European Medicines Agency

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ASSESSMENT REPORT
FOR
Xeristar

International non-proprietary name/Common name:
duloxetine hydrochloride

Procedure No. EMEA/H/C/573/II/27

Variation Assessment Report as adopted by the CHMP with all information of a commercially confidential nature deleted

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1. Introduction

Duloxetine is classified as a serotonin norepinephrine reuptake inhibitor (SNRI). It is a selective inhibitor of both serotonin (5-HT) and norepinephrine (NE) receptors. Both 5-HT and NE have been implicated in the mediation of endogenous pain inhibitory mechanisms via the descending inhibitory pain pathways in the brain and spinal cord.

Duloxetine is currently approved under the trade name Cymbalta/Xeristar for the treatment of major depressive disorder (MDD) and diabetic peripheral neuropathic pain (DPNP) in adults and under the trade name Yentreve/Ariclaim for the diabetic peripheral neuropathic pain (DPNP) in adults and the treatment of stress urinary incontinence (SUI).

This variation concerns an application for extension of the approved indication for Xeristar to include the treatment of generalised anxiety disorder (GAD).

2. Non Clinical Aspects

Environmental risk assessment (ERA)

Based on the updated Environmental Risk Assessment and the study reports submitted by the MAH the CHMP asked the MAH to update the Predicted Environmental Concentration in surface water ($PEC_{surface\ water}$) refinement since there were two basic concerns: 1. The No Observable Effect Concentration (NOEC) in the algae toxicity study and 2. The refinement of the $PEC_{surface\ water}$ based on binding of duloxetine to sludge solids.
In reply to CHMP concerns, the MAH concluded that using a lowered algae NOEC (4.3 µg/L) and a lowered predicted binding to sludge, the risk quotient for surface water is unfavourable. Therefore the MAH proposed to refine the $PEC_{surface\ water}$ using sales forecasts and metabolism as allowed by the Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use and then use this $PEC_{surface\ water}$ to recalculate the risk quotient.

A further commitment is made by the MAH to provide a revised Duloxetine ERA no later than the end of June.

3. Clinical Aspects

GCP aspects

According to the MAH all studies were conducted in accordance with the International Conference on Harmonisation Guidelines for Good Clinical Practice (GCP) and the Declaration of Helsinki.

3.1 Clinical efficacy

The clinical plan for the efficacy of duloxetine in the treatment of GAD includes four placebo-controlled short-term studies, (**Study HMBR, Study HMDT, Study HMDU, and Study HMDW)**, and one long-term placebo-controlled relapse prevention study **(Study HMDV)**. Table 1 summarizes all the studies.

Table 1: summarizes the study centers location, design, drug doses, number of patients randomized and completed duration, and primary efficacy endpoint measure of all five studies.

	Number of Study Centers/ Location	**Design**	**Doses**	**Number of subjects By arm randomized/ completed**	**Primary efficacy endpoint**	**Duration**
HMBR	41 study centers in the US, Finland, France, Germany, South Africa, Spain, and Sweden	Multicenter, randomized, double-blind, parallel, fixed dose, placebo controlled, Phase 3 study with a single blind placebo lead-in	Duloxetine 60 mg QD PO Duloxetine 120 mg QD PO Placebo QD PO	Randomized: 168 DLX60 , 170 DLX120, 175 placebo Completed: 132 DLX60, 122 DLX120, 129 placebo	HAMA (mean change from baseline to endpoint in anxiety symptoms).	9 week
HMDT	28 study centers in the US	Multicenter, randomized, double-blind, flexible-dose placebocontrolled, Phase 3 study with a singleblind placebo lead-in	Duloxetine 60 mg QD PO Duloxetine 120 mg QD PO Placebo QD PO	Randomized: 168 DLX60-120, 159 placebo Completed: 93 DLX60-120, 109 placebo	HAMA (mean change from baseline to endpoint in anxiety symptoms).	10 weeks
HMDU	42 study centers in the US	Multicenter, randomized, double-blind, flexible-dose, placebo- and activecontrolled, Phase 3 study	Duloxetine 20 mg QD PO Duloxetine 120 mg QD PO Venlafaxine extended release 75 to 225 mg QD PO Placebo QD PO	Randomized: 162 DLX60-120, 164 VEN 75-225, 161 placebo Completed: 88 DLX60-120, 102 VEN 75-225, 100 placebo	HAMA (mean change from baseline to endpoint in anxiety symptoms).	10 weeks
HMDW	35 study centers in Australia, Argentina, Belguim, Canada, Mexico, Russia, Taiwa, United Kingdom	Multicenter, double-blind, randomized, placebo- and comparatorcontrolled, Phase 3 study	Duloxetine 60 to 120 mg QD PO Duloxetine 20 mg QD PO Venlafaxine extended release 75 to 225 mg QD PO Placebo QD PO	Randomized: 84 DLX20, 158 DLX60-120, 169 VEN75-225, 170 placebo Completed: 63 DLX20, 109 DLX60-120, 112 VEN75-225, 15 placebo	HAMA (mean change from baseline to endpoint in anxiety symptoms	10 weeks
HMDV	52 study centers in Austria, France, Germany, Netherlands, Portugal, US	Multicenter, double-blind, randomized, placebo- and comparatorcontrolled, Phase 3 study	Duloxetine 60 mg QD PO Duloxetine 120 mg QD PO Placebo QD PO	Open Label: 887 DLX 60-120QD Randomized: 216 DLX60-120, 213 placebo Completed: 167 DLX60-120, 116 placebo	HAMA (time to relapse and mean change from baseline to endpoint)	6 months open-label, 6 months double-blind

Short-term efficacy

Design of short-term studies

All studies started with a 3-30 days screening phase followed by a one week placebo run-in in two studies (HMBR and HMDT). Eligible patients were randomised to 9-10 weeks treatment with one or two dosage groups of duloxetine or placebo. Two studies (HMDU and HMDW) also had an active control (venlafaxine).

Study population

Male or female, in or outpatients of at least 18 years of age, fulfilling the DSM-IV (Diagnostic and Statistical Manual of Mental Disorders) criteria for GAD of at least moderate severity as defined by a Hospital Anxiety and Depression Scale (HADS) anxiety sub-score ≥10 and a Covi Anxiety Scale (CAS) score ≥9.

Key Exclusion Criteria

- Any current DSM-IV Axis I diagnosis other than GAD.
- Patients diagnosed with major depressive disorder (MDD) within the past 6 months and any items>3 of Raskin Depression Scale.
- Patients diagnosed with panic disorder, post-traumatic stress disorder, or an eating disorder within the past year.
- Obsessive-compulsive disorder, bipolar affective disorder, psychosis, factitious disorder, or somatoform disorders during their lifetime.
- The presence of an Axis II disorder or history of antisocial behaviour which, in the judgment of the investigator, would interfere with compliance with the study protocol.
- A history of alcohol or any psychoactive substance abuse or dependence within the past 6 months.

Efficacy measurements

The primary efficacy variable was the reduction of the baseline Hamilton Anxiety Rating Scale (HAMA). The secondary variables included HAMA factor scores, percentage of patients with sustained improvement (≥30% reduction in total HAMA score at a visit prior to the final visit sustained through the final visit), percentage responders (≥50% reduction in total HAMA score), percentage of patients in remission (HAMA≤7) and Clinical and Patient Global Impression of Improvement (CGI-I and PGI-I, respectively). Health outcome and Quality of Life were evaluated with Sheehan Disability Scale (SDS), Quality of Life Enjoyment and Satisfaction Questionnaire-Short Form (Q-LES-Q-SF) and Euro-QoL – 5 Dimension (EQ-5D). Somatic symptoms were measured with a visual analogue scale for pain and Symptom Questionnaire-Somatic subscale (SQ-SS) in two studies (HMBR and HMDT).

