with food, which seems reasonable.

Although the majority of measured AEs were numerically higher in the duloxetine arm, no statistically significant result was found but for sexual dysfunction events in CLBP-EO study. Most TEAEs were mild or moderate in severity, with a higher reporting rate in the highest duloxetine dosage groups. When stratified by severity all most common AEs were more frequent in the duloxetine groups and the differences were statistically significant.

No deaths were reported during the studies only one death occurred after completing the extension phase of study CLBP-EN. The patient died due to cardiopulmonary arrest, however the event did not seem to be attributed to the study drug. Regarding other serious adverse events, 2.3% duloxetine-treated and 1.2% placebo treated patients in the primary placebo-controlled studies experienced 1 SAE. One case of suicidal ideation was observed in the extension phase of CLBP-EN. Overall the profile of AEs in the primary placebo-controlled analysis set was in line with the safety findings from previous duloxetine studies.

As hepatic events were previously identified as important risks in other applications, the safety assessment of this application was focused on the possible synergistic effect that the concomitant use of duloxetine with acetaminophen could have. Although no significant differences were observed in the incidence of hepatic related AEs between treatment groups by acetaminophen use, the increased risk cannot be ignored as the number of cases of ALT elevations identified in patients who were receiving concomitantly duloxetine and acetaminophen was greater than in the placebo/acetaminophen arm. The CHMP concluded that monitoring of hepatic events should continue as it was unknown to what extent the concomitant use of duloxetine and acetaminophen could increase the risk of hepatic events.

Upper GIT (UGIT) bleeding is considered an identified risk of duloxetine use. In the primary placebo controlled analyses set at least 1 GIT-related bleeding was 0.23% for duloxetine vs. 0.15% for the placebo. The most frequently reported GIT bleeding events with duloxetine were rectal haemorrhage (0.10%) and haematochezia (0.04%). New information from clinical trials and postmarketing data has

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been submitted by the MAH in response to the CHMP request to clarify the potential risk for UGIT bleeding with concomitant use of duloxetine and NSAIDs. According to the MAH, there has been no evidence of an interaction of duloxetine and NSAIDs when combined on bleeding events. Nevertheless, the CHMP did not consider reassuring these findings due to the intrinsic limitations of the source of the information (e.g. retrospective health-claims database without confirming with medical records, and controlling for confounding factors; a post-hoc review of the clinical trial database with limited information on doses, exposures, and other covariates; spontaneous reporting). In the CHMP's opinion, the association of UGIT bleeding with concomitant use of SSRIs/SNRIs and NSAIDs would represent a safety concern for duloxetine in the treatment of chronic pain.

Similarly cardiovascular events could be expected when duloxetine is administered concomitantly with NSAIDs. Due to the known mechanism of action of duloxetine the noradrenergic-related events would be also expected to appear, particularly an increase in blood pressure and clinically significant hypertension.

Although no significant results were observed in the performed analyses stratified by NSAIDs, the CHMP felt that the risk of UGIT bleeding and cardiovascular events could not be ruled out. A trend for an increase in some GIT and CV AEs was observed even in the studies supporting the current indication. No firm conclusions could be drawn, as the number of patients and events was too limited. However, the committee felt that from a mechanistic point of view, and based on the available evidence, an increased risk for these AEs could be expected following concomitant use of NSAIDs and duloxetine. The lack of detailed information regarding NSAIDs dose, duration, and frequency of concomitant use with duloxetine was considered to be an important unknown in this application. The existence of studies that associate UGIT bleeding with SSRIs/SNRIs (venlafaxine) added to the concern.

The CHMP found the applicant's proposal to withdraw the indication for duloxetine in add-on therapy to NSAIDs/acetaminophen reassuring. It was felt that restriction of target population would address, at least partially, some of the concerns providing appropriate warnings on how to minimise, or avoid risks related to the concomitant use of duloxetine with analgesic therapies (including sporadic use). Nonetheless the uncertainty regarding potential synergistic adverse effects of duloxetine and NSAIDs could not be ignored in particular as it was felt that a concomitant use can hardly be avoided, even on a non-regular basis.

The CHMP noted that the information in the elderly population with the greatest burden of chronic somatic pain, in particular the very elderly (>75 years of age) who are likely to be most vulnerable to any adverse events, was limited. It was felt that routine and enhanced pharmacovigilance activities as proposed by the applicant would not be sufficient to adequately address the duloxetine safety profile in this population.

Conclusion on clinical safety

Overall, it is acknowledged that the safety profile of duloxetine is well established and that from the evidence provided to support the current indication no unexpected AEs have been identified. The profile of observed AEs was similar to that known for duloxetine in the authorised indications. Treatment with duloxetine is associated with several risks including suicidality, hypertension, CV events, hepatotoxicity, and GI bleeding that require continuous monitoring. An important uncertainty regarding the potential synergistic adverse effects of duloxetine and NSAIDs remained unsolved in particular as it was felt that a concomitant use could not be avoided, even on a non-regular basis. In addition, safety of duloxetine in the elderly population was considered as important missing information.

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Risk Management Plan

The MAH submitted an updated risk management plan (RMP version 8).

The CHMP, having considered the data submitted in the application was of the opinion that the proposed risk minimisation activities were not able to reduce the risks to an acceptable level and did not endorse the changes proposed in the version 8 of the RMP.

4. Overall conclusion and Benefit-risk assessment

Benefits

Beneficial effects

The clinical program for duloxetine in the treatment of chronic low back pain (CLBP) and osteoarthritic (OA) pain includes five clinical studies, three in CLBP and two in OA. All the studies but one have shown that duloxetine 60/120 mg QD produces a statistically significant decrease in pain intensity as compared to placebo. This effect has been shown in the patient population with an overall basal pain of 6, which is deemed a moderate-severe pain. After 12-13 weeks of treatment, duloxetine reduced the basal pain by more than 2 points, though differences when compared to placebo were smaller. Either the MRMM analysis or at least one of the two sensitive analyses carried out (LOCF & BOCF) were statistically significant in favour of duloxetine for the main variable. Moreover, when the subjects with a 30 to 50% reduction in pain intensity as compared to baseline, were compared between placebo and the experimental arms, a statistically significant effect could be observed for duloxetine in some studies.

The results for the primary endpoints were generally supported by the analyses of the secondary variables. With respect to health outcome measures the overall consistent effect was seen for the 36-Item Short Form Health Survey bodily pain subscale.

Uncertainty in the knowledge about the beneficial effects

The clinical relevance of the observed effect, albeit statistically significant, is uncertain. In the overall population the results of the primary endpoint analysis showed, at best, a difference of 0.80 points over an 11-point scale between duloxetine and placebo arms. In some studies, those differences were of 0.40 or 0.60 points. The observed effect remained marginal from clinical point of view even if less conservative methods of handling missing data (i.e. LOCF) were applied.

The population included in trials was not adequately defined. The concerns regarding the heterogeneity of the studied population add further uncertainty as to what target population was intended for this application.

The analysis of subgroups has shown that the favourable effect of duloxetine seen in clinical trials was mainly determined by the results in the subset of patients for whom duloxetine was given in 'monotherapy' (patients not taking NSAIDs regularly). Based on the above-mentioned subgroup analyses results in the monotherapy subset were statistically significant in only 2 out of 5 studies. Differences observed ranged from 0.55 to 0.67 points (studies CLBP-GC and OA-FG respectively). Nonetheless, the usefulness of duloxetine monotherapy in the treatment of chronic pain remains uncertain due to the limited benefit and the delay in reaching the therapeutic effect.

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Moreover, the lack of comparison to standard treatment makes it even more difficult to establish the potential value of duloxetine as monotherapy. The doubts on whether the marginal results are due to duloxetine or whether they are a consequence of including a mild population remain unsolved. The lack of active comparator cannot be resolved with the presented historical comparisons. Apart from the usual limitations of such comparisons there is uncertainty about the representativeness of the selection of studies for analysis.

Furthermore, data on rescue medication was not properly recorded for any of the studies, adding uncertainties to the net contribution of duloxetine to the observed effect. Of note, only partial information can be found in the applicant's responses, which does not cast any light on this subject.

The results supporting maintenance of effect were considered to have very limited value as a small number of patients completed the open-label extension study and the effect was likely to be overestimated adding to the uncertainty on the long-term efficacy.

The efficacy in the elderly, in particular the very elderly, was studied in a very limited number of patients.

Risks

Unfavourable effects

Overall, statistically significantly more duloxetine-treated patients experienced TEAEs compared with placebo-treated patients. Nausea, dry mouth, constipation, insomnia, diarrhoea, dizziness, somnolence and fatigue were reported with a significantly greater frequency as compared to placebo and by more than 5% of patients. Most of AEs tended to appeared early in duloxetine treatment and subside quickly, whilst fatigue and dry mouth seemed to persist longer during treatment. 2.3% duloxetine-treated patients in the primary placebo-controlled studies experienced 1 SAE.

Duloxetine patients showed greater percentages of abnormal values of hepatic enzymes than placebo patients. ALT elevations returned to normal levels or were decreasing by the patient's last visit, regardless of whether they continued or discontinued study drug.

Gastrointestinal tract bleeding was reported in placebo-controlled trials (all indications regardless of NSAID use) more frequently in duloxetine groups than in placebo. The frequency of cardiovascular adverse events was slightly higher in the duloxetine arm as compared to placebo irrespective of NSAIDs use in placebo-controlled trials.

Overall, the safety profile of duloxetine is well established and from the evidence provided to support the current indication no unexpected AEs have been identified. The profile of observed AEs was similar to that known for duloxetine in the authorised indications. Treatment with duloxetine is associated with several risks including suicidality, hypertension, CV events, hepatotoxicity, and GI bleeding that require continuous monitoring.

Uncertainty in the knowledge about the unfavourable effects

In the context of the current application, the potential effect of concomitant use of duloxetine with NSAIDs on cardiovascular events is of concern. NSAIDs have common and potentially severe adverse effects including cardiotoxicity. This effect is particularly worrying as many patients in the potential target population will have both cardiovascular disease and chronic pain due to musculoskeletal disease.

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The potential risk of upper gastrointestinal tract bleeding with concomitant use of SSRIs/SNRIs and NSAIDs represents a safety concern highlighted also by the available literature data.

Importantly, due to the fact that the use of NSAIDs can induce different forms of acute renal failure (e.g. haemodynamically-mediated; acute interstitial nephritis often accompanied by a nephrotic syndrome), the possibility of a synergic effect with the concomitant use of duloxetine and NSAIDs cannot be ruled out.

The initially applied for broader indication does not allow to ignore the known and potential risks of the add-on therapy. The restriction of target population would address, at least partially, some of the concerns providing appropriate warnings on how to minimise, or avoid risks related to the concomitant use of duloxetine with analgesic therapies (including sporadic use) were included. However, the uncertainty regarding potential synergistic adverse effects of duloxetine and NSAIDs could not be ignored in particular as it was felt that a concomitant use can hardly be avoided, even on a non-regular basis.

Safety of duloxetine in the elderly population with chronic pain remains uncertain due to underrepresentation of this population in the studies.

Balance

Importance of favourable and unfavourable effects

During the procedure the applicant decided to restrict the initially applied for indication 'Treatment of moderately severe chronic somatic pain' to 'Treatment of chronic somatic pain (as established in chronic low back pain and osteoarthritis) of at least moderate severity in patients not taking NSAIDs regularly'.

Albeit some concerns can be solved by means of this restriction in the indication, the main efficacy concerns are still maintained.

The magnitude of the differences between placebo and duloxetine are of questionable clinical relevance. The concerns related to the absence of comparator and the delay in reaching the therapeutic effect undermine the potential value of duloxetine monotherapy in the treatment of chronic pain conditions. The contribution of the rescue medication used during the studies remains unknown adding further uncertainties to the relevance of the observed effect. Additionally, if a monotherapy use of duloxetine is considered, concerns arise regarding the representativeness of the target population in the submitted clinical trials. Patients taking NSAIDs for less than 15 days per month were defined as "non users", which questions to what extend this population represents truly a monotherapy use. Furthermore, to what extent the observed results might be extrapolated to the newly proposed target population, i.e. patients intolerant, with contraindications for NSAIDs including potential bleeding or cardiovascular risk when using NSAIDs remains uncertain.

The maintenance of effect was studied in a small number of patients in the open-label extension study adding to the uncertainty on the long-term efficacy. Moreover, the information on the duloxetine efficacy in the elderly in chronic somatic pain is limited.

If a convincing effect could be demonstrated, the safety profile of duloxetine when used truly in monotherapy would not be a limitation; however the uncertainty regarding potential synergistic adverse effects of duloxetine and NSAIDs remained unsolved and it was felt that a concomitant use would be expected. Moreover, the limited safety information in the elderly with the greatest burden of chronic somatic pain made uncertain the duloxetine benefit in this population.

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Benefit-risk balance

In the overall population statistically positive results were observed for all studies but one. However, when a more conservative method for missing data imputation was used, the results were even less convincing and only in 3 out of 5 studies reached statistical significance. Therefore, the clinical significance of these finding is highly questionable. The difference between placebo and duloxetine does not seem to be perceptible by patients. In addition, the small positive effect of duloxetine is reduced in the presence of NSAIDs. No effect appears to be observed when these two therapies are administered concomitantly. Moreover, the absence of a concurrent comparator in the studies makes it even more difficult to put the findings into perspective and to establish the potential benefit/risk of duloxetine as an alternative to NSAIDs, which is the claimed restricted indication.

Following the initially identified major concerns, the applicant has restricted the indication to the subset of patients receiving duloxetine as monotherapy. In this regard, efficacy conclusions do not change substantially, the observed effect is not deemed clinically relevant, and the lack of a concurrent comparator does not allow putting findings into perspective. The unknown contribution of the rescue medication to the overall effect adds further uncertainties to the efficacy assessment. In addition concerns arise regarding the heterogeneous trial population, which makes it even more difficult to ascertain whether these results can be extrapolated to the intended target population.

The maintenance of the effect has not been adequately demonstrated as very limited number of patients was evaluated in the long-term extension study. In addition, the information on the duloxetine efficacy in the elderly in chronic somatic pain was limited.

The safety in the elderly remains uncertain due to underrepresentation of this population in the studies. There is also uncertainty regarding potential synergistic adverse effects of duloxetine and NSAIDs in particular in light of the expected sporadic concomitant use.

Although it is not the remit of the CHMP to establish the place of a new drug in therapeutic armamentarium, in the absence of an active comparator, particularly in the treatment of pain conditions for which there are highly effective drugs, it is particularly difficult to conclude on the benefit/risk of duloxetine as an alternative therapy to NSAIDs on the basis of the evidence provided.

Divergent positions are presented in Appendix 1.

Discussion on the benefit-risk assessment

The use of duloxetine in the applied for indication the 'treatment of chronic somatic pain (as established in chronic low back pain and osteoarthritis) of at least moderate severity in patients not taking NSAIDS regularly' is not supported.

The applicant's proposal to modify the indication is reassuring and solves, at least partially, some concerns regarding clinical safety as long as a true monotherapy indication is intended. Nonetheless, duloxetine-placebo differences in the subset of patients "not using NSAIDs regularly" do not change the CHMP view regarding the clinical relevance. In the absence of a concurrent comparator it is difficult to interpret the relevance of the observed effect of duloxetine in the relief of chronic somatic pain as an alternative to NSAIDs in monotherapy. The unknown contribution of the rescue medication to the overall effect and doubts as to whether a true monotherapy setting was tested in clinical trials supporting this application, add further uncertainties to the efficacy assessment.

Additionally, the delay in reaching therapeutic effect cannot be accepted for drug intended to be used in monotherapy as a symptom relieving medication.

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Furthermore, the maintenance of the effect over time has not been demonstrated, which is not considered acceptable since duloxetine is intended for chronic use. In addition, the information on the duloxetine efficacy in the elderly in chronic somatic pain was limited.

Overall, it is acknowledged that the safety profile of duloxetine is well established, and from the evidence provided to support the claimed indication no unexpected AEs have been identified. The profile of observed AEs was rather similar to that known for duloxetine in the authorised indications, whereby, in addition to the tolerability concerns that can be handled in clinical practice, there are well known AEs requiring continuous monitoring, i.e. suicidality, hypertension, cardiovascular risk, hepatotoxicity, gastrointestinal bleeding. However, the lack of safety information in the elderly population with the greatest burden of chronic somatic pain represents an important limitation of the current application. There is also important uncertainty regarding potential synergistic adverse effects of duloxetine and NSAIDs in particular in light of the expected sporadic concomitant use.

As the benefit of duloxetine in treatment of chronic pain remains to be demonstrated, the benefit/risk balance of duloxetine in the claimed indication is deemed negative.

5. Conclusion

On 21 July 2011 the CHMP considered this Type II variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008 not to be acceptable, due to an unfavourable risk-benefit balance of Ariclaim, Cymbalta and Xeristar in the treatment of chronic somatic pain (as established in chronic low back pain and osteoarthritis) of at least moderate severity in patients not taking NSAIDs regularly and therefore did not recommend the granting of this indication.

The CHMP considered that:

1. The clinical relevance of the effect is not established.
2. The limited evidence provided to support the maintenance of the effect over time can hardly be taken as sufficient for a medicinal product intended for the treatment of a chronic condition.
3. Safety has not been sufficiently established in the population specified in the indication.
4. Efficacy and safety have not been adequately established in the elderly.
5. Taking into account that the duloxetine efficacy was not convincingly demonstrated in the treatment of chronic somatic pain (as established in chronic low back pain and osteoarthritis) of at least moderate severity in patients not taking NSAIDS regularly, and in light of the safety profile the positive benefit-risk balance in the applied for indication has not been established.

6. Re-examination of the CHMP opinion of 21 July 2011

Following the CHMP conclusion that the proposed extension of indication for Ariclaim, Cymbalta and Xeristar was not approvable, the applicant submitted detailed grounds for the re-examination of the opinion.

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6.1. Detailed grounds for re-examination submitted by the applicant

The applicant presented their detailed grounds for re-examination in writing and at an oral explanation to the CHMP. Additional analyses of previously submitted data together with literature data and expert statements were provided. No new clinical data were submitted.

Following a request from the applicant at the time of the re-examination, the CHMP convened an ad hoc expert group to provide experts' views on the CHMP questions in relation to the application for the variation, taking into account the applicant´s response to the grounds for refusal.

6.1.1. Ground #1 The clinical relevance of the effect is not established.

MAH's position

The applicant presented a three-fold approach to the assessment of the clinical relevance of duloxetine efficacy results which includes:

- Responder analysis (50% reduction in average pain) from the duloxetine chronic pain studies;
- Indirect comparisons with established pain medications;
- Assessment against IMMPACT recommendations for clinically meaningful effect at the group mean level.

Clinical relevance – response rates, indirect comparison and IMMPACT criteria

In the MAH's view response rates were deemed a very important secondary efficacy endpoint in the studies and were considered of key importance in assessing clinical relevance. Analyses of the 50% response rates, which in MAH's view is considered to represent substantial improvement in a patients' chronic pain, are the focus of this section. Response rates, ranging from 33% to 51%, were consistent across all duloxetine studies, with the frequency of patients achieving response being statistically significantly greater with duloxetine than placebo in 3 of the 4 positive studies including supportive study OA-EP (Figure 1). This finding was confirmed by pooling of all studies by disease state, where in both OA and CLBP studies, statistically significantly more duloxetine patients (40.3% and 38.4%, respectively) attained a clinically meaningful response compared with placebo patients (25.7%and 25.9%, respectively; $p < .05$) (Figure 2). The same patients who attained a substantial pain reduction (50% reduction in average pain) also experienced a clinically meaningful improvement in physical function (Figure 3), as measured by the change in WOMAC physical function scores and the RMDQ-24 scores for all duloxetine chronic pain studies (secondary endpoints).

Figure 1. 50% response rates (percent change from baseline to endpoint of average pain (BOCF) - NSAID nonusers only) by duloxetine study; greyed part of the graph represents data from a failed study CLBP-EO.

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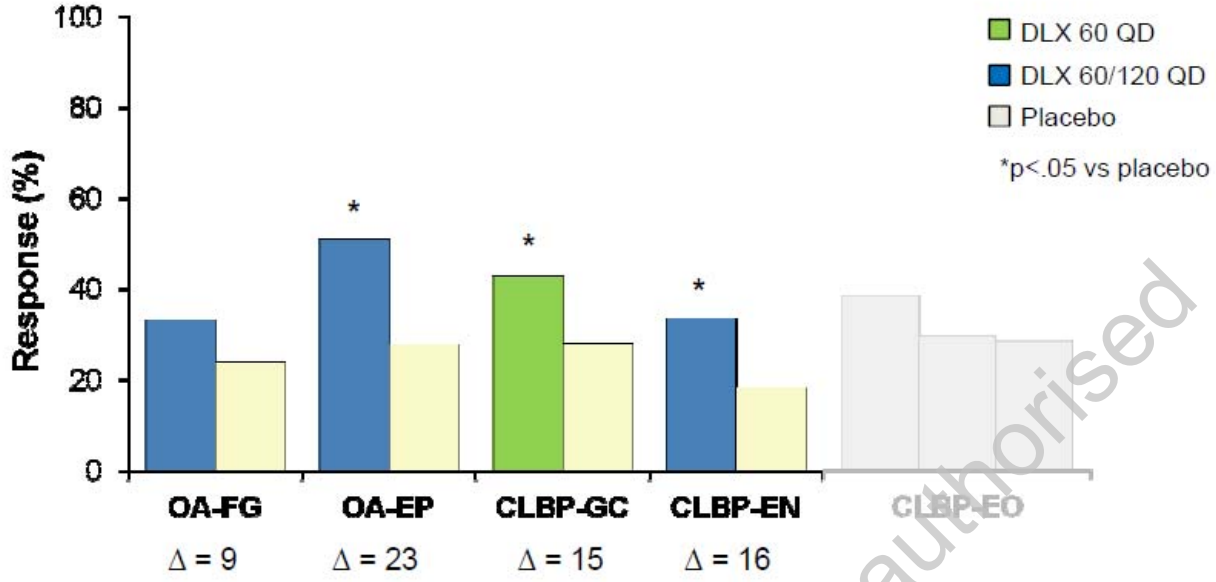

Figure 2. 50% response rates (percent change from baseline to endpoint of average pain) in NSAID nonusers by pooled OA and pooled CLBP duloxetine studies (BOCF); greyed part of the graph represents data from a failed study CLBP-EO.

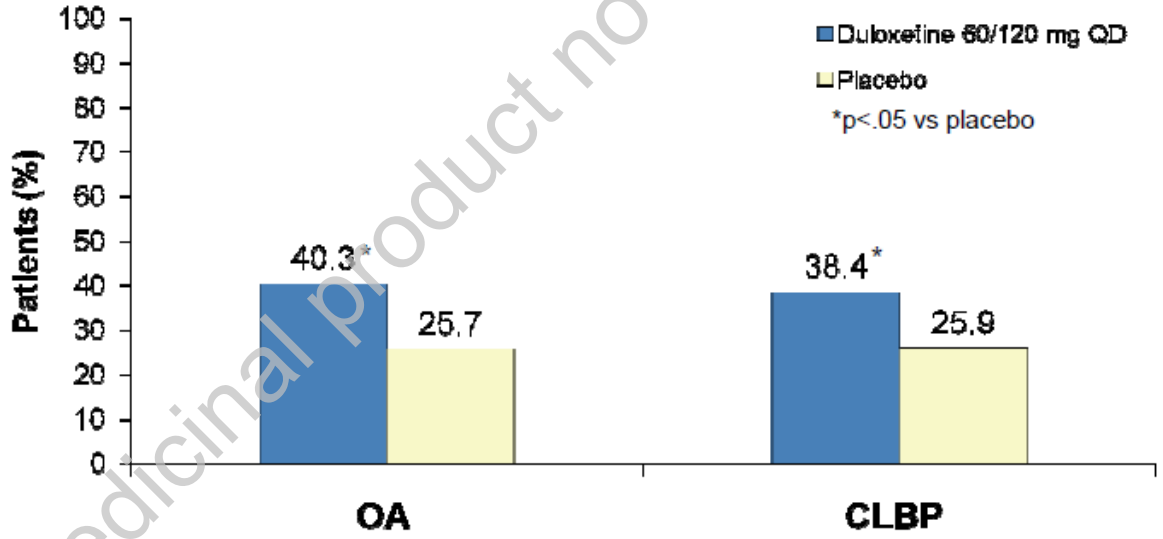

Figure 3. Improvement in physical functioning by categorical response status for duloxetine-treated NSAID nonusers using WOMAC in the pooled OA (left) and using RMDQ-24 in the pooled CLBP (right) studies.