Short-term efficacy results

Table 2. HAMA Total Score: Analysis of Mean Change Difference in LSMean Change from Baseline to Endpoint All Randomized Patients Acute Therapy Phase Placebo-Controlled Study HMBR, Study HMDT, Study HMDU, Study HMDW

Study	Treatment Group	N	Baseline	Endpoint	LSMean Change	p- value vs placebo
HMBR	Duloxetine 60 mg QD	165	25.05	12.32	-12.8	<.001
	Duloxetine 120 mg QD	169	25.13	12.74	-12.5	<.001
	Placebo	173	25.82	17.19	-8.4	-
HMDT	Duloxetine 60 to 120 mg QD	161	22.54	14.27	-8.1	.023
	Placebo	158	23.49	17.00	-5.9	-
HMDU	Duloxetine 60 to 120 mg QD	149	25.77	13.95	-11.8	.007
	Venlafaxine 75 to 225 mg QD	159	24.92	12.90	-12.4	<.001
	Placebo	158	24.98	16.06	-9.2	-
HMDW	Duloxetine 20 mg QD	83	27.65	12.49	-14.7	.007
	Duloxetine 60 to 120 mg QD	151	27.74	11.85	-15.3	<.001
	Venlafaxine 75 to 225 mg QD	158	27.36	11.66	-15.5	<.001
	Placebo	163	27.33	15.77	-11.6	-

Table 3. SDS Global Functional Impairment Score Analysis of Mean Change Difference in LSMean Change from Baseline to Endpoint All Randomized Patients Acute Therapy Phase Placebo-Controlled Study HMBR, Study HMDT, Study HMDU, and Study HMDW

Study	Treatment group	N	Baseline	Endpoint	LSMean Change	p- value vs placebo
HMBR	Duloxetine 60 mg QD	156	15.26	7.38	-7.8	<.001
	Duloxetine 120 mg QD	160	14.97	8.08	-7.0	<.001
	Placebo	163	15.05	11.39	-3.8	-
HMDT	Duloxetine 60 to 120 mg QD	144	14.26	8.42	-5.8	.004
	Placebo	141	14.64	11.42	-3.1	-
HMDU	Duloxetine 60 to 120 mg QD	122	17.41	9.49	-8.0	.007
	Venlafaxine 75 to 225 mg QD	139	17.55	9.57	-8.0	.006
	Placebo	125	17.52	12.08	-5.4	-
HMDW	Duloxetine 20 mg QD	77	17.21	8.87	-8.5	.027
	Duloxetine 60 to 120 mg QD	142	17.80	8.72	-8.9	.002
	Venlafaxine 75 to 225 mg QD	149	18.15	8.58	-9.1	<.001
	Placebo	150	18.00	11.69	-6.2	-

Table 4. Response Rate at Endpoint. All Randomized Patients Acute Therapy Phase. Placebo-Controlled Studies HMBR, HMDT, HMDU, HMDW

Study	Treatment group	N	Responders n (%)	p- value vs placebo
HMBR	Duloxetine 60 mg QD	165	95 (58.0)	<.001
	Duloxetine 120 mg QD	169	94 (56.0)	<.001
	Placebo	173	53 (31.0)	-
HMDT	Duloxetine 60 to 120 mg QD	161	67 (42.0)	.029
	Placebo	158	48 (30.0)	-
HMDU	Duloxetine 60 to 120 mg QD	149	70 (47.0)	.057
	Venlafaxine 75 to 225 mg QD	159	86 (54.0)	.001
	Placebo	158	58 (37.0)	-
HMDW	Duloxetine 20 mg QD	83	50 (60.0)	.009
	Duloxetine 60 to 120 mg QD	151	98 (65.0)	<.001
	Venlafaxine 75 to 225 mg QD	158	97 (61.0)	<.001
	Placebo	163	69 (42.0)	-

Table 5. Remission Rate at Endpoint. All Randomized Patients. Acute Therapy Phase Placebo-Controlled Study HMBR, Study HMDT, Study HMDU, and Study HMDW

Study	Treatment group	N	Remitters n (%)	p- value vs placebo
HMBR	Duloxetine 60 mg QD	165	51 (31.0)	.009
	Duloxetine 120 mg QD	169	64 (38.0)	<.001
	Placebo	173	33 (19.0)	-
HMDT	Duloxetine 60 to 120 mg QD	161	45 (28.0)	.272
	Placebo	158	36 (23.0)	-
HMDU	Duloxetine 60 to 120 mg QD	149	34 (23.0)	.368
	Venlafaxine 75 to 225 mg QD	159	48 (30.0)	.016
	Placebo	158	30 (19.0)	-
HMDW	Duloxetine 20 mg QD	83	35 (42.0)	<.001
	Duloxetine 60 to 120 mg QD	151	67 (44.0)	<.001
	Venlafaxine 75 to 225 mg QD	158	70 (44.0)	<.001
	Placebo	163	32 (20.0)	-

Study HMBR
In study HMBR fixed doses were used and, taking into account all the CI, better results were achieved in comparison with the other Acute Placebo-Controlled Studies. Both used doses (60mg and 120 mg) showed significant improvement compared with placebo for primary and secondary outcome measures. Results were similar between doses with no statistically significant differences between them.

Study HMDT
Patients treated with duloxetine 60 mg to 120 mg QD (Once Daily) showed significant improvement compared with placebo-treated patients as measured by the primary efficacy measure HAMA total score (p=0.23). Results were closer to placebo in comparison with the results achieved in study HMBR, the mean change was over placebo (-2.67) but still significant (-4.48,-0.86).

Study HMDU
In study HMDU, patients randomized to duloxetine 60 mg to 120 mg QD showed significant improvement compared with placebo-treated patients as measured by the primary efficacy measure, HAMA total score. Venlafaxine was also statistically significantly superior to placebo and also experienced a mean decrease of more than 2 points greater than that of placebo. Nevertheless, in terms of responder rate and remission rate, the differences compared to placebo did not reach statistical significance, in contrast to venlafaxine.
Most secondary outcome measures including: SDS Global Functional Improvement score, the HAMA psychic anxiety factor score, the HADS anxiety subscale score, the CGI-Improvement and the PGI-Improvement and Q-LES-Q-SF showed statistically greater improvements for duloxetine and venlafaxine treated patients. Some other secondary outcome did not achieve statistically significantly results (HAMA somatic anxiety factor score).

Study HMDW

Study HMDW included a fixed dose for duloxetine (20 mg), a variable dose (60 to 120 mg) and a variable dose also for venlafaxine (75 to 225 mg). All these treatment groups obtained significant improvement in improving symptoms of anxiety as measured by the primary efficacy variable (HAMA total score) and for practically all secondary efficacy outcomes. The 20 mg dose obtained results were not much different than for 60 mg or 120 mg in other studies (HMBR, HMDL, HMDU); however the minimum dose proposed is 60 mg.

Combination of Study HMDU and HMDW
Data from study HMDU and Study HMDW were combined to ensure adequate power for comparison between duloxetine and venlafaxine. PP analyses showed that the lower bound of the interval of mean change in HAMA total score (DLX60-120 minus VEN75-225) exceeded the non-inferiority margin of -1.5 defined by the external expert consensus panel. The ITT analysis showed a lower bound which did not exceed the non-inferiority margin.

Table 6. Hamilton Anxiety Rating Scale Total Score Mean Change from Baseline to Endpoint Per Protocol and Intent-to-Treat Populations

	Placebo	**DLX60-120**	**VEN75-225**	**DLX60-120 minus Placebo**	**VEN75-225 minus Placebo**	**DLX60-120 minus VEN75-225**
Per Protocol Population	-11.60	-15.42	-15.22	-5.29, -2.35	-5.05, -2.19	-1.28, 1.67
ITT Population	-10.36	-13.58	-14.00	-4.62, -1.82	-5.02, -2.26	-1.82. 0.99

Special patient populations and subgroup analyses

Children and adolescents
No data have been provided for children and adolescents.

Elderly
In a subgroup analysis the effect was similar in patients above and below 55 years of age. Nevertheless, efficacy and safety data of duloxetine when treating the elderly are limited.

Gender
Females constitute 63% of the total study population. Overall the effect seemed more pronounced in males compared to females (as shown in Table 7). In particular, the 20 mg dose seemed to be less effective in females. Furthermore, in study HMDU there was a gender-by-treatment interaction with no significant effect in females. The difference in change in total HAMA score versus placebo was -0.52 ($p=0.680$) in females compared to -5.84 ($p<0.001$) in males.

Table 7. Gender specific results in short-term studies. Difference in change from baseline in total HAMA score. Duloxetine vs placebo

Study/Dose	**Females**	**Males**
HMBR 60 mg	-4.60	-4.31
120 mg	-3.18	-6.40
HMDT 60-120 mg	-2.62	-1.04
HMDU 60-120 mg	***-0.52***	***-5.84***
HMDW 20 mg	-2.63	-4.43
60-120 mg	-3.63	-4.78

Race
A significant effect was seen in Caucasians but not in patients of other origin. Eighty percent of the patients were Caucasians.

Severity
The effect was more pronounced in patients with higher baseline HAMA score.

Effects on pain
The effects on pain were mixed. In one out of two studies a significant effect on pain was observed with VAS-ratings. In neither of the studies an effect on somatic symptoms measured with SQ-SS could be seen.

Long-term-efficacy

Study HMDV

Design

Study HMDV was a Phase 3, randomized, double-blind, placebo-controlled relapse prevention study, with an open-label, flexible dose acute therapy phase (6 months) and double-blind continuation therapy phase (6 months).