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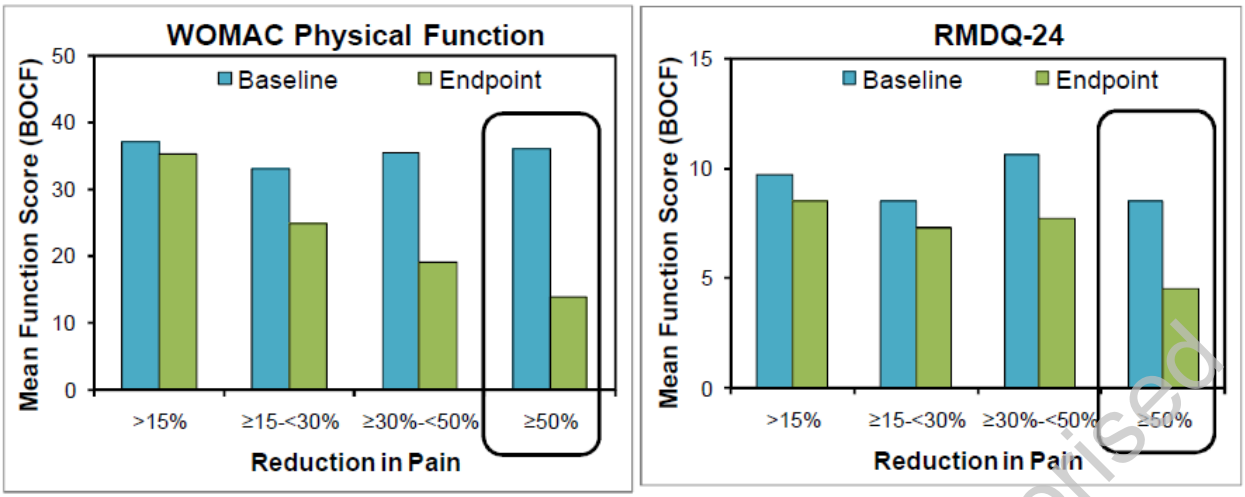
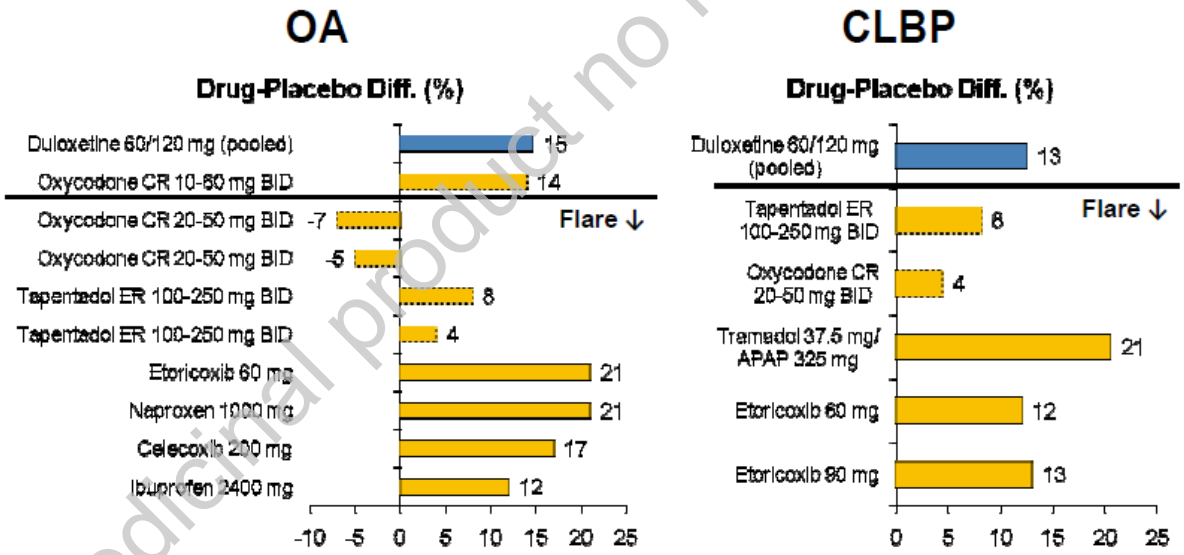


The drug-placebo difference of substantial pain relief (at least 50% reduction in pain) for historical comparator data was the subject of an external expert report by Dr. Andrew Moore, who provided data in an external expert report (Figure 4). Except where indicated, the response rates were calculated using a BOCF approach. The choice of the historical comparator was driven primarily by the availability of data analysed using the BOCF approach, though response rate data from tapentadol studies, only analysed using LOCF methodology, were included due to recent approval of tapentadol in the EU.

Figure 4. 50% response rates for duloxetine compared with other monotherapy analgesics.



Comparative Data Derived from Published Values - LOCF (dotted bars); all others BOCF
Source: Tapentadol AUS Assessment Report; Markenson JA et al. 2005; Moore et al. ARD. 2010; Moore et al. Pain. 2010; Peloso et al. 2004

Tapentadol is considered an important comparator for duloxetine by the MAH for the following reasons: a) it is recently approved for treatment of chronic pain in a number of EU countries and b) it has been studied in the same disease states of OA, CLBP, and DPNP. Also, when considering the proposed target chronic pain population for duloxetine, tapentadol is a newer drug of an established class of analgesic medication that represents an alternative treatment option for such patients.

As summarised in Figure 5 below, the treatment effect of duloxetine (drug-placebo difference) was greater than that observed for tapentadol by BOCF methodology, despite the use of flare design in the

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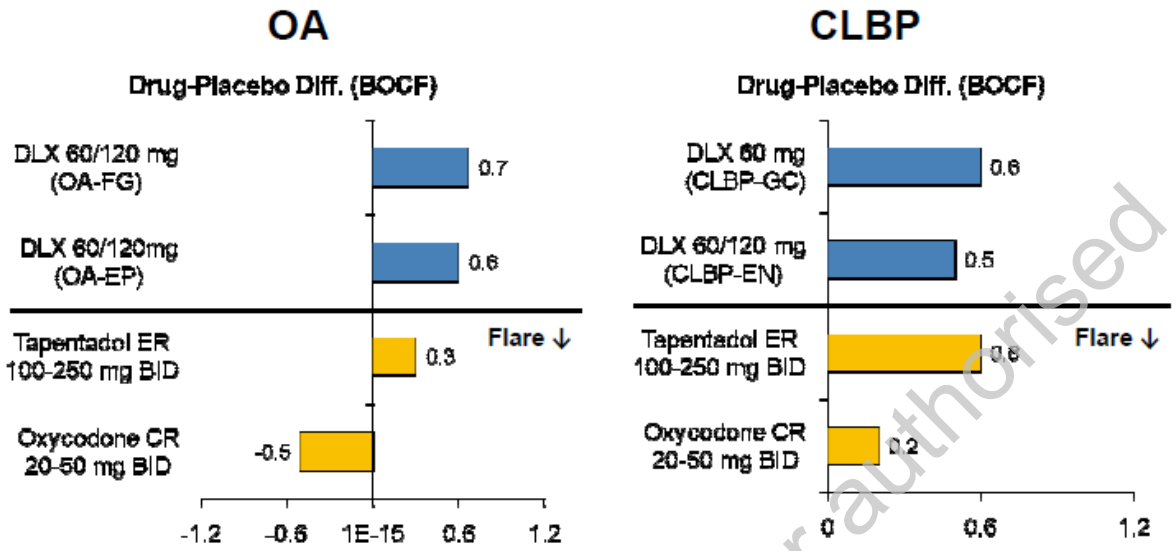
case of tapentadol. A greater proportion of patients achieved 50% response status with duloxetine than tapentadol.

Figure 5. Treatment effect of duloxetine and tapentadol.



Comparative Data Derived from Published Values (BOCF) Duloxetine NSAID nonusers only
Source: Tapentadol AUS Assessment Report; Afilalo et al. 2010; Buynak et al. 2010

The MAH compared indirectly also published data from randomised clinical trials of NSAIDs, COX-2, and opioids for OA with similar study duration and patient selection criteria. Based on these publications, the treatment effect of duloxetine (drug-placebo difference, baseline to LOCF) was comparable to the currently used analgesics including tapentadol (duloxetine 1-1.3; oxycodone CR 10-60 mg BID 1.1; Lumiracoxib 100-400 mg 0.5-0.8; celecoxib 200 mg 0.5-0.7; tapentadol 100-250 mg BID 0.3-0.7). This conclusion holds even in light of duloxetine's treatment effect as assessed using the BOCF methodology: -0.63 for pooled OA studies.

In order to come to a formal comparison of duloxetine with a variety of existing treatments, the MAH applied a meta-analytical framework to combine the results of independent trials. In the case of OA, the meta-analysis was based on the WOMAC pain subscale, as this represents an identical validated measure that has been used in recent clinical trials. In the case of CLBP, normal values of the used pain scales (VAS, NRS, and BPI) were applied in order to be able to compare the studied treatment alternatives. In order to limit potential bias in line with principles of good practice for standard meta-analysis (NICE 2008a; EMEA 2001), a detailed review protocol was pre-specified. Most included trials had a quality rating of at least 5 (out of 7) indicating trials of sufficient quality for inclusion. With regard to the meta-analysis of CLBP trials, even though the number of randomised controlled trials of similar duration and population in CLBP is substantially smaller than in OA, duloxetine appears to be as efficacious as alternative treatments (without correction for confounders).

In conclusion, while the magnitude of effect for duloxetine appears moderate, the meta-analyses confirmed in the MAH's view that duloxetine's analgesic effect was in line with the moderate group mean differences observed with other analgesics widely acknowledged and used to manage chronic pain.

Furthermore, the MAH has based its assessment of clinical relevance upon the consensus statement of the Initiative on Methods, Measurements, and Pain Assessment in Clinical Trials (IMMPACT) an expert group developing consensus reviews and recommendations for improving the design, execution and interpretation of clinical trials of treatments for pain (IMMPACT [WWW]). In order to place duloxetine's

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magnitude of effect into perspective, a detailed assessment of duloxetine clinical data against each of these recommendations was provided with a summary of this review. In the MAH's view, on all applicable IMMPACT criteria, the magnitude of effect for duloxetine was consistently demonstrated as clinically meaningful.

Other efficacy-related issues

Target population - Use of subgroups

The MAH enrolled both NSAID users and non users into 4 of the 5 duloxetine chronic pain studies (the 5th study CLPB-GC required all patients to wash out of all analgesics). The MAH agrees with the CHMP's view that chronic pain patients who are regular NSAID users and those who are not regular NSAID users may represent different subpopulations. Therefore, the randomisation was stratified by this baseline characteristic, i.e. whether patients were or were not regularly taking a therapeutic dose of NSAIDs, to pre-specify this subgroup analysis (although the power calculation was based on all randomised patients).

Regular use was defined as taking an NSAID/paracetamol for longer than 15 days over three consecutive months prior to randomization. Conversely, patients using NSAIDs/paracetamol less frequently (or not at all) were randomised as NSAID nonusers.

The above described approach to the clinical trial was considered appropriate by the MAH for the following reasons:

1) The intention of the trials was to assess the efficacy and safety of duloxetine in a setting that best reflects clinical situations. It was not MAH's intention to study duloxetine specifically in the population of patients for whom NSAIDs are contraindicated and who, consequently, would not take an NSAID under any circumstance (although such patients were not excluded either).