Treatment started with duloxetine 30 mg which was increased to 60 mg after one week. Patients not tolerating 60 mg were withdrawn. The maintenance dose could be adjusted in steps between 60 and 120 mg until week 16 and after randomisation of responders between week 22 and 24 the duloxetine dose was down-titrated during two weeks in the placebo group. The randomised treatment continued for 26 weeks or until relapse. Patients and investigators were not aware of the exact time of randomisation. Responder was defined as a decrease from baseline in HAMA total score by at least 50% to a score not higher than 11 and a CGI-Improvement score ≤2 (much or very much improved) for at least two consecutive visits. Relapse was defined as an increase in CGI-Severity score by at least 2 points to a score ≥ 4 and a Mini International Neuropsychiatric Interview diagnosis of GAD or discontinuation due to lack of effect.

The primary objective of this study was to assess the long-term maintenance of efficacy of duloxetine 60 mg to 120 mg QD compared with placebo by a comparison of the time to relapse among patients with GAD who responded to duloxetine during the open-label acute therapy phase after 6 months.

Patients

Male and female patients at least 18 years of age fulfilling the DSM-IV-TR criteria for GAD with no major depressive disorder and a CGI-Severity score of at least 4 were included in an open label phase.

Efficacy measures

In Study HMDV, the primary measure was Time to Relapse using CGI-Severity and the Mini International Neuropsychiatric Interview (MINI).

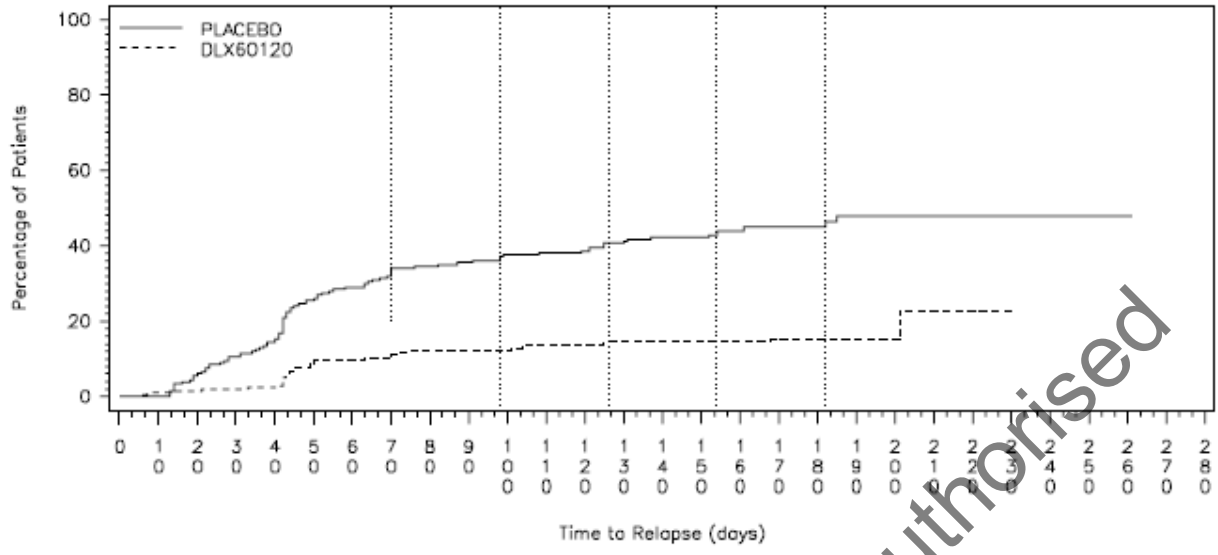
Long-term efficacy results

Study HMDV provides substantial evidence that duloxetine at flexible doses of 60 mg to 120 mg QD was efficacious for long-term treatment of GAD and significantly reduced the risk of relapse.

The 3-fold higher relapse rate of placebo-treated patients (compared with duloxetine-treated patients) during the continuation phase indicates the need for ongoing treatment for patients with GAD.

Eight hundred and eighty-seven patients entered the open label phase and 429 were randomised. Time to relapse was significantly prolonged in the duloxetine group ($p<0.001$). After 26 weeks of double-blind treatment the relapse rate was 13.7 and 41.8% in the duloxetine and placebo group, respectively.

Figure 1. Time to relapse in study HMDV



CHMP Assessment of Efficacy data

Initial recommended dose

The CHMP suggested that the recommended dose 60 mg QD needs further substantiation. Considering the similar effect observed with 20 mg QD and 60-120 mg in Study HMDW and the overall tendency of less adverse events on 20 mg, a lower starting dose might be useful for males and also for females.

The CHMP concluded that the observed results indicate that lower doses could achieve good efficacy results at least for some groups of patients. The 20 mg dose has clearly shown global statistically significant efficacy results as primary variable, secondary variables, percentage of patients with sustained improvement, percentage of responders, and percentage of patients in remission, similar to those obtained for 60-120 mg dose. The frequency of lack of efficacy as reason for study discontinuation was similar between both strengths (20mg: n=2 (2.4%); 60-120mg: n=3 (1.9%)) meanwhile the study discontinuation due to adverse events was superior for patients treated with 60-120 mg regimen in comparison with those treated with 20 mg (n=21; 13.3% vs n=4 ; 4.8%).

The CHMP agreed with the MAH that in the analysis, some subgroups have shown significant results for 60-120 mg and not for 20 mg. Therefore, 60 mg could be considered as the lower starting dose in accordance with the available data.

The MAH admitted that there is evidence for the efficacy of a 20 mg dose in some GAD patients from the clinical program, and that patients treated with lower doses of duloxetine may experience a lower incidence of discontinuations due to adverse events than those treated with 60-120 mg once daily (QD).

The MAH commented that efficacy of duloxetine can be clearly identified following treatment for a period of 1-2 weeks in all of the short term GAD studies. Given these data, it was acceptable for the MAH to balance the efficacy at a lower dose for some patients with a risk of inadequate treatment for others by recommending a lower initial dose while providing prescribers with an expected timeframe for therapeutic response to ensure that patients do not remain on an ineffective lower dose indefinitely.

The lowest dose where efficacy was showed was 20 mg QD, and a significant number of patients in the clinical program received 30 mg QD as their initial starting dose. Therefore, the lowest initial dose proposed by the MAH was either 20 mg or 30 mg. Nevertheless, the MAH considered that those patients with GAD suffering co-morbid depression, need an adequate treatment for their depressive symptoms and taking into account that duloxetine 60 mg is the lowest effective dose specified in the SPC for major depressive disorder, it was proposed to also apply this dose to GAD patients with co-morbid MDD.

The CHMP pointed out that taking into account the favourable efficacy data obtained for lower doses, the MAH's recommendation for a 30 mg initial dose is considered acceptable. The CHMP suggested that the 20 mg dose is not needed since considering the closeness to the 30 mg strength and also the known large inter-individual variability in duloxetine plasma levels, clinical differences are unlikely to be detectable with a 30 mg dosing form. Furthermore, adding a 20 mg dosage to the existing 30 and 60 mg is unlikely to add anything but potential confusion to prescribers and patients. Therefore the CHMP suggested that the recommended starting dose in patients with GAD should be only the 30 mg one.

Justification of dose escalation

The CHMP pointed out that the proposed dose escalation of duloxetine in GAD does not mimic the one used in active comparator clinical trials with optional titration. This more flexible approach is also used by other drugs indicated for GAD. The CHMP requested the MAH to further justify the rational for the two step dose recommendation in the SPC (60 mg up to 120 mg).

In reply to the CHMP concern, the MAH mentioned that the method of dose escalation for patients taking duloxetine in the active comparator trials was consistent with the dosing method that was used for patients taking venlafaxine in these studies. Venlafaxine was titrated from 75 mg to 150 mg to 225 mg and duloxetine was titrated from 60mg to 90 mg to 120 mg. Although this method of dose escalation was used in these studies, data from Study HMBR, as well as from MDD and diabetic neuropathic pain (DNP) studies of duloxetine show that patients can titrate from 60 mg to 120 mg without employing the intermediate 90 mg dose.

The MAH commented that at the conclusion of the flexible dose studies, the majority of patients who completed the study were taking a dose higher than 60 mg QD at endpoint (mean final duloxetine dose: 103.32 mg QD). 60% of responders demonstrated efficacy with duloxetine 120 mg QD and 25% demonstrated efficacy with duloxetine 90 mg QD for the duration of this study and considered that duloxetine 90 mg QD can be effective for some GAD patients. Therefore, the MAH proposed titration from 60 mg QD up to 120 mg QD, based on the clinical judgment of the physician.

The CHMP concluded that the dose escalation method used in the clinical trials provided data which indicate the inter-individual variability in the response. Approximately 15% were not eligible for dose escalation during the clinical trials, approximately 30% increased their dose to Duloxetine 90 mg QD and approximately 55% increased their dose to Duloxetine 120 mg QD. Therefore intermediate doses between 60 mg and 120 mg are considered effective for some GAD patients and this should be reflected in the SPC.