2) NSAIDs are the most widely used class of drugs worldwide. With regard to their use, patients with chronic pain can be divided into two categories: a) those taking NSAIDs regularly (daily or almost daily); and b) those who take them sporadically. The former group consists of patients who tolerate NSAIDs well and who perceive treatment benefit. The latter group is made of a clinically different type of patients including those who take NSAIDs only for a flare-up of their primary condition, for an activity-induced pain exacerbation, or for an unrelated acute or intermittent painful condition. Alternatively, they may be less able to tolerate NSAIDs.

3) It is important to recognize that the above two categories of patients are likely different because of complex and not fully understood differences in the underlying mechanisms of their pain, pharmacogenomic profiles, or other factors. Consequently, it is scientifically justified to explore potential differences in their response to an investigational analgesic.

As acknowledged by the CHMP, the analgesic effect of duloxetine over placebo in all randomised patients has been demonstrated by the analyses of mean reduction in average pain severity using both the primary analysis method of MMRM (4 out of 5 studies positive), and the sensitivity analysis using BOCF methodology (3 out of 5 studies positive). The remaining studies are supportive because they showed a numerically greater pain reduction with duloxetine treatment relative to placebo. Since the pivotal studies met the primary objective and there was a priori stratification on the basis of NSAID use, the MAH considered it appropriate to further analyse the data by NSAID use status (using the BOCF approach), even though the studies themselves were not powered to detect statistically significant differences between subgroups.

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Figure 6. Change from baseline to endpoint of Average Pain (BOCF) - NSAID nonusers only; greyed part of the graph represents data from a failed study CLBP-EO.

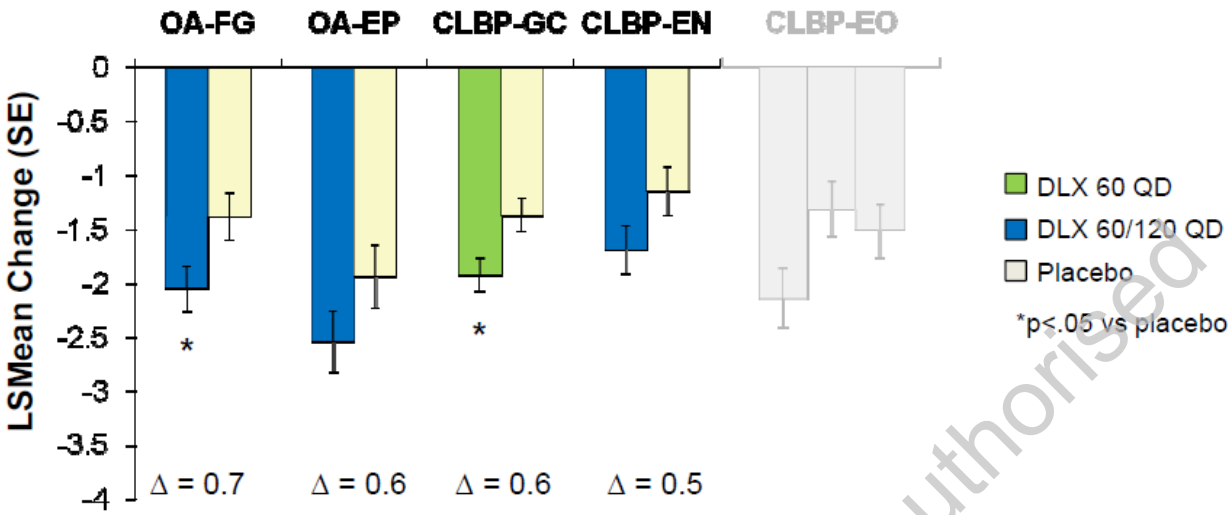
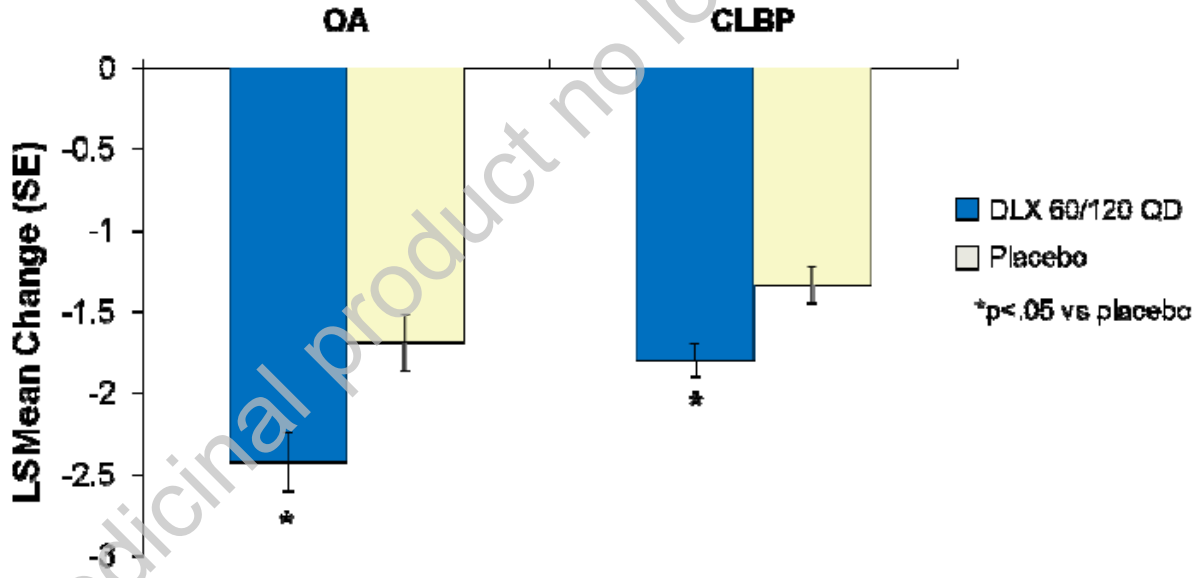


Figure 7. Change from baseline to endpoint of average pain (BOCF) for 5 pooled studies (OA-FG/EP and CLBP-EN/GC/EO) - NSAID nonusers only.



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As shown above (Figure 6), despite the smaller sample size and subsequent loss of statistical power with the subgroup analysis using BOCF, NSAID nonusers experienced statistically significant greater decrease in average pain with duloxetine compared with placebo in 2 of the 4 positive studies, with the remaining studies being numerically consistent. Further, the magnitude of difference among all studies was similar (duloxetine-placebo difference range: -0.5 to -0.7) and, when pooling by disease state (Figure 7), the duloxetine-placebo differences were statistically significant.

Non-inferiority margin and group mean versus individual response

During the assessment the clinical relevance of duloxetine's effect was questioned based on the duloxetine-placebo difference being smaller than published non-inferiority margins. In their grounds for re-examination the MAH underlines than in the case of the etoricoxib reference results (Pallay et al. 2004) that study used flare design and imputed results using a time weighted average, both of which were likely to inflate the drug -placebo difference (a point made by one of the experts contacted by the MAH, Dr Dougados). In MAH's view a fair comparison should include only the studies of similar design and analytical approach. This point is considered further in the indirect comparison carried out by the MAH.

Moreover, in support of a cautious use of thresholds to assess the clinical relevance of results observed with duloxetine in OA and CLBP the MAH quotes opinions from experts in the field.

- Letter from Dr Maxime Dougados, Professor of Rheumatology, Rene Descartes University, Paris France, the senior author of the Tubach et al. 2005 paper,
- Letter from Dr John Farrar, Department of Biostatistics and Epidemiology, Center for Clinical Epidemiology and Biostatistics (CCEB), Medical Center, The University of Pennsylvania,
- Letter from Dr Robert H. Dworkin, the chairman of the IMMPACT group.

The experts quoted by the MAH stated also that "The threshold published in this paper should not be used for interpretation of data presented in terms of between group differences in mean changes of continuous variables (e.g. VAS or Likert scale) [Tubach et al. 2005]" and that a clinically meaningful change from baseline to endpoint for an individual patient should not be used as the basis for determining the threshold at which the magnitude of the drug-placebo difference becomes clinically meaningful at a group level (Dworkin).

Lack of active comparator and historic comparisons

The lack of an active comparator in the duloxetine chronic pain studies has been viewed by the CHMP as a flaw that prevents an effective evaluation of the clinical relevance of duloxetine's effect. However, in the MAH's view the lack of active comparator in these studies arose out of valid scientific concerns and there are scientifically valid approaches for assessing clinical relevance which are appropriate for use with the duloxetine studies.

The placebo was selected as the sole comparator for all studies for several reasons, which in the MAH's view justify placebo use alone.

1. Use of a NSAID as an active comparator would have resulted in the exclusion of patients with established CV, GI, or renal disease consistent with the Warnings and Precautions contained within NSAID labelling, even if the protocol mandated only short term use of NSAIDs.

2. 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 respect to blinding any trial.

3. Use of a selective COX2 inhibitor was not viewed as acceptable since duloxetine studies were initiated 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.

4. Use of any opioid as active comparator was not seen as an option. Apart from the many medical reasons for not using an opioid (such as narrow therapeutic index, abuse potential, and diversion), the differences in adverse event profile and tolerability between duloxetine and any opioid would likely lead to an unblinding of the study.

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5. While paracetamol may be used for the first line treatment of low back pain, such a comparator would not be appropriate for a patient population with established CLBP and a pain severity of at least 4 on the BPI average pain scale.

The MAH has also considered the aspects highlighted in the reflection paper from the CHMP (EMA /759784/2010) that need to be addressed if no direct comparison to active control is included in a marketing authorisation application for a product. Using these criteria the MAH concluded that it was reasonable in this case, to base the scientific conclusions on efficacy and safety from placebo-controlled studies alone.

The historical comparisons provided to CHMP comprised a meta-analysis of published studies in osteoarthritis and CLBP, a historical comparison of treatment effect for published studies using LOCF, and a historical comparison of data available to the MAH using BOCF. The Applicant fully acknowledged that a direct comparison with an active drug would better answer questions on comparative efficacy, but choice of an appropriate comparator was carefully considered and deemed not feasible. In the MAH's view these duloxetine comparisons have been undertaken in a manner consistent with the EU guidance for historical comparison. Selection of studies used for historical comparisons was not based on the conclusions of the studies, but rather based on their design. In order to minimise selection bias, the inclusion and exclusion criteria for published literature were predefined before performing the literature search. Studies were included if they met the following criteria: placebo-controlled studies in OA and CLBP; 12-week duration; pain severity as primary; design and analysis similar, except that some used flare design; study populations comparable. In addition to comparisons which included all studies meeting these criteria, a further historical comparison was undertaken with all data available to the MAH where data from chronic pain studies were analysed using BOCF. In the MAH's view while this approach may be less valuable as the use of a direct comparator, such a careful historical comparison provides useful insight into the relative efficacy of duloxetine and well established analgesics and hence the clinical relevance of duloxetine.

Rescue medication use

In accordance with the ethical principles of placebo-controlled clinical trials in chronic pain, episodic use of analgesics as rescue treatment was allowed in all studies in order to increase patient retention. However, for all studies rescue medication use was restricted - episodic use was defined as <3 consecutive days and <20 days total during the 3-month treatment period. Tramadol was the only disallowed rescue analgesic due to the potential risk of serotonin syndrome.

Table 23. Concomitant rescue analgesics reported with a frequency of at least 5% in all randomised patients.

Therapy	N	Diclofenac n (%)	Ibuprofen n (%)	Meloxicam n (%)	Naproxen n (%)	Paracetamol (Acetaminophen) n (%)
HMFG (OA)						
Placebo	128	6(4.7)	2 (1.6)	9(7.0)	5 (3.9)	16(12.5)
DLX60/120QD	128	7(5.5)	4 (3.1)	6(4.7)	4 (3.1)	18(14.1)
HMGC (CLBP)						
Placebo	203	9(4.4)	42(20.7)	1 (0.5)	8 (3.9)	19 (9.4)
DLX60QD	198	3 (1.5)	25 (12.6)	1 (0.5)	6 (3.0)	10 (5.1)
HMEN (CLBP)						
Placebo	121	10(8.3)	6(5.0)	1 (0.8)	2 (1.7)	11 (9.1)
DLX60/120QD	115	5 (4.3)	7 (6.1)	0 (0.0)	0 (0.0)	10 (8.7)
HMEO (CLBP)						

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Placebo	117	3 (2.6)	24(20.5)	0 (0.0)	9 (7.7)	13(11.1)
DLX20/60/120QD	287	12 (4.2)	61(21.3)	4 (1.4)	22 (7.7)	35(12.2)
HMEP (OA)						
Placebo	120	6 (5.0)	18(15.0)	5(4.2)	18(15.0)	14 (11.7)
DLX60/120QD	111	5 (4.5)	12(10.8)	7(6.3)	17(15.3)	21(18.9)

Based on the data from all studies and the more detailed analysis from Study CLBP-GC/HMGC (the frequency and duration of rescue medication use was recorded in patient daily diaries), which it is reasonable to extrapolate to the other highly comparable studies, the MAH concludes that the duloxetine study results are fully interpretable and not confounded by use of rescue analgesics.