The CHMP considered that since MAH had indicated this issue in the SPC, it was resolved.

Gender specific analyses

The CHMP concluded that due to an overall lower effect in females and one study with almost no effect in females it is questionable whether a clinically relevant effect in this dominating group of GAD patients has been convincingly demonstrated. Gender-specific analyses of sustained improvement, responder and remission rates in pooled analyses of all short-term studies were also requested by CHMP. In these analyses discontinuing patients should be counted as failures.

The data submitted by the MAH are summarised in the table below:

Table 8. Remission, Response, and Sustained Improvement Rates LOCF and BOCF by Gender Subgroup Pooled Data from Studies: HMBR, HMDT, HMDU, and HMDW

Measure	Therapy	LOCF			BOCF		
		N	n (%)	p-Value	N	n (%)	p-Value
Remission Rates[a]							
Female	Placebo	414	87 (21)	<.001	414	75 (18)	<.001
Female	Duloxetine	509	161 (32)		509	148 (29)	
Male	Placebo	238	44 (18)	<.001	238	38 (16)	.003
Male	Duloxetine	286	100 (35)		286	77 (27)	
Response Rates[b]							
Female	Placebo	414	147 (36)	<.001	414	121 (29)	<.001
Female	Duloxetine	509	267 (52)		509	236 (46)	
Male	Placebo	238	81 (34)	<.001	238	69 (29)	<.001
Male	Duloxetine	286	157 (55)		286	129 (45)	
Sustained Improvement Rates[c]							
Female	Placebo	419	180 (43)	<.001	419	157 (37)	<.001
Female	Duloxetine	511	300 (59)		511	267 (52)	
Male	Placebo	238	96 (40)	<.001	238	81 (34)	.001
Male	Duloxetine	287	170 (59)		287	142 (49)	

Abbreviations: BOCF = baseline observation carried forward; HAMA = Hamilton Anxiety Rating Scale; LOCF = last observation carried forward; N = total number of patients; n = number of patients in this category.

[a] Remission rate: HAMA total score of ≤7 at endpoint.

[b] Response rate: 50% or greater reduction from baseline in the HAMA endpoint total score.

[c] Sustained Improvement: at least a 30% improvement (reduction) on the HAMA total score from baseline to endpoint, at an earlier visit prior to the last visit of the study period, and at all visits in between.

This issue was, however, considered by the CHMP to have been addressed satisfactorily.

Exclusion of patients from study

The CHMP commented that patients were excluded from the study if patients were diagnosed with MDD within the past 6 months. All enrolled patients should not have any items>3 of Raskin Depression Scale (RDS). HADS Depression subscale was conducted at baseline (with a score variation from 0 to 21 points). The CHMP suggested that considering that Duloxetine could achieve good responses with depressive patients, measured at baseline of HAMD17 scale would have been of great interest.

The MAH explained that the exclusion criteria (DSM-IV criteria) used in these clinical trials, excluding patients with a current or recent history of major depression (within 6 months of study entry) are in accordance with CHMP Guidance (CPMP/EWP/4284/02). The RDS and the HADS depression subscale, helped to assess the depressive symptoms. The CHMP considered this concern to have been addressed.

Population of elderly patients

Efficacy results in the elderly and detailed age distributions was also considered to be needed by the CHMP.

The data submitted by the MAH are summarised below:

Patient Demographics
All Randomized Patients by Age Subgroup
Pooled Data from Studies: HMBR, HMDT, HMDU and HMDW

	Patients ≥65 years				Patients <65 Years			
Variable	**Placebo N=28**	**DLX N=45**	**Total n=73**	**p-Value**	**Placebo N=637**	**DLX N=781**	**Total N=1418**	**p-Value**
Gender	n(%)	n(%)	n(%)		n(%)	n(%)	n(%)	
Female	13(46.4)	27(60.0)	40(54.8)	.335	410(64.4)	501(64.2)	911(64.3)	.956
Male	15(53.6)	18(40.0)	33(45.21)		227(35.6)	280(35.9)	507(35.8)	
Age (yrs)								
Mean	70.9	70.0	70.4		41.2	40.9	41.0	
Median	70.3	68.8	69.5	.489	41.3	40.8	40.8	.403
SD	5.1	4.3	4.6		12.3	11.7	12.0	
Min	65.1	65.0	65.0		18.0	18.4	18.0	
Max	83.5	78.2	83.5		64.9	64.9	64.9	
Race	n(%)	n(%)	n(%)		n(%)	n(%)	n(%)	
African	1(3.6)	2(4.4)	3(4.1)	1.00	48(7.5)	56(7.2)	104(7.3)	
Caucasian	27(96.4)	43(95.6)	70(95.9)		498(78.2)	637(81.7)	1135(80.1)	
E. Asian	0(0.0)	0(0.0)	0(0.0)		21(3.3)	17(2.2)	38(2.7)	.042
Hispanic	0(0.0)	0(0.0)	0(0.0)		67(10.5)	58(7.4)	125(8.8)	
Nativ Am	0(0.0)	0(0.0)	0(0.0)		1(0.2)	1(0.1)	2(0.1)	
W. Asian	0(0.0)	0(0.0)	0(0.0)		2(0.3)	11(1.4)	13(0.9)	

Abbreviations: DLX = duloxetine; E = East; Min = minimum; Max = maximum; N = total number of patients; n = number of patients in this category; Nativ Am = Native American; SD = standard deviation; W = west; yrs = years.

Source: Program: RMP.F1JSGISE.SASPGM(FQDMGYA1).

Primary and Secondary Efficacy Measures – ANCOVA
All Randomized Patients by Age Subgroup
Pooled Data from Studies: HMBR, HMDT, HMDU and HMDW

Efficacy Measure	Patients ≥65 years			Patients <65 Years		
	Placebo N=28	DLX N=45	p-Value	Placebo N=637	DLX N=781	p-Value
HAMA Total						
Baseline	23.3	22.4	.029	25.5	25.4	<.001
Endpoint	16.9	12.4		16.5	13.1	
LSMean Change (SE)	-5.9 (1.5)	-10.1 (1.2)		-9.0 (0.4)	-12.3 (0.3)	
HAMA Psychic anxiety						
Baseline	13.9	13.6	.034	14.6	14.4	<.001
Endpoint	10.2	7.4		9.7	7.2	
LSMean Change	-3.6 (0.9)	-6.1 (0.8)		-4.8 (0.2)	-7.3 (0.2)	
HAMA Somatic Anxiety						
Baseline	9.3	8.8	.074	11.0	10.9	<.001
Endpoint	6.7	5.0		6.8	5.9	
LSMean Change (SE)	-2.4 (0.7)	-4.0 (0.6)		-4.2 (0.2)	-5.1 (0.2)	
HAMA Item 1 Anxious Mood						
Baseline	3.0	2.7	.138	2.9	2.8	<.001
Endpoint	2.0	1.5		2.0	1.4	
LSMean Change (SE)	-0.9 (0.2)	-1.3 (0.2)		-0.9 (0.0)	-1.4 (0.0)	
HAMA Item 2 Tension						
Baseline	2.4	2.6	.209	2.6	2.7	<.001
Endpoint	1.6	1.3		1.8	1.3	
LSMean Change (SE)	-0.9 (0.2)	-1.2 (0.2)		-0.9 (0.0)	-1.3 (0.0)	
HADS Anxiety						
Baseline	12.1	11.8	.049	13.7	13.5	<.001
Endpoint	9.9	7.6		10.0	7.5	
LSMean Change (SE)	-2.2 (0.7)	-4.1 (0.6)		-3.7 (0.2)	-6.0 (0.2)	
HADS Depression						
Baseline	7.4	7.1	.026	8.3	8.2	<.001
Endpoint	6.6	4.5		6.4	4.8	
LSMean Change (SE)	-0.8 (0.6)	-2.6 (0.5)		-1.9 (0.2)	-3.4 (0.1)	
SDS Global Functioning						
Baseline	12.7	12.6	.324	16.4	16.1	<.001
Endpoint	10.3	8.3		11.7	8.4	
LSMean Change (SE)	-2.2 (1.5)	-4.1 (1.2)		-4.6 (0.3)	-7.8 (0.3)	

Abbreviations: DLX = duloxetine; HADS = Hospital Anxiety and Depression Rating Scale; HAMA = Hamilton Anxiety Rating Scale; LSMean = least-squares mean; N = total number of patients; SDS = Sheehan Disability Scale; SE = standard error.

Source: Program: RMP.F1JSGISE.SASPGM(LOEFFYA2).

Remission, Response, and Sustained Improvement Rates
All Randomized Patients by Age Subgroup
Pooled Data from Studies: HMBR, HMDT, HMDU, and HMDW

Measure	Patients ≥65 years			Patients <65 Years		
	Placebo N=28 n (%)	DLX N=45 n (%)	p-Value	Placebo N=637 n (%)	DLX N=781 n (%)	p-Value
Remission[a]	2 (7.0)	10 (24.0)	.053	129 (21.0)	251 (33.0)	<.001
Response[b]	8 (29.0)	20 (48.0)	.149	220 (35.0)	404 (54.0)	<.001
Sustained Improvement[c]	10 (36.0)	26 (62.0)	.050	266 (42.0)	444 (59.0)	<.001

Abbreviations: DLX = duloxetine; N = total number of patients; n = number of patients in this category.

[a] Remission rate: HAMA total score of ≤7 at endpoint.

[b] Response rate: 50% or greater reduction from baseline in the HAMA endpoint total score.

[c] Sustained Improvement: at least a 30% improvement (reduction) on the HAMA total score from baseline to endpoint, at an earlier visit prior to the last visit of the study period, and at all visits in between.

Source: Program: RMP.F1JSGISE.SASPGM(FQSUSVP1); RMP.F1JSGISE.SASPGM(FQRESVP1); RMP.F1JSGISE.SASPGM(FQREMVP1).

The CHMP suggested that the MAH should indicate in the SPC the limitation of the data base for the elderly and should further explore this population group. The MAH agreed to perform a study assessing the safety and efficacy of duloxetine in elderly patients with GAD and to submit a draft of the prospective study by Q4 2008. The SPC has been revised regarding the use in the elderly with GAD. The CHMP considered that the MAH had convincingly addressed this concern, which was thus resolved.

Explanation of the use of the Last Observation Carried Forward (LOCF) method

Alternative analyses where all discontinuing patients are counted as non-responders for the acute GAD studies were also considered to be needed by the CHMP.

As requested, analyses of response, remission, and sustained response counting all discontinuing patients as non-responders (BOCF (Baseline Observation Carried Forward) analysis) for the acute GAD studies, are presented below by study and as pooled data (Table 9).

Table 9. Remission, Response, and Sustained Improvement Rates LOCF and BOCF Individual and Pooled Data from Studies: HMBR, HMDT, HMDU, and HMDW

	Remission[a]		Response[b]		Sustained Improvement[c]	
	LOCF n (%)	BOCF n (%)	LOCF n (%)	BOCF n (%)	LOCF n (%)	BOCF n (%)
HMBR						
DLX60	51 (31)**	47 (28)*	95 (58)***	90 (55)***	105 (64)***	100 (60)***
DLX120	64 (38)***	58 (34)***	94 (56)***	86 (51)***	113 (67)***	100 (59)***
PLA	33 (19)	31 (18)	53 (31)	50 (29)	74 (43)	70 (40)
HMDT						
DLX60-120	45 (28)	35 (22)	67 (42)*	55 (34)*	70 (44)*	59 (37)
PLA	36 (23)	30 (19)	48 (30)	37 (23)	52 (33)	45 (29)
HMDU						
DLX60-120	34 (23)	23 (15)	70 (47)	46 (31)	82 (55)**	60 (37)
VEN75-225	48 (30)*	36 (23)	86 (54)***	63 (40)*	86 (54)**	69 (42)*
PLA	30 (19)	25 (16)	58 (37)	45 (28)	61 (39)	49 (30)
HMDW						
DLX20	35 (42)***	33 (40)***	50 (60)**	44 (53)**	56 (67)*	50 (60)*
DLX60-120	67 (44)***	62 (41)***	98 (65)***	88 (58)***	100 (65)*	90 (57)*
VEN75-225	70 (44)***	67 (42)***	97 (61)***	88 (56)***	111 (67)**	103 (61)***
PLA	32 (20)	27 (17)	69 (42)	58 (36)	89 (53)	74 (44)
Acute GAD Studies Pooled Data[d]						
DLX	261 (33)***	225(28)***	424 (53)***	365(46)***	470 (59)***	409 (51)***
PLA	131 (20)	113 (17)	228 (35)	190 (29)	276 (42)	238 (36)

Abbreviations: BOCF = baseline observation carried forward; DLX = duloxetine; GAD = generalized anxiety disorder; LOCF = last observation carried forward; PLA = placebo; VEN = venlafaxine extended release.

a Remission rate: HAMA total score of ≤7 at endpoint.

b Response rate: 50% or greater reduction from baseline in the HAMA endpoint total score.

c Sustained Improvement: at least a 30% improvement (reduction) on the HAMA total score from baseline to endpoint, at an earlier visit prior to the last visit of the study period, and at all visits in between.

d The pooled duloxetine data does not include patients who were randomized to duloxetine 20 mg QD.

*p≤.05
**p≤.01
***p≤.001

The BOCF-results are consistent with the initially reported LOCF-results. Thus it has been made plausible that the LOCF-results are not biased due to the differential withdrawal pattern.

The CHMP considered this concern to have been addressed.

3.2 Clinical safety

Patient exposure

A total of 1797 subjects (shown in the Table 10 as Primary overall duloxetine exposures), representing approximately 570 patient-years of exposure were treated with duloxetine for GAD. A total of 1228 patients (162 patient-years) received short-term treatment and 1094 (879 open label therapy phase and 215 double-blind continuation phase) patients (419 patient-years) received long-term treatment (up 1 year) with duloxetine.

The patient exposure in GAD studies as well as in studies on other indications is presented in Table 10.

Table 10. Patient exposure in studies I GAD and other indications

	Duloxetine		**Placebo**		**Venlafaxine**	
	N	**Patient-years**	**N**	**Patient-years**	**N**	**Patient-years**
Primary acute placebo-controlled Study HMBR, Study HMDT, Study HMDU, Study HMDW	910	114.0	665	104.0	N/A	N/A
Primary active-comparator-controlled Study HMDU and Study HMDW	318	48.0	330	52.7	332	52.6
Primary long-term **- open-label therapy phase** **- double-blind continuation phase** Study HMDV (both phases)	 879 215	 327.3 92.0	 N/A 212	 N/A 72.7	 N/A N/A	 N/A N/A
Primary overall duloxetine exposures Study HMBR, Study HMDU, Study HMDT, Study HMDV, Study HMDW	**1797**	569.8	N/A	N/A	N/A	N/A
All placebo-controlled All placebo-controlled studies, all indications	9445	1642.9	6770	1242.0	N/A	N/A
Overall duloxetine exposures All completed studies, all indications	27,229	12,428.4	N/A	N/A	N/A	N/A

Patients in the primary analyses sets were predominantly Caucasian (83.0%) and females (61.8%) with a median age of 43 years of age.

Adverse events

Treatment-emergent adverse events (TEAEs) from double-blind trials in the primary placebo-controlled database for which the incidence in the duloxetine treatment group was ≥5.0% and significantly greater than the incidence in the placebo group were nausea (33.8% vs 10.2%), dry mouth (11.62% vs 3.6%), insomnia (7.6% vs 3.6%), fatigue (10.7% vs 3.5%), diarrhoea (7.9% vs 5.6%), dizziness (13.5% vs 7.5%), somnolence (7.8% vs 1.8%), hyperhidrosis (7.4% vs 2.0%)

Table 11. Frequencies of most common adverse events in All placebo controlled studies and placebo controlled GAD studies.

	All Pla Studies		**HMBR**		**HMDT**		**HMDU**		**HMDW***		**HMDV****
Adverse Events %	PL	DLX	PL	DLX	PL	DLX	PL	DLX	PL	DLX	DLX
N	6770	9445	175	338	159	168	161	162	170	158	887
Nausea	7.5	24.3	7.4	42.6	10.1	36.9	13.7	31.5	10.0	22.2	28.3
Headache	9.9	12.6	13.7	18.6	16.4	16.1	23.0	13.6	18.8	15.2	18.7
Dry mouth	4.1	12.9	3.4	14.5	1.9	6.5	6.2	11.7	2.9	13.3	14.3
Constipation	3.3	10.3	2.3	8.0	3.1	8.3	4.3	14.2	4.1	11.4	12.5
Dizziness	4.0	9.5	6.9	15.1	6.9	16.7	9.3	11.1	7.1	12.0	13.4
Fatigue	3.8	9.2	1.7	13.3	5.7	11.9	3.7	7.4	2.9	8.9	11.5
Insomnia	3.9	8.7	3.4	9.5	3.1	6.5	1.9	7.4	5.9	6.3	9.8

Diarrhoea	4.9	7.6	2.9	5.3	6.3	7.7	8.7	13.6	4.7	8.9	14.2
Somnolence	1.6	6.9	1.1	4.7	0.6	11.9	3.7	11.7	1.8	8.2	8.2
Hyperhidrosis	1.3	5.7	4.6	11.8	1.9	1.8	0.0	4.3	1.2	8.2	10.0
Nasopharyngitis	4.1	3.7	10.3	2.7	6.3	4.2	6.8	3.7	1.8	4.4	5.0
Vomiting	2.0	4.5	0.6	4.7	4.4	7.1	1.9	2.5	3.5	5.1	5.4
Libido decreased	0.5	1.9	1.1	5.6	2.5	5.4	0.6	6.8	0.0	3.8	5.4

* Only includes patients taking 60-120 mg QD (20 mg QD excluded)
** Study HMDV is a relapse prevention study with both and open-label and a placebo controlled part

Method of analyses

The integrated safety data of duloxetine in the treatment of GAD was classified into four primary analyses sets based on study design:

a. The primary acute placebo-controlled analyses set includes data on GAD placebo-controlled studies (HMBR, HMDT, HMDU and HMDW) with up to 10 weeks treatment in which most subjects were randomly assigned to doses of 60 mg to 120 mg daily throughout the trial.
b. The primary active-comparator-controlled analysis set includes data on GAD, using venlafaxine as active comparator (Study HMDU and Study HMDW).
c. The primary long-term analyses set includes data from the long-term relapse-prevention study (HMDV) of 6 months open-label and 6 months double-blind in which subjects were treated with duloxetine 60 mg to 120 mg daily.
d. The primary overall duloxetine analyses set includes data from patients treated with duloxetine in all GAD studies (Study HMBR, Study HMDU, Study HMDT, Study HMDV and Study HMDW).