Timing and onset of efficacy

In MAH's view the most informative approach to examine the earliest time to response was a 30% response analysis using average pain data collected from patient diaries, which was performed using data from Study HMGC (CLBP), the study where concomitant use of NSAIDs was not allowed.

The results from this analysis demonstrated that 15% of all randomised duloxetine-treated patients responded (defined as at least 30% decrease from baseline average pain rating) by Week 1 and 40% had responded by Week 3. There was a statistically significant difference in response rates versus placebo starting at Week 1 (8%, 95% confidence interval [CI] 0.011, 0.14). The results were consistent with those observed in the already approved indication of diabetic peripheral neuropathic pain (DPNP) (Pritchett et al. 2007).

Based on these data and good clinical practice, the MAH proposed a recommendation in the SmPC to re-evaluate patients at 4 weeks post-duloxetine initiation to assess response status, and cautions that "additional response after this time is unlikely". In order to further strengthen this recommendation, the statement "consideration should be given to discontinuing treatment." could be added to the proposed SmPC.

MAH's conclusions

Three different approaches to the assessment of the clinical relevance of the therapeutic effects of duloxetine have shown that, a significant proportion of patients in the target population have substantial benefit and the analgesic effect is consistent with that seen for other well established chronic pain medications, comparing favourably with the newly approved opioid, tapentadol. In addition, when assessed against a set of internationally recognised recommendations for what constitutes a clinically meaningful response, duloxetine is judged well against all applicable criteria, in particular in light of no general consensus as to what constitutes evidence of a clinically relevant magnitude of treatment effect on a group mean level within chronic pain studies.

Furthermore, in MAH's view the use of the subgroup of NSAID nonusers has been sufficiently justified; adequate detail of rescue medication was collected; acceptable onset of meaningful effect taking into account the chronicity of the disease was attained. In addition, there were scientific reasons for the use of placebo at the time of the studies' initiation and the program met the criteria for the use of placebo as comparator described in the CHMP Reflection Paper on this issue (EMA/759784/2010).

CHMP's conclusions

The CHMP acknowledges that the short-term efficacy in the target population of NSAIDs non-users (patients not using NSAIDs regularly) has been shown from a statistical significance perspective.

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However, the magnitude of the effect at a group level as well as at a responder rate level is small, and it is questionable whether it is clinically relevant. In the only study evaluating the effect of duloxetine in a true monotherapy setting, study CLBP-GC, the absolute differences over placebo in the average pain intensity change from baseline was -0.55 on an 11-point scale (BOCF). When considering the rate of responders, differences over placebo were 7.1% for the 30% Responder Rate and 14.8% for the 50% Responder Rate.

It is uncertain how the magnitude of the observed effect as compared to placebo translates into clinical relevance, particularly in the treatment of a chronic condition. In this light, the lack of an active control is a limitation, since the intention of the MAH would be to place duloxetine as an alternative to NSAIDs or opioids.

The comparisons presented by the applicant with data from other pain medicines are only indirect, and cannot obviate for the lack of a comparator. Historical comparisons do not seem valid nor justified for this common condition. Without a direct comparison in head to head trials, it is difficult to put the observed effect into clinical perspective.

The contribution of the background anti-inflammatory medication to the overall effect is unknown which adds further uncertainties to the efficacy assessment.

Moreover, the higher discontinuation rate observed in the duloxetine treatment arms could suggest that the moderate treatment efficacy did not outweigh the burden of adverse events.

The clinical relevance of the modest effect shown has to be considered in light of the safety and tolerability profile of duloxetine in the target population. Various amendments to the definition, in the indication, of the proposed target population were discussed during the procedure, but the CHMP considered them of doubtful clinical applicability. This is further discussed under Grounds for refusal number 3 and 5.

Ground #2 The limited evidence provided to support the maintenance of the effect over time can hardly be taken as sufficient for a medicinal product intended for the treatment of a chronic condition.

MAH's position

The extension phase of study CLBP-EN (HMEN) was designed to assess the maintenance of duloxetine's analgesic effect in CLBP. Study CLBP-EN (HMEN), the maintenance-of-effect study with the 41-week open-label extension phase after 13-week, placebo-controlled treatment phase, was designed to be similar to the maintenance-of-effect study (HMEM), the long term study provided in support of the duloxetine DPNP submission. Study CLBP-EN (HMEN) was designed to be consistent with CHMP Follow-up Scientific Advice (September 2006, EMEA/CHMP/SAWP/ 364064/2006) which stated that the 12-week pivotal studies "should be complemented by 12 months' data to exclude tolerance. It was accepted previously that this 12 months' data could be acquired in an open label extension". In MAH's view the extension period (up to 41 weeks after 13 weeks of placebo-controlled treatment) better reflects the long-term treatment requirement for chronic pain, consistent with CHMP Scientific Advice (15 December 2005) for duration and sets a higher bar to demonstrate the maintenance of effect. To the best of the MAH's knowledge of the literature relating to the management of CLBP, study CLBP-EN (HMEN) represents the longest study in patients with CLBP.

A margin of 1.5 was chosen to assess whether maintenance of effect was achieved after 12 months of treatment. This margin was based on the following consideration: DPNP and CLBP are degenerative diseases, and, upon consultation, the clinical advisors suggested that a worsening of up to 1.5 points during the maintenance period would still retain an improvement that is clinically meaningful

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(compared with the pain that patients would feel if they had not taken treatment and the disease had progressed). To address the concern in the CHMP that the LOCF approach potentially overestimates the maintenance effect, a post-hoc non-inferiority analysis using the BOCF method was performed to construct a 97.5% CI based on the mean change from baseline to BOCF endpoint. The analysis used data from patients who met response criteria during the 13-week treatment phase of the study and subsequently entered the extension phase (referred to as "duloxetine responders").

Using BOCF methodology, the mean change in BPI average pain was 0.70, and the upper bound of the one-sided 97.5% CI was -0.28, which was less than the prespecified margin of 1.5 points, and also less than zero. This result, therefore, shows that duloxetine responders maintained response to duloxetine throughout the extension phase.

Additionally, a response rate analysis using the BOCF approach (defined as at least 30% average pain reduction from study baseline) was performed in which patients who discontinued the extension phase were treated as non-responders regardless of the average pain rating collected during the extension phase. For duloxetine responders (N=61), the BOCF response rate at the end of a 41-week extension phase was 63.9% (39 out of 61 responders), which indicated the majority of patients maintained the pain reduction obtained during 13-week acute treatment.

MAH's conclusions

In study CLBP-EN (HMEN), patients who remained on duloxetine for 9 months continued to improve throughout the study. Both BOCF and LOCF analysis found that the majority of acute phase duloxetine responders still met response criteria at the end of the 41-week extension phase and the upper bound of the one-sided 97.5% CI was less than 0, indicating a further significant pain reduction from the end of acute phase during extension treatment. In addition, the sample size of 61 patients provides more than 90% power to demonstrate non-inferiority, it can be concluded that duloxetine's effect is maintained for up to 1 year. These data are supported by the long-term efficacy results in the 181 duloxetine-treated patients (all randomised patients) entering the extension phase. These patients, on average, experienced a continuous pain reduction during the entire 54 week extended-treatment period, comparable to that seen for DPNP.

CHMP's conclusions

The CHMP maintained its initial opinion that the results supporting the maintenance of effect have limited value due to the small number of patients that completed the open label extension.

Again, comparative data would undoubtedly have been preferable to substantiate the clinical relevance of the effect in this chronic condition, however the current analysis provides some evidence that patients are at least not deteriorating when using duloxetine.

It is difficult to see, however, how an effect can be maintained if it has not been robustly demonstrated in the first place.

It was discussed at the oral explanation whether this concern could be resolved with an SmPC recommendation to re-evaluate and stop treatment in case of non-response after 4 weeks. In the CHMP opinion, it will not be easy to attribute worsening/ non-response/ lack of effect to an episodic increase in pain due to the condition or lack of efficacy or both. The incorrect interpretation could be that, in absence of duloxetine, the pain would have even been worse and the probable outcome would be to use a concomitant NSAID, an incorrect recommendation.

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The CHMP noted that the MAH proposed to commit to providing additional data on the maintenance of effect post-authorisation, but it was considered that this information should be part of the benefit/risk evaluation.

Ground #3 Safety has not been sufficiently established in the population specified in the indication.

MAH's position

The safety profile of duloxetine has been well-characterised in more than 31,000 patients participating in clinical trials and more than 42 million patient exposures in postmarketing experience worldwide. Moreover, the product is already indicated in a pain condition, diabetic peripheral neuropathic pain (DPNP), which involves the use of duloxetine in an aged and vulnerable population, who will be taking a significant number of concomitant medications.

Risk with concomitant NSAID Use

The MAH performed clinical trial analysis focusing on the incidence of serious AEs and treatment emergent adverse events (TEAE), specifically CV and GI bleeding events, in two groups of patients (with and without concomitant use of NSAIDs or paracetamol) in two datasets. The two datasets used were: chronic pain studies, excluding Study CLBP-GC (HMGC) and all placebo-controlled duloxetine studies (that is patients from all studied indications: MDD, GAD, DPNP, SUI/LUTD, fibromyalgia and chronic pain).

When assessing the frequency of SAEs in the chronic pain studies (excluding CLBP-GC (HMGC)), no significant treatment-by-NSAID use interactions were observed for patients experiencing at least 1 SAE or for any individual SAE (Table 24). Similarly, the overall frequency of treatment emergent adverse events (TEAEs) in the chronic pain studies (excluding study CLBP-GC (HMGC)) was comparable between duloxetine NSAID users and nonusers, and no statistically significant treatment-by-NSAID use interaction was found. Overall, GI bleeding-related TEAEs were reported by duloxetine-treated patients in the chronic pain studies in 1/377 (0.35%) in duloxetine only and in 0/264 (0.0%) in duloxetine plus NSAIDs. These results are similar to data from all placebo-controlled studies combined, where GI bleeding events were uncommon. No statistically significant treatment-by-NSAID interactions were found for any individual GI-related bleeding event (Table 24).

With respect to CV-related events in the chronic pain studies (excluding CLBP-GC (HMGC)), though no statistically significant treatment-by-NSAID use (p-value 0.251) was found for patients experiencing at least 1 event, the percentage of duloxetine-treated patients experiencing at least 1 cardiovascular-related TEAE was greater among NSAIDs users than NSAID nonusers (driven by reports of palpitations -duloxetine plus NSAIDs 2.3%, placebo plus NSAIDs 0.0%; duloxetine monotherapy 0.3%, placebo monotherapy 0.7%). The clinical significance of this observation is uncertain. In the all placebo-controlled studies, however, there was little difference between the reporting rates of palpitations in duloxetine-treated patients with NSAID (1.9%) than without (1.6%). For all CV-related events, this imbalance between NSAID users and nonusers was not observed in all placebo-controlled studies, where a larger sample size analysis resulted in a similar percentage of patients experiencing at least 1 cardiovascular-related TEAE between treatment groups with no NSAID use (duloxetine 3.9%, placebo 3.2%; p=.026) and with concomitant NSAIDs use (duloxetine 4.7%, placebo 4.2%; p=.493) (Table 24).

Table 24. Adverse events by NSAID use in all randomised patients in chronic pain studies and all placebo-controlled studies.

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NSAID use*	CLBP/OA (excluding HMGC) dataset					All Placebo-controlled dataset				
	Yes n (%)		No n (%)		Trt-by-NSAID p-val	Yes n (%)		No n (%)		Trt-by-NSAID p-val
	DLX N= 264	PBO N= 194	DLX N= 377	PBO N= 292		DLX N= 2261	PBO N= 1797	DLX N= 9044	PBO N= 6427	
Pts with ≥1 SAE	5 (1.9)	3 (1.5)	9 (2.4)	5 (1.7)	.886	43 (1.9)	37 (2.1)	127 (1.4)	78 (1.2)	.395
Pts with ≥1 TEAE	163 (62)	96 (50)	228 (61)	123 (42)	.217	1886 (83.4)	1339 (74.5)	6340 (70.1)	3438(53.5)	<.001
Pts with ≥1 CV event	12 (4.6)	4 (2.1)	7 (1.9)	6 (2.1)	.251	106 (4.7)	76 (4.2)	353 (3.9)	207 (3.2)	.607
Pts with ≥1 GI-bleeding	0 (0.0)	1 (0.5)	1 (0.3)	1 (0.3)	-	11 (0.3)	6 (0.2)	15 (0.2)	6 (0.1)	.742

Abbreviations: CLBP = chronic low back pain; DLX = duloxetine; n = number of patients; NSAID = nonsteroidal anti-inflammatory drug; OA = osteoarthritis of the knee; PBO = placebo; Trt-by-NSAID = treatment by NSAID subgroup analysis; CV =cardiovascular; GI-bleeding = gastrointestinal bleeding.

* NSAID use in the all pbo-studies was defined as any report of an NSAID; NSAID use in the chronic pain studies (excluding HMGC) was defined based on stratification factor (i.e. - therapeutic NSAID use vs. sporadic).

Additionally, the MAH presented analyses comparing patients with previously reported GI bleeding or cardiovascular-related conditions (referred to as "vulnerable patients") with patients with no reported prior history, using both clinical trial data and postmarketing data. The clinical trial dataset included all placebo-controlled studies (up to 3 months duloxetine exposure) and all longer-term duloxetine studies (studies with at least 6 months of exposure; placebo group was not inluded). In all placebo-controlled studies, there were no statistically significant treatment-by-subgroup interactions for CV events or GI-bleeding events in all randomised patients (NSAIDs user and non NSAIDs user combined). These results, however, need to be viewed with caution considering the relatively small numbers in the "vulnerable patient" groups (N=552 in CV group; N=1364 in GI-bleeding group). In longer-term studies, when compared with "not vulnerable" patients, duloxetine-treated "vulnerable" patients in the all randomised patient population and the NSAID nonusers only population experienced a higher frequency of all CV events combined; however, in light of the placebo-controlled data above where the treatment by subgroup interaction was not statistically significant, the MAH attributed this finding to the intrinsic characteristics of the patient population. The rates for cardiovascular events (including myocardial infarction [MI] and stroke) in the longer-term studies were consistent with incidence rates of cardiovascular outcomes seen in epidemiological studies cited by the MAH (Steg et al 2007). A numerical trend was seen in terms of in increased incidence in GI bleeding events in duloxetine-treated "vulnerable patients" in placebo-controlled trials; however no increase in GI-bleeding events in the longer-term was seen with respect to frequency of events observed during short-term treatment. Any GI-bleeding in "vulnerable patients" treated long term with duloxetine did not worsen with concomitant NSAID use.

A higher discontinuation due to an AE was observed with duloxetine than placebo, the duloxetine-placebo difference for discontinuation due to an AE in "non-vulnerable patients" was statistically significantly greater than the duloxetine-placebo difference in the "vulnerable patients" (p=.001). This finding indicates that "vulnerable patients" were not more likely to discontinue due to an AE than "non-vulnerable" patients. The MAH proposed that these areas of risk assessment (CV related and GI bleeding related events) will continue to be closely monitored as described in the Risk Management Plan (RMP), including routine surveillance, active surveillance of a health claims database twice a year,

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the conduct of an upper GI bleeding observational study, and an additional subgroup analysis of duloxetine and NSAID use in hepatic injury cases.

Safety profile of duloxetine vs. opioids

The MAH also presented the indirect comparison of the safety profile of duloxetine with available information for opioids through SmPC and literature data comparisons and pharmacovigilance activities for duloxetine. In MAH's view the important identified and potential risks of duloxetine are well characterised, do not have a significant impact on the healthcare burden, and can be managed without needing additional risk minimisation requirements (beyond labelling). All the identified and potential duloxetine risks are described appropriately in the SmPC, enabling prescribers to understand the benefit risk balance when prescribing duloxetine across all indications. On the contrary, according to the MAH opioids carry a disproportionate risk of abuse, dependence and addiction, an increased risk of fatalities and serious public health implications. In addition to these issues, there are several other risks related to opioids use, namely the risks of fractures, opioid induced endocrine dysfunction and immunosuppression.

MAH's conclusions

Duloxetine has well characterised, acceptable safety profile as a treatment option for patients with chronic pain who are not taking NSAIDs regularly (the targeted population). Moreover, duloxetine has more favourable safety profile in comparison to opioids, the most likely alternative medication for this population.

CHMP's conclusions

Uncertainties remain in the short and long term safety profile of duloxetine in the target population. Gastrointestinal (GI) and cardiovascular (CV) side effects are known for duloxetine, and are expected to be particularly relevant for a population for which NSAIDs use is not indicated.

The definition of NSAID non users as presented in the clinical trials is vague (patients using NSAIDs for less than 15 days) and covers a broad population, including patients for which NSAIDs treatment was not appropriate or contraindicated. In addition, NSAIDs are available as OTC medication and it will be impossible, in real life, to prevent patients from using them when considered needed, either sporadic or on a regular basis. In practice, on demand NSAIDs will be taken potentially increasing the risk of CV, GI and hepatic adverse events.

The translation of the definition "use of NSAIDs for less than < 15 days" into an appropriate indication, either "patients not taking NSAIDs regularly" or "where the prolonged use of NSAIDs is not appropriate or contraindicated", is therefore considered by CHMP of doubtful clinical applicability and does not solve the concerns.

Ground #4 Efficacy and safety have not been adequately established in the elderly.

MAH's position

Efficacy in the elderly

Duloxetine efficacy in the elderly (≥65 yrs) and very elderly (≥75 yrs), although limited in terms of available data, was assessed using the BPI-average pain data (the mean change from baseline to endpoint) and proportion of 50% responders at endpoint as the outcomes of interest. In these

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analyses no statistically significant treatment by age interaction was observed in the elderly group (age ≥65) on either of the two efficacy endpoints. Overall, elderly patients aged ≥65 treated with duloxetine (or placebo), demonstrated a similar level of analgesic efficacy relative to non-elderly adults (Table 25). Although data from the chronic pain studies are limited, they are consistent with the overall clinical experience with duloxetine in the DPNP, which is mostly a disease of elderly.

The sample size for the very elderly subgroup is very limited (31 in total for pooled OA studies and 33 in total for pooled CLBP studies), which makes the interpretation of results in this subgroup not valuable, and therefore was not presented.

Table 25. Treatment by age subgroup interaction of mean change and clinically relevant response rates by BOCF. All randomised patients who were NSAID non-users (pooled OA and pooled CLBP studies).

Subgroup	**Pooled OA Studies**			**Pooled CLBP studies**		
	DLX 60/120	Placebo	**Trt-by-age p-value**	DLX 60/120	Placebo	**Trt-by-age p-value**
BPI average pain [LSMean change (SE)]						
<65 years	N=67 -2.03 (0.24)	N=81 -1.62 (0.22)	0.436	N=304 -1.85 (0.12)	N=282 -1.44 (0.13)	0.425
≥65 years	N=66 -2.53 (0.25)	N=54 -1.71 (0.27)		N=100 -1.67 (0.20)	N=76 -0.97 (0.24)	
50% Response [n/N (%)]						
<65 years	24/68 (35.3)	21/81 (25.9)	0.344	119/304 (39.1)	75/282 (26.6)	0.850
≥65 years	30/66 (45.5)	14/55 (25.5)		36/100 (36.0)	18/77 (23.4)	

Safety in the elderly

Exposure

As of April 2010, 3.4% of the 11,305 duloxetine-treated patients in the integrated placebo-controlled duloxetine studies were 75 years of age or older and 17% were at least 65 years of age. For the 5 chronic pain studies, 6.7% of the 839 patients were at least 75 years of age and 28% were at least 65 years of age. When considering postmarketing experience, it is estimated that of all patients exposed to duloxetine, 17% were age 65 and older and 5.8% were over the age of 75 (as of 31 July 2011). Considering an estimated world-wide exposure of approximately 42.9 million patients for the same period, approximately 7.4 million patients aged 65 and older and 2.5 million patients over the age of 75 have been exposed to duloxetine. For the purpose of statistical analysis the data were divided in 3 age groups: 18 years up to 65 years (18 to <65 years); 65 up to 75 years, (65 to <75 years), and patients 75 or older (≥75 years).

Serious Adverse Events by Age

No deaths were reported in the chronic pain studies, including the long term extension phase of study CLBP-EN (HMEN). One death occurred in an 82-year-old female 11 days after last drug dose (duloxetine) due to cardiopulmonary arrest (Study CLBP-EO/HMEO). The investigator considered the event as not related to study drug or protocol procedure.

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For all other placebo-controlled studies, excluding chronic pain (OA/CLBP) studies, 9 deaths (5 patients treated with duloxetine and 4 patients treated with placebo) were reported; three of the deaths occurred in patients aged ≥65 years old, and 2 were in duloxetine-treated patients: one in 70 yr female hospitalised after 50 days of duloxetine treatment due to a haemothorax and 2 rib fractures 15 days earlier. In the opinion of the investigator the events of cerebrovascular accident and haemothorax were not related to the study drug or to the protocol procedures. Another death occurred in 77 yr female with a history of AV block and diclofenac treatment hospitalised with a myocardial infarction after 38 days of duloxetine treatment. In the investigator's opinion, there was no reasonable causal relationship between the rupture of descending aortic aneurysm and myocardial infarction and study medication.

With respect to SAEs in all placebo-controlled studies, a significant treatment-by-strata interaction (the duloxetine/placebo difference across the age strata) was observed for the frequency of patients experiencing at least 1 SAEs, which appears to be driven by the ≥75 year old age group where more placebo patients (4.6%) experienced an SAE compared with duloxetine-treated patients (2.0%). Further, the 8 duloxetine-treated patients aged ≥75 years old experienced 10 SAEs (myocardial infarction, nausea, concussion, road traffic accident, acute myocardial infarction, wrist fracture, abdominal mass, ankle fracture, aortic aneurysm rupture, and atrioventricular block complete) did not represent an unusual pattern considering comorbid health events typical of this age group. In the chronic pain studies, no significant treatment-by-strata interaction was observed and the frequency of events within the very elderly groups (≥75 years old) were similar between treatment groups.

Adverse Events Leading to Discontinuation by Age

With respect to discontinuations due to adverse events, no significant treatment-by-strata interactions, with the exception of nausea, were observed in the pooled chronic pain studies or the all placebo-controlled studies.

The reporting rate for nausea in all placebo-controlled studies was similar in the 3 duloxetine-treated age subgroups (2.9%, 3.5%, 3.3%) and was higher than in placebo group (0.4%, 0.6%, 1.6%); the difference was not significant (p=0.086).

Treatment-Emergent Adverse Events by Age/NSAID use

In all placebo-controlled studies, the overall percentages of duloxetine-treated patients reporting a TEAE in each age group were similar: 74% of patients <65 years, 67% of patients ≥65 to <75 years, and 67% of patients ≥75 years. Of the placebo-treated patients 47% reported TEAEs in the in ≥75 years subgroup, 59% of patients <65 years, and 55% in the ≥65 to <75 years subgroup. This observation was not statistically significant (p=0.064). These data were similar to data from the pooled chronic pain studies and there were no significant treatment-by-strata interactions in this data set. For individual events in all placebo-controlled studies, the most common events for the ≥75 years age subgroup (that is, a frequency ≥5% in the duloxetine treatment group and reported significantly more frequently with duloxetine than with placebo) included: constipation, fatigue, dry mouth, dizziness, headache, somnolence, diarrhoea, falls and insomnia. The profile of TEAEs in the ≥75 years age group was similar to the known TEAE profile of duloxetine (as listed in SmPC).