Two additional analyses set covering all indications were included for comparisons:
e. the all placebo-controlled analyses set with data from all placebo-controlled duloxetine studies for all indications (Fibromyalgia (FM), Diabetic Peripheral Neuropathic Pain (DPNP), Generalised Anxiety Disorder (GAD), Lower Urinary Tract Disorder (LUTD), Major Depressive Disorder (MDD), and
f. the overall duloxetine exposures analyses set with duloxetine data coming from all completed studies, all indications as of the data cut-off date of 12 May 2007.

CHMP assessment of Safety Data
According to the findings identified during the continuous safety assessment of duloxetine in its different indications the following key events were closely monitored:

a) Suicidality: A total of eight suicide ideations were reported in GAD studies, four of them in the open-label long term study. There was 1 case of self-injurious behaviour in the primary acute placebo-controlled analyses set and 2 reports of suicide attempts in Study HMDV. One duloxetine- treated patient died due to completed suicide in the open-label phase of study HMDV. These findings indicate that the concerns about suicidal behaviour associated with duloxetine remain. This issue is considered in the pharmacovigilance activities for duloxetine and reflected in the SPC.
b) Hepatic risk: Duloxetine treated patients involved in GAD studies showed greater increases of AST and alkaline phosphatase. No significant dose relationship was observed. No new hepatic safety concerns regarding duloxetine were observed. This issue is considered in the pharmacovigilance activities for duloxetine and reflected in the SPC.
c) Duloxetine did not appear to adversely affect glycaemic control or lipid profiles in GAD patients.

Incidence of adverse events with higher doses
The CHMP asked the MAH to provide adverse events frequencies distribution observed for 60 mg treated patients in comparison to 120 mg treated patients for all aggregated studies.

The data submitted by the MAH are summarised below:

Common Treatment-Emergent Adverse Events by Decreasing Frequency
MedDRA Preferred Term
All Randomized Patients
Acute Therapy Phase
Study HMBR

Event	Placebo N=175 n (%)	DLX60 N=168 n (%)	DLX120 N=170 n (%)	p-Value DLX60 versus DLX120
Nausea	13 (7.4)	70 (41.7)	74 (43.5)	.743
Dizziness	12 (6.9)	19 (11.3)	32 (18.8)	.068
Dry Mouth	6 (3.4)	18 (10.7)	31 (18.2)	.063
Fatigue	3 (1.7)	21 (12.5)	24 (14.1)	.749
Constipation	4 (2.3)	13 (7.7)	14 (8.2)	1.00
Diarrhea	5 (2.9)	5 (3.0)	13 (7.6)	.088
Insomnia	6 (3.4)	18 (10.7)	14 (8.2)	.463
Somnolence	2 (1.1)	6 (3.6)	10 (5.9)	.443
Hyperhidrosis	8 (4.6)	14 (8.3)	26 (15.3)	.063
Libido Decreased	2 (1.1)	11 (6.5)	8 (4.7)	.489

Abbreviations: DLX60 = duloxetine 60 mg once daily; DLX120 = duloxetine 120 mg once daily; MedDRA = Medical Dictionary for Regulatory Activities; N = total number of patients; n = number of patients in this category.
Source: Program: RMP.F1JSHMBR.SASPGM(FQAESA11).

The submitted data showed that patients who were up-titrated to 120 mg QD did not experience a significantly higher frequency of TEAEs (Treatment Emergent Adverse Events) compared with patients who stayed on 60 mg QD, although the incidence of the majority of the events experienced were numerically higher for the 120 mg treatment group. The CHMP considered this issue to have been resolved.

Comparison of Venlafaxine and Duloxetine safety profiles
Another issue of concern for CHMP was the difference in incidence of serotoninergic adverse events between duloxetine and venlafaxine.

The MAH commented in their response that study HMDU and study HMDW (placebo versus duloxetine versus venlafaxine) showed that both duloxetine and venlafaxine are associated with a significantly higher frequency of TEAEs compared with placebo, but that overall the adverse event profile of the two drugs was very similar, both across the large majority of commonly reported TEAEs and for all TEAEs combined. No statistically significant difference was observed for all TEAEs combined (duloxetine 73.8%; venlafaxine 76.6%), and of the most frequently reported TEAEs, half were more frequently reported with duloxetine (nausea, constipation, diarrhoea, somnolence, decreased appetite, hyperhidrosis) and half were more frequently reported with venlafaxine (headache, dizziness, dry mouth, fatigue, insomnia, vomiting). While nausea (26.9 versus 20.1), diarrhoea (11.3 versus 6.0%) and nasopharingitis (4.1% versus 1.5%) were reported statistically more frequently with

duloxetine compared with venlafaxine, it is of note that the rates of diarrhoea and nasopharingitis were in fact higher for placebo than for venlafaxine.

Nausea and diarrhoea are both listed in the current SPC and are reported with their incidence ("very common" and "common even", respectively) that properly reflects the safety experience with duloxetine in clinical trials for all indications combined.

In summary, the MAH considered that the adverse event profile of the two drugs appears similar, across the large majority of commonly reported TEAEs, for all TEAEs combined, and also for serotoninergic adverse events.

The CHMP considered this issue to have been resolved.

Age differences in the safety profile

The CHMP asked the MAH to further analyse the applicability of the safety data available from the overall safety data of duloxetine in the elderly patients.

In reply to CHMP request the MAH provided an analysis of treatment-emergent adverse events by demographic subgroup in patients treated for GAD. The data show that while placebo-treated patients aged ≥55 years old reported more TEAEs than placebo-treated patients aged <55 years, such relation with age is not seen in duloxetine treated patients. A similar finding is observed for patients aged <65 years and ≥65 years.

Moreover, the MAH commented that older patients with GAD treated with duloxetine did not report more TEAEs than younger patients and considering the total exposure to date it could be concluded that the safety profile is similar across different indications.

The MAH summarized the main safety conclusions as follows:

- The safety profile in elderly and very elderly patients is similar to the overall duloxetine safety profile.
- The pattern of deaths and SAEs does not appear to be related to duloxetine therapy with increasing age.
- The relationship of duloxetine to TEAEs increases or decreases with age depending on the type of TEAEs analyzed.
- There is no age-related pattern to the effects of duloxetine on vital signs, laboratory measures, or electrocardiogram (ECG) parameters.

The MAH concluded that the elderly and very elderly patients are well represented and characterized in the overall duloxetine database. Taking into account that there is no excess of TEAEs in elderly GAD patients treated with duloxetine compared with younger GAD patients, and the safety profile in this subgroup of patients is similar to the overall duloxetine safety profile, the MAH considered that it would not be appropriate to restrict the use of duloxetine in elderly patients with GAD. However the MAH agreed that data on duloxetine 120 mg QD are limited in this population and dose increases to 120 mg QD in the elderly or very elderly should be made with caution.

The CHMP considered the MAH response acceptable. There is no special reason to conclude that the elderly and very elderly patients will have a different safety profile to that already known for this group of population in other indications. However, considering that data on elderly GAD patients are limited a special warning for physicians has been included in the SPC. In addition, a further commitment is made by the MAH to submit a draft of a prospective study assessing the safety and efficacy on duloxetine in elderly patients with GAD by Q4 2008.

Pregnancies

A further issue of concern for the CHMP was the relationship between duloxetine and miscarriage or abnormalities. Based on the data submitted by the MAH, a total of 77 pregnancies possibly exposed to duloxetine have been reported during clinical development of the product. At least 27% of the pregnancies with known outcomes resulted in an unexpected or undesirable result (ectopic pregnancy, abortion, preterm delivery with fetal demise, congenital abnormalities).