In all placebo-controlled studies and the pooled chronic pain studies, there was no significant evidence that duloxetine-treated patients aged 75 years and older were at increased risk for sustained blood pressure elevations compared with patients in other age groups, as no significant treatment-by-strata interactions were observed.

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When stratified by NSAIDs use, the TEAE profile of duloxetine monotherapy in elderly patients was similar to that observed for duloxetine plus NSAIDs in all placebo-controlled studies, with the possible exception of hypercholesterolemia.

In longer-term duloxetine studies duloxetine-treated patients <75 years of age experienced a statistically significantly greater frequency (416.8 % patient years) of TEAEs than the very elderly (335.9 % patient years; p=.011). Patients <65 years of age also experienced a greater frequency (423.42 % patient years) of TEAEs than the elderly (364.6 % patient years), but the difference was not statistically significant (p=0.208). With respect to discontinuations due to an adverse event, a similar pattern was observed in both >=65 and >=75 age groups, namely, that both groups discontinued more frequently due to an adverse event (>=65 years old: 24.37 % patient year; >=75 years old: 28.69 % patient year) than the <65 (18.41 % patient year, p<.001) years and <75 years groups (18.99 % patient year; p=.004), respectively. The frequency of DCAEs in >=75 patients was numerically higher than that in >=65 age group. The frequency of discontinuations was higher in NSAID nonusers subgroup irrespective of age group, suggesting that concomitant NSAID use did not lead to a higher rate of discontinuations compared with NSAID nonuser. Event frequency decreased over time.

Comparison between Chronic Pain (OA/CLBP) and DPNP Clinical Trial Data

Another patient population that has been studied by the MAH are patients with DPNP. In MAH's view data in the DPNP population are relevant to the data in the chronic pain population because the 2 patient groups are similar with respect to demographic characteristics, comorbid illnesses and concomitant medication use. Moreover, the DPNP studies provide controlled data for longer-term treatment of up to 15 months with duloxetine (580 patients were treated with duloxetine 120 mg per day, and 287 patients received routine care). In summary, a significantly greater percentage of patient in the control group (routine care) experienced one or more SAEs compared with duloxetine-treated patients in those studies. In addition data demonstrate that DPNP patients treated for long term with duloxetine did not have more cardiovascular SAEs compared with DPNP patients receiving routine care.

Analyses of Postmarketing Data by Age

From postmarketing data it has been observed over time that, with the exception of hyponatraemia, the spontaneous adverse event profile of elderly patients 65 years and older was similar to younger patients. Based on a review of spontaneous cases presented in the duloxetine PSUR 9, the Company Core Data Sheet (CCDS) was updated to give more detail on hyponatraemia in the Special Warnings and Special Precautions for Use section, and the SmPC was updated accordingly. Ischaemic CV and GI bleeding events were very rarely reported (<0.01%) in all age groups. The reporting rates of these events increased with increasing age, but were not inconsistent with the known epidemiology of these events

MAH's conclusions

Elderly patients treated with duloxetine experienced a similar level of analgesic efficacy as non-elderly adults. Although efficacy data for elderly are limited in the chronic pain studies, particularly with respect to the very elderly, the data are consistent with the overall clinical experience with duloxetine in DPNP, which is mostly a disease of elderly, further supporting duloxetine's analgesic effect in the elderly population. With respect to the safety profile in the elderly, there is an extensive duloxetine exposure data base of all duloxetine clinical trials allowing assessment of the safety of duloxetine in patients >65 years of age. Safety data in the very elderly (>=75 years), while more limited in clinical trial data, is supplemented by the postmarketing experience. Based on clinical trial data, no new

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important safety signals were identified for duloxetine-treated patients ≥75 years of age in the chronic pain studies compared with all studies. Data from all placebo-controlled duloxetine studies, indicated that patients ≥75 years of age maybe at higher risk for reporting ≥1 TEAEs, specifically fatigue, and falls; these events are recorded in the current SmPC. Patients in this age group do not otherwise seem to be at higher risk, for example, for adverse events leading to death, discontinuation from treatment, SAEs or sustained blood pressure elevation. Although the data from the chronic pain studies constitutes a smaller analyses set, the data are consistent with the findings from all placebo-controlled, duloxetine studies. Postmarketing data indicate that, with the exception of hyponatremia, the AE profile for elderly patients (65 years and older) is similar to younger patients. Analyses of spontaneous postmarketing adverse event reports showed that ischaemic CV events and GI bleeding events had higher reporting rates in the elderly and that proportionally more elderly patients in the MAH's Safety Database reported concomitant use of NSAIDs when compared with younger adults which is expected considering the epidemiology of cardiovascular disease and the known patterns of use of NSAIDs by age. With respect to risks in combination with NSAID use, no synergistic effect between duloxetine and NSAIDs were observed in elderly patients in clinical trials. Additional pharmacovigilance activities include the addition to the SmPC of a statement noting the limited data in the very elderly and an enhanced twice yearly retrospective analysis of relevant events (GI-bleeding, cardiovascular events) in the elderly compared with the non-elderly patients. In summary, therefore, elderly patients do benefit from treatment with duloxetine with a magnitude similar to non-elderly patients and the risks associated with duloxetine use in the elderly are comparable with those in non-elderly patients. The uncertainty of the data, due to small numbers in the very elderly patients, are appropriately addressed with the enhanced PV activities and with a modification to the SmPC to ensure that prescribers are aware of this limitation in data.

CHMP's conclusions

The CHMP maintained its initial position that the data in the elderly, especially in the very elderly, who would represent high percentage of the target population and a particularly vulnerable population for CV and GI adverse events were limited. In the 5 chronic pain studies, 6.7% of the 839 patients were ≥75 years of age and 28% were ≥65 years of age. The only analysis provided in support of duloxetine efficacy in the elderly was the comparison of an average pain and 50% response rates in the subgroup NSAID nonusers <65 and ≥65. Albeit this analysis showed no difference in the treatment effects between adults and the elderly the data were considered too limited to draw definite conclusions on duloxetine efficacy in this subgroup. The uncertainties remain regarding the safety of duloxetine in the elderly, particularly when combined with the concomitant use of NSAIDs.

Ground # 5 Taking into account that the duloxetine efficacy was not convincingly demonstrated in the treatment of chronic somatic pain (as established in chronic low back pain and osteoarthritis) of at least moderate severity in patients not taking NSAIDS regularly, and in light of the safety profile the positive benefit-risk balance in the applied for indication has not been established.

MAH's position

The MAH claims that the overall benefit-risk profile of duloxetine in patients with chronic somatic pain is favourable for those not taking NSAIDs regularly, and that a clearly targeted population exists who have very limited choice of safe and effective alternatives.

Unmet Medical Need

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Uncontrolled pain is a significant public health problem and it is expected that its impact will grow dramatically as the population ages and people live longer with chronic pain. Currently, pharmacological treatment options for chronic pain in EU primarily include non-steroidal anti-inflammatory drugs (NSAIDs) and opioids. Approximately 50% of patients with chronic pain are prescribed treatment other than an NSAID, e.g. an opioid, the predominant alternative therapy, followed by numerous adjuvant medication such as tricyclic antidepressants and anticonvulsants (Breivik et al 2006). The number of patients on extended opioid treatment for chronic pain has increased about 10-fold over 15 years within various EU countries and other regions. This increasing trend has serious public health implications, leading to significant increases in prescription opioid addiction and unintentional overdose-related mortality (Office for National Statistics, 2011; Okie et al 2010; Gomes et al 2011). A recent survey of EU patients has highlighted the unmet medical need in treating chronic pain, with nearly half of patients being unsatisfied with their prescription medication and nearly a quarter not taking any medications at all (DASSA 2008). Therefore, alternative treatment options to opioids with an acceptable benefit risk profile are critically needed for patients with chronic pain who are not taking NSAIDS regularly (Langley 2011).

Beneficial effects of duloxetine in the proposed target population

The duloxetine-placebo difference, derived from the group mean change from baseline in BPI-average pain change using the BOCF method, was -0.67 and -0.60 in the OA studies and -0.55 -0.54, -0.62, and 0.20 in the CLBP studies. The magnitude of effect of duloxetine, as assessed using BOCF methodology, was similar to a number of other analgesics including the recently approved opioid, tapentadol, where the drug-placebo difference was -0.3 for OA studies and -0.6 for CLBP studies. Moreover, as assessed in the duloxetine trials, using the BOCF methodology, the duloxetine-placebo difference of 50% response rate was 15% in pooled OA studies and 13% in pooled CLBP studies. This difference between treatment groups was statistically significant for the pooled OA (p=.008) and CLBP (p=<.001) studies. This result represents a significant proportion of patients with chronic pain of, on average 7 years duration, achieving a substantial improvement in their pain over a 3 months treatment period and starting in some patients at one week from initiation of treatment. Importantly, these clinically significant improvements in pain severity were paralleled by substantial improvements in physical function. These rates were comparable to those seen in other commonly used analgesics (ranging from 10-21%), including the recently approved analgesic tapentadol (4% and 8% in OA and CLBP studies).

The MAH acknowledges the lack of an active control in the duloxetine studies and the legitimate concerns that CHMP has raised in that regard. There were, however, several valid scientific concerns at the time of study design which lead to the conclusion that placebo alone should be used. Another important concern raised by the CHMP is the use of rescue medication in the chronic pain studies. Results from study CLBP-GC (HMGC) demonstrated that the episodic use of rescue medication did not confound the efficacy in NSAID nonusers, where responders and nonresponders reported comparable frequency of rescue medication use (30-40%). CHMP has raised the time of onset as a concern, however, given that duloxetine is not for use in acute pain or as a rescue treatment in chronic pain, the time to onset would still be clinically meaningful for patients who suffer from chronic pain for many years. Finally, CHMP raised an uncertainty regarding maintenance of effect. The design of the long term study (uncontrolled for 12 months) meets the requirements specified at the time of Scientific Advice and represents a similar, but enhanced design, over the maintenance DPNP study. By applying the BOCF method to the analyses of maintenance of effect the conclusion remained the same – the majority of duloxetine responders maintained the clinically relevant response achieved during acute treatment for up to 1 year in this adequately powered study comparable with results for DPNP.

Unfavourable Effects

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The safety profile of duloxetine has been well-characterised in more than 31,000 patients participating in clinical trials and more than 42 million patient exposures in postmarketing experience worldwide. A significant amount is known about the risks associated with use of duloxetine and these are described in the SmPC and Package Leaflet. In summary, duloxetine has an acceptable safety profile as a treatment option for patients with chronic pain who are not taking NSAIDs regularly, the safety profile of duloxetine seems more favourable in comparison to opioids.

The analyses of vulnerable patients within the duloxetine clinical trials demonstrated that there was no significant treatment-by-subgroup effect between patients with or without risk factors for CV and GI bleeding. Overall, these results, along with the longer-term clinical trial data, indicated that when treating with duloxetine, there were no significantly increased risks for CV events or GI-bleeding events in "vulnerable" patients compared with patients without risk factors. The safety and tolerability data from chronic pain studies are consistent with those from other indications. The combined safety database for duloxetine (all studied disease states) includes 1883 elderly patients (>=65 years of age) in clinical trials and 7.4 million elderly patients with postmarketing exposure. With the exception of falls and hyponatremia, elderly patients with duloxetine exposures have not reported adverse events at a higher rate than younger patients. Data presented also support the conclusion that elderly patients who take NSAIDs in combination with duloxetine have a similar risk profile as elderly patients who take duloxetine alone. Given the more limited data available in duloxetine chronic pain studies in the very elderly (>=75 yrs), this information will be reflected in the SmPC, and the MAH will continue to closely monitor this group during postmarketing surveillance. This population will also be listed under the "missing information" section of the RMP along with associated PV activities that include a semi-annual retrospective cohort analysis of an insurance claims database assessing the targeted safety topics of hepatic eventscardiovascular events, hypertension, and GI bleeding events stratified by age (RMP 9).

Benefit-Risk Balance

Based on the demonstrated unmet medical need, alternative treatment options to opioids with an acceptable benefit/risk profile are needed to treat patients with chronic pain who are not taking NSAIDs regularly. Duloxetine has demonstrated a clinically relevant analgesic effect, as shown by statistically significant response compared with placebo (that is at least equivalent to that seen with tapentadol and other opioids), maintenance of response in CLBP patients and, in those seeing pain reduction, a parallel improvement in physical functioning. Based on the benefit-risk summary provided above, and in conjunction with less burdensome and well-established risk management for duloxetine compared with opioids, the MAH considers that the overall benefit-risk profile of duloxetine in patients with chronic somatic pain is favourable for patients not taking NSAIDs regularly, and that a specific targeted population exists who currently have very limited safe and effective treatment alternatives.

CHMP's conclusions

The therapeutic indication initially considered by the CHMP during the re-examination procedure was: 'treatment of chronic somatic pain (as established in chronic low back pain and osteoarthritis) of at least moderate severity in patients not taking NSAIDS regularly'.

The indication was modified further during the re-examination procedure to reflect the submitted data more appropriately and in an effort to further explore the target population, where efficacy could be considered as demonstrated and where the benefit risk ratio could be considered as positive.

The final indication proposed by the MAH was: 'treatment of chronic low back pain or chronic osteoarthritic pain of at least moderate severity in patients for whom the prolonged use of NSAIDs is not appropriate or is contraindicated'.

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In the CHMP's view the benefit risk of duloxetine in the final indication applied for was considered unfavourable. The CHMP remained of the opinion that the clinical relevance of the observed short term effect of duloxetine in chronic low back pain and chronic osteoarthritic pain was questionable. Several factors including the absence of an active comparator, the limited long term evidence, the contribution of the background analgesic treatment and the discontinuation rate in duloxetine treatment arms made it difficult to interpret the clinical relevance of the effect.

In the CHMP's view the concerns about the safety of the product in the target population where 'the prolonged use of NSAIDs is not appropriate or contraindicated' were not alleviated and would not be mitigated with the proposed pharmacovigilance and risk management measures.

The CHMP acknowledged the argument provided by the MAH for the unmet medical need in chronic pain treatment. However in light of the evidence provided, the difficulties to identify a priori patients who would benefit from the treatment and the safety concerns surrounding the potential concomitant use of NSAIDs, the CHMP considered that the unmet medical need does not constitute sufficient grounds in itself to support the use of duloxetine in chronic low back pain and chronic osteoarthritic pain.

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Ad hoc expert group meeting conclusions

Following a request from the applicant at the time of the re-examination, the CHMP convened an ad hoc expert group to provide experts' views on the CHMP questions in relation to the application for the variation, taking into account the applicant´s response to the grounds for refusal.

The conclusions from the ad hoc expert group meeting were the following:

Q1. Has the efficacy of duloxetine in chronic somatic pain of at least moderate severity been convincingly demonstrated (for monotherapy and/or add-on therapy)? Do you consider the differences to placebo to be clinically relevant? Has the efficacy been documented in elderly patients?

1. The efficacy has been studied and shown for pain in OA and CLBP of moderate severity and only in monotherapy. The improvement in 50% responder rate is considered more clinically meaningful than mean reduction in numeric rating scales (NRS).

The difference to placebo with NNT of 7 for OA and 8 for CLBP may be considered as clinically relevant in light of limited treatment options. In particular in OA the NNT of 7 (1 in 7 patients respond well) could suggest a possibility of delaying surgical treatment, i.e. joint replacement surgery. When looking at CLBP, the NNT result of 8, it is difficult to define the clinical relevance as clearly as in OA.

There is limited data on efficacy in the elderly. Presenting data only on the lack of significant difference between patients >65 y and <65 years is not enough, since the subgroup analysis showed a significant difference between duloxetine and placebo in patients >65 in one out of two studies in OA. In the studies on CLBP 55 years was used as a cut off and no statistical analysis of duloxetine vs. placebo has been presented with cut-off of 65 in those studies.

Q2. Has the maintenance of effect of duloxetine in chronic somatic pain of at least moderate severity been adequately documented?

2. One open trial in CLBP in 117 patients provided convincing indication of maintenance of effect. The data on maintenance were considered limited but acceptable to the group. More data on the functional improvement should be required post-approval to further document the maintenance of a clinically relevant effect.

Experts noted that the maintenance of effect was not studied in the OA pain.

Q3. What are the experts' expectations in terms of maintenance of effect and long term data in this chronic condition (the expert group should discuss also within this context the potential contribution of the use of rescue medication)?

The experts agreed that the design of the study (open label extension) was appropriate as it is not reasonable to ask for a placebo long term study.

The experts concluded that the appropriate target population should be patients who do not use NSAIDs/COX-inhibitors continuously therefore the experts found it difficult to determine the extent of the contribution of rescue medication.

Q4. What is your view on the lack of an active comparator in the pivotal clinical trials? To what extent does it hamper the evaluation of the efficacy and safety of duloxetine in chronic somatic pain relative to other available treatment options?

4. Ad hoc expert group agree that the lack of active comparator, in OA and CLBP would not hamper the evaluation of efficacy and safety in the studies. The group considered the study designs to be acceptable as there are limited treatment options available for chronic pain (inclusion of cox-inhibitors or opioid analgesic drugs would have excluded many patients from the trial).

The experts were aware that there are other medicines with a similar mechanism of action which from a scientific point of view could be used to elucidate the mechanism of efficacy of duloxetine in OA and CLBP (e.g. tricyclic antidepressants). However these are not approved for such use.

Q5. Do you consider the safety and tolerability of duloxetine in chronic somatic pain sufficiently documented? Please also consider elderly patients in your assessment. Is the safety and tolerability profile of duloxetine in chronic somatic pain likely to be different from that seen in already approved indications for duloxetine?

The ad hoc group considers duloxetine to be a safe alternative to NSAIDs and opioids used chronically. Safety of duloxetine in other indications is well documented and could be extrapolated to this patient group including the elderly. In other duloxetine approved indications (diabetic neuropathy) elderly patients have more co-morbidities and therefore the AE profile is not expected to be different in the sought indication.

The low drop-out rate seems to indicate that the drug is well tolerated.

The experts want to highlight the fact that stopping treatment without slow tapering induces withdrawal symptoms (this is well known for other antidepressants as well).

Q6. How do you assess the safety and tolerability of duloxetine in chronic somatic pain in the perspective of other treatment options (such as NSAIDs and opioids)?

In the absence of head to head comparison, the experts could only compare the safety and tolerability of DLX to NSAIDS and opioids in general and not in the sought indication.

Overall, duloxetine seems to have a favourable safety and tolerability profile in OA pain and CLBP.

Q7. Is it possible to identify a restricted target population where the benefit risk ratio of duloxetine is positive in chronic somatic pain?

The experts considered that 'patients with OA or CLBP who are not using NSAIDs (including coxibs) regularly' is an acceptable restricted target population.

In the beginning of the discussions, one expert considered that even the broad indication could be accepted; however he seemed not to oppose the final conclusion given that OA pain and CLPB represent around 80% of chronic pain.

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Overall conclusion on grounds for re-examination

In conclusion, the CHMP considered the benefit/risk of duloxetine in 'the treatment of chronic low back pain or chronic osteoarthritic pain of at least moderate severity in patients for whom the prolonged use of NSAIDs is not appropriate or is contraindicated' unfavourable.

In the CHMP's view the clinical relevance of the marginal short term effect over placebo was questionable and difficult to interpret in the absence of an active comparator, and precluded any conclusion in the long term, particularly in the light of the limited long term evidence provided. The uncertainties in relation to the contribution of the background analgesic treatment and the high rate of withdrawals in duloxetine treatment arms remained, which further questioned the clinical relevance of the effect.

In the CHMP's view there are remaining concerns about the safety of the product in the target population where 'the prolonged use of NSAIDs is not appropriate or contraindicated' as this population would mostly include patients which are cardiovascularly compromised or have a history of GI problems, which could be exacerbated by duloxetine. The CHMP was of the opinion that without longer term data it could not be concluded that duloxetine would be a safe alternative for this population.

The committee maitained its position that the data on the efficacy and safety in the elderly, who would represent a high percentage of the target population and a particularly vulnerable population for CV and GI adverse events, were limited.

6.2. Recommendation following re-examination

Based on the review of the submitted data the CHMP considers the following variation not acceptable and therefore recommends, by a majority of 18 out of 29 votes, the refusal of the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation(s) rejected		**Type**
C.I.6.a	Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	II

The Icelandic and the Norwegian CHMP members agreed with the above-mentioned recommendation of the CHMP.

Grounds for refusal:

Whereas:

- The clinical relevance of the demonstrated marginal short term effect is questionable. It is difficult to put the observed effect into clinical perspective in the absence of the active comparator. The uncertainties in relation to the contribution of the background analgesic treatment and the high rate of withdrawals in duloxetine treatment arms further question the clinical relevance of the effect;

- The limited evidence provided to support the maintenance of the effect over time can hardly be taken as sufficient for a medicinal product intended for the treatment of a chronic condition;

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- The potential risk of CV and GI bleeding events, which may occur particularly if the patient has risk factors for these conditions that prohibit use of NSAIDs or, if the patient concomitantly uses NSAIDs would not be adequately mitigated by the proposed pharmacovigilance and risk management activities, including warnings in the Product information;

- Efficacy and safety has not been adequately established in the elderly;

- The benefit-risk of duloxetine in the treatment of chronic low back pain or chronic osteoarthritic pain of at least moderate severity in patients for whom the prolonged use of NSAIDs is not appropriate or is contraindicated, remains negative;

the CHMP has recommended the refusal of the variation to the terms of the Marketing Authorisation.

Divergent positions are presented in Appendix 1.

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Appendix

1. Divergent positions

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Appendix 1

Divergent Positions following the re-examination

- Short term efficacy of duloxetine in 'The treatment of chronic low back pain or chronic osteoarthritic pain of at least moderate severity in patients for whom the prolonged use of NSAIDs is not appropriate or is contraindicated' has been adequately documented in randomised, placebo-controlled clinical trials. Based on responder analyses with acceptable responder definitions (such as at least 50% reduction in BPI average pain), the absolute benefit over placebo is statistically significant and clinically meaningful when the difference in proportion of responders is taken into consideration.

- In terms of the primary efficacy endpoint analyses, based on the BOCF method presented by the applicant, the following trials provide evidence for efficacy of duloxetine as a treatment for chronic pain in patients with osteoarthritis and chronic low back pain in non NSAID regular users:

a. Trial CLBP-EN (HMEN) demonstrated efficacy of duloxetine 60-120 mg in the treatment of chronic low back pain.

b. Trial CLBP-GC (HMGC) demonstrated efficacy of duloxetine 60 mg in the treatment of chronic low back pain.

c. Trial OA-FG (HMFG) demonstrated efficacy of duloxetine 60-120 mg in the treatment of chronic pain associated with osteoarthritis.

- Although there is a lack of long term comparator data, the results from the open-label study are considered acceptable with appropriate recommendations in the SmPC. In addition, the results of a long-term study in diabetic peripheral neuropathic pain further supported maintenance of effect. Furthermore, the company's proposal to conduct a post marketing maintenance of effect and safety study in OA pain would further substantiate the data of this application.

- The safety and tolerability profile of duloxetine in the proposed restricted population is sufficiently established. In this regard, it should be noted that there is extensive experience with duloxetine in other patient populations, including elderly patients, and that there is no reason to assume that the safety and tolerability profile in the proposed indication will be significantly different from indications already approved.

- The adverse effects associated with duloxetine are not trivial, but are manageable and should be viewed in the perspective of adverse effects observed with available treatment options such as gastrointestinal and cardiovascular effects (NSAIDs) and sedation, risk of fall and addiction potential (opioids).

- In conclusion, considering the provided clinical data and the currently available treatment options, the benefit-risk balance of duloxetine in the proposed population is considered to be positive.

- Duloxetine would be a potentially valuable alternative for some categories of patients where NSAIDs are not appropriate and where currently the only other pharmacological option is opioids.

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London 17 November 2011

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……	……
Mila Vlaskovska	Dana Gabriela Marin
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Andrea Laslop	Romaldas Mačiulaitis
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