The MAH argued that a relationship between duloxetine and miscarriage or abnormalities cannot be ruled out at this point. For this reason, the MAH pointed out that the current SPC wording on pregnancy appropriately warns the prescribing physician of the need to carefully balance the benefit versus the potential risk before exposing a pregnant woman to duloxetine. The CHMP agreed with the MAH's proposal and the issue has been resolved.

Suicidality

The CHMP commented that although suicidality is a key aspect of the pharmacovigilance program and RMP (Risk Management Plan) for duloxetine in its different indications (psychiatric and non-psychiatric), no specific actions are proposed for the GAD indication.
In reply to CHMP concern, the MAH pointed out that psychiatrists are well informed about the role of depression and SSRI/SNRI treatment in relation to the risk of suicidability, and the suicide-related events experienced by GAD patients could be properly identified and reported by these physicians.

The CHMP considered this issue to have been resolved.

Withdrawal symptoms
The CHMP asked the MAH to provide comparative data on the withdrawal signs when the treatment is stopped in GAD as compared to those observed in the depression indication (frequency, nature of events, effect of tapering).
The MAH has provided the following comparative data on the withdrawal signs when the treatment is stopped abruptly or tapered in GAD patients and in MDD patients.

Discontinuation-Emergent Adverse Events and Taper-Emergent Adverse Events GAD and MDD

Event	GAD AD		GAD Taper		MDD AD		MDD Taper	
	PLC N=130 n(%)	DLX N=129 n(%)	PLC N=448 n(%)	DLX N=491 n(%)	PLC N=661 n(%)	DLX N=871 n(%)	PLC N=323 n(%)	DLX N=348 n(%)
≥1 TEAE[a]	**21(16.2)**	**43(33.3)**	**75(16.7)**	**109(22.2)**	**173(26.2)**	**337(38.7)**	**41(12.7)**	**61(17.5)**
Dizziness	**2(1.5)**	**12(9.3)**	**6(1.3)**	**33(6.7)**	**8(1.2)**	**95(10.9)**	**2(0.6)**	**12(3.4)**
Headache	4(3.1)	10(7.8)	7(1.6)	17(3.5)	**16(2.4)**	**54(6.2)**	5(1.5)	11(3.2)
Nausea	**0(0.0)**	**5(3.9)**	**2(0.4)**	**13(2.6)**	**1(0.2)**	**46(5.3)**	**2(0.6)**	**10(2.9)**
Diarrhea	1(0.8)	1(0.8)	1(0.2)	7(1.4)	**6(0.9)**	**22(2.5)**	3(0.9)	3(0.9)
Irritability	1(0.8)	3(2.3)	2(0.4)	5(1.0)	**3(0.5)**	**19(2.2)**	1(0.3)	1(0.3)
Paraesthesia	**0(0.0)**	**5(3.9)**	1(0.2)	3(0.6)	**1(0.2)**	**18(2.1)**	0(0.0)	1(0.3)
Vomiting	-	-	0(0.0)	2(0.4)	**2(0.3)**	**16(1.8)**	0(0.0)	2(0.6)
Fatigue	-	-	0(0.0)	1(0.2)	**4(0.6)**	**13(1.5)**	2(0.6)	4(1.1)
Hyperhidrosis	0(0.0)	2(1.6)	2(0.4)	3(0.6)	**1(0.2)**	**13(1.5)**	1(0.3)	3(0.9)
Abnormal Dreams	0(0.0)	1(0.8)	0(0.0)	4(0.8)	**1(0.2)**	**11(1.3)**	0(0.0)	1(0.3)
Nightmare	0(0.0)	1(0.8)	0(0.0)	1(0.2)	**0(0.0)**	**12(1.4)**	-	-
Tinnitus	0(0.0)	1(0.8)	2(0.4)	0(0.0)	**1(0.2)**	**9(1.0)**	0(0.0)	1(0.3)
Vertigo	0(0.0)	1(0.8)	0(0.0)	4(0.8)	**0(0.0)**	**10(1.1)**	0(0.0)	3(0.9)
Somnolence	-	-	0(0.0)	1(0.2)	**1(0.2)**	**8(0.9)**	0(0.0)	1(0.3)
Insomnia	1(0.8)	4(3.1)	**2(0.4)**	**10(2.0)**	9(1.4)	21(2.4)	0(0.0)	3(0.9)
Tremor	0(0.0)	2(1.6)	**0(0.0)**	**6(1.2)**	1(0.2)	2(0.2)	0(0.0)	1(0.3)

Abbreviations: AD = abrupt discontinuation; DLX = duloxetine; GAD = generalized anxiety disorder; MDD = major depressive disorder; N = total number of patients; n = number of patients in this category; PLC = placebo; TEAE = treatment-emergent adverse event.

[a] Bolded numbers indicate events that were significantly greater in duloxetine-treated patients compared with placebo since these were not consistent across indications.

Source: Program: RMP.F1JSFMSS.SASPGM(FQAESC11); RMP.F1JSFMSS.SASPGM(FQAESC12); RMP.F1JSFMSS.SASPGM(FQAESC13); RMP.F1JSFMSS.SASPGM(FQAESC14).

The CHMP considered this issue to have been resolved.

In conclusion, all the safety issues identified by the CHMP during this procedure have been satisfactorily addressed by the MAH.

3.3. Risk Management Plan

The MAH submitted a Risk Management Plan (RMP).

Table Summary of the risk management plan

Safety issue	Proposed pharmacovigilance activities	Proposed risk minimisation activities
Hepatic risks	• Study F1J-MC-B021: Duloxetine Retrospective Cohort Study- Hepatic Events: 'Hepatic and Cardiovascular Events in Adults Taking Duloxetine Compared with Depressed Treated, Depressed Not Pharmacologically Treated, and Nondepressed Patients in a Large US-managed Care Database' Final report completion date: Q2 2008	The SPC wording covers the identified risks of mild to moderate liver enzyme elevations and also more severe (>10 times ULN) transaminase elevations.
	• Targeted questionnaire for follow-up investigation of hepatic events ongoing activity on a case-by-case basis	
	• Genotyping of patients Ongoing	
	• Quarterly FDA AERS analysis of hepatic adverse events for all cases and fatal case series, both in overall database and against antidepressant-only background. AERS fatal case series followed by individual case expert review to evaluate causality. Quarterly evaluations and reporting incorporated within PSURs	
	• Continued assessment of hepatic-related adverse event data and laboratory data at the time of completion of each clinical trial. Sites instructed to use the Hepatic Monitoring Plan Guidance for further course of action upon clinical suspicion of potential liver damage. • Periodic review of the clinical trial database and spontaneous AE data for hepatotoxicity. • Updates provided in every PSUR. Ongoing	
Suicidality	• General Practice Research Database (GPRD) analysis of suicidality in SUI patients Results for the assessment of the association between SUI status and suicide-related behaviors and ideation were presented in the Risk Management Plan (rv 2). An evaluation of any potential association between duloxetine exposure and suicide-related outcomes in females with SUI in GPRD is proposed for Q3 2007 (with data through March 2007).	The SPC wording takes into account the available data within the MAH as well as the FDA meta-analyses of antidepressant class-related association with suicidality.

	• Concept being developed for a retrospective cohort study of suicide attempts leading to hospitalization in depressed adult patient population using a large US claims database Lilly is aiming to discuss study concept with the CHMP Rapporteur in Q3 2007.	
	• Targeted questionnaire for follow-up investigation of suicide-related events Not applicable as it is an ongoing activity on a case-by-case basis	
Suicidality (continued)	• Study F1J-SB-B007 (DUROSA study) Study ongoing, from February 2005 -July 2008 Estimate study timeline: - Q4 2007: 12,000 patients expected to be enrolled - Q4 2008: analysis of those patients should be available	
	• Continued assessment of all suicidality at the time of completion of each clinical trial. • Periodic review of the clinical trial database and spontaneous AE data for suicidality. • Updates provided in every PSUR. Ongoing	
Hyperglycemia	• Continued assessment of all hyperglycemia-related adverse events and laboratory data at the time of completion of each clinical trial. • Periodic review of the clinical trial database for hyperglycemia. • Updates on severe hyperglycemia provided in every PSUR. Ongoing	The SPC wording provides information from DPNP clinical trial data and also states that hyperglycemia is an undesirable effect in the postmarketing adverse event section.
Hyperglycemia (continued)	• Further assessment of clinical trial data as well as post-marketing data focusing on specific hyperglycemia related outcomes - severe hyperglycemia events (*diabetic coma*, *diabetic ketoacidosis* [DKA], or blood glucose levels reported as >250 mg/Dl) to identify any specific risk factors/ sub-populations at risk within the diabetic patient population. • An assessment of patients with uncontrolled hyperglycemia at baseline will also be undertaken to determine effects of duloxetine treatment in this patient population. Analyses to be completed Q4 2007	

Stevens-Johnson Syndrome	• Targeted questionnaire for follow-up investigation of severe skin reactions • Evaluation of reports of TEN in temporal association with duloxetine treatment • As sufficient data for duloxetine becomes available in the FDA AERS database, Lilly will assess the proportional reporting ratios of Stevens-Johnson Syndrome (SJS) and related events for duloxetine compared with other products known to be associated with these reactions, such as lamotrigine and carbamazepine. • Continued assessment of SJS at the time of completion of each clinical trial. • Periodic review of the clinical trial database and spontaneous AE data for SJS. • Updates provided in every PSUR. ongoing activity on a case-by-case basis	SPC wording. Stevens-Johnson Syndrome (SJS) is a listed event in the postmarketing adverse event section. Due to the lack of any recent findings or increased trends in reporting, no further risk minimization has been implemented.
Potential Risk Renal Failure	• Continued assessment of renal failure-related adverse events and laboratory data at the time of completion of each clinical trial. • Periodic review of the clinical trial database for renal failure. • Updates on renal failure provided in every PSUR. Ongoing	As this is a potential issue where a definite association has not been established, no risk minimization has been implemented.
Potential Risk Cardiovascular events	• Study F1J-MC-B021: Duloxetine Retrospective Cohort Study- Cardiovascular Events: 'Hepatic and Cardiovascular Events in Adults Taking Duloxetine Compared with Depressed Treated, Depressed Not Pharmacologically Treated, and Nondepressed Patients in a Large US-managed Care Database. Final report completion date: Q2 2008	SPC wording. Many cardiovascular events are listed in the Undesirable Effects section, such as tachycardia, palpitations, hypertensive crisis, and supraventricular arrhythmias. In addition, there is a precaution related to blood pressure changes in Section 4.4 of the SPC.
	• Targeted questionnaire for follow-up investigation of CV SAEs (clinical trial data) and all adverse events (serious and non-serious for postmarketing reports) for events including Myocardial Infarction, Ventricular Fibrillation, and hypertension Ongoing	
	• Quarterly FDA AERS analysis of CV adverse events singly and by clinical clusters, for all cases and fatal case series, both in overall database and against antidepressant-only background. Quarterly evaluations and reporting incorporated within PSURs	

Potential Risk Cardiovascular events	• Ongoing assessment of CV parameters, including ECGs (when collected), vital signs data, and CV events (serious and nonserious) for Lilly-sponsored clinical trials at the time of trial completion • Periodic review of the clinical trial database for CV events. • Updates on specific CV safety topics provided in every PSUR. Ongoing	
All risks	• Prescription Event Monitoring Study (Xeristar) Q1 2007: first interim reports completed Final reports to be completed when data from 10,000 patients have been collected.	Not applicable. Should a new safety signal be detected, risk minimization measures will be considered.
	• Study F1J-SB-B007 (DUROSA study) Study ongoing, from February 2005 -July 2008 Estimate study timeline: - Q4 2007: 12,000 patients expected to be enrolled - Q4 2008: analysis of those patients should be available	
	• Routine pharmacovigilance practices: target surveillance terms , safety surveillance activities, periodic reports, and expedited ADRs Ongoing	
Potential interaction with warfarin	• Study F1J-MC-HMFP: Evaluation of the Effect of Duloxetine on the Pharmacodynamics of Warfarin at Steady-State in Healthy Subjects First patient visit Q2 2007 Final report completed: Q2 2008	As this is a potential issue where a definite association has not been established, no risk minimization has been implemented. However, this potential interaction has been acknowledged in the EU SPC.
Missing Information: Better characterization of the relative risk profiles of hepatotoxicity and cardiovascular events with duloxetine compared with other antidepressants	• Study F1J-MC-B021: Duloxetine Retrospective Cohort Study: 'Hepatic and Cardiovascular Events in Adults Taking Duloxetine Compared with Depressed Treated, Depressed Not Pharmacologically Treated, and Nondepressed Patients in a Large US-managed Care Database' Final report completion date: Q2 2008	Currently not applicable

Missing Information: Characterization of the safety and tolerability in pediatric patients	• Study F1J-MC-HMFN: An Open-Label Study of Tolerability, Safety, and Pharmacokinetics of Duloxetine in the Treatment of Children and Adolescents with Major Depressive Disorder First patient visit Q3 2007 Final report completed: Q1 2009	SPC wording, which currently specifies that duloxetine has not been studied in patients under 18 years of age.

Abbreviations: AERS = Adverse Event Reporting System; CCDS = Company Core Data Sheet; CV = cardiovascular; DPNP = diabetic peripheral neuropathic pain; DUROSA = Duloxetine Routine Safety; ECGs = electrocardiograms; EU = European Union; FDA = Food and Drug Administration; HCP = Health Care Provider; Q = quarter; PSUR = Periodic Safety Update Report; Q = quarter; SPC = Summary of Product Characterisitics; TEN = toxic epidermal necrolysis; ULN = upper limit of normal; US = United States.

The Annex II has been updated accordingly.
The CHMP, having considered the data submitted with the application, is of the opinion that no additional risk minimisation activities are necessary for the safe and effective use of the medicinal product. The RMP was acceptable to the CHMP.

4. *Changes to the Product Information*

In addition to the above-described concerns, a number of other aspects relating to the SPC wording proposed by the MAH were identified as issues by the CHMP during this procedure.

In section 4.2 of the SPC the following wording included in order to consider the 30 mg as the initial dose (new text: bold)

Generalised Anxiety Disorder
The recommended starting dose in patients with Generalised Anxiety Disorder is 30 mg once daily with or without food. In patients with insufficient response the dose should be increased to 60 mg, which is the usual maintenance dose in most patients.

In patients with co-morbid Major Depressive Episodes, the starting and maintenance dose is 60 mg once daily (please see also dosing recommendation above).
Doses up to 120 mg per day have been shown to be efficacious and have been evaluated from a safety perspective in clinical trials. In patients with insufficient response to 60 mg, escalation up to 90 mg or 120 mg may therefore be considered. Dose escalation should be based upon clinical response and tolerability.
After consolidation of the response, it is recommended to continue treatment for several months, in order to avoid relapse.

In section 4.4 of the SPC a special warning was included regarding the limited data on elderly GAD patients.

5. Elderly

Major Depressive Episodes: Data on the use of XERISTAR 120mg in elderly patients with major depressive disorders are limited. Therefore, caution should be exercised when treating the elderly with the maximum dosage (see sections 4.2 and 5.2).
Generalised Anxiety Disorder: Data on the use of XERISTAR in elderly patients with generalised anxiety disorder are limited.

The MAH submitted revised product information (sections 4.2, 4.4, 4.8 and 5.1 of the SPC and sections 1, 3 and 4 of the PL), in accordance with the requests from the CHMP.

6. *Conclusions and Benefit / Risk Assessment*

The application to extend the indication for Xeristar (Duloxetine) to treatment of generalised anxiety disorder was evaluated by the CHMP.

An overall effect of duloxetine was demonstrated in the submitted short-term and long-term GAD studies; however some efficacy concerns were raised mainly with regard to initial dose and to the remaining gender-specific analyses.
With regard to the initial dose, the MAH was requested to further sustain the proposed starting dose (60 mg) as the observed results with lower doses indicate that it can be effective at least for some group of patients. In the responses, the MAH proposed a revised SPC wording considering 20 or 30 mg as initial doses. However, the 20 mg pharmaceutical form is not authorized, and considering the closeness to the 30 mg strength and also the known large inter-individual variability in duloxetine plasma levels, clinical differences are unlikely to be detectable. This issue has been addressed since section 4.2 of the SPC reflects the 30 mg as the initial dose.

The second major concern was related to the fact that the MAH had not submitted the requested gender-specific analyses of sustained improvement, responder and remission rates in pooled analyses of all short-term studies, counting all discontinuing patients as failures. These analyses were considered important in order to explore possible gender differences, moreover taking into account that GAD is shown to be more common in women than in men. The analyses were presented by the MAH and the submitted data show no indications of gender differences.

The MAH was also requested to submit alternative analyses to the LOCF approach used in the analysis of responder, remission and sustained responses data to count all discontinuing patients as non-responders. Data provided show that the BOCF-results are consistent with the initially reported LOCF-results.

The MAH has also agreed to perform a study assessing the efficacy and safety of elderly patients in the proposed indication (draft of a prospective study will be given by Q4 2008).

In conclusion, the benefit-risk balance of duloxetine in the treatment of GAD can be considered positive.

7. Conclusion

On 26 June 2008 the CHMP considered this Type II variation to be acceptable and agreed on the amendments to be introduced in the Summary of Product Characteristics, Annex II and Package Leaflet.