European Medicines Agency

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ASSESSMENT REPORT
FOR
CYMBALTA

International Nonproprietary Name:
duloxetine hydrochloride

Procedure No. EMEA/H/C/572/II/0036

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

7 Westferry Circus, Canary Wharf, London, E14 4HB, UK
Tel. (44-20) 74 18 84 00 Fax (44-20) 74 18 86 13
E-mail: mail@ema.europa.eu http://www.ema.europa.eu

1. Introduction

The active substance of Cymbalta is duloxetine hydrochloride. Duloxetine is a combined serotonin and noradrenaline reuptake inhibitor. Cymbalta has been approved in the European Union since 14 December 2004.

Cymbalta is currently approved for the treatment of major depressive episodes, treatment of diabetic peripheral neuropathic pain in adults and treatment of generalised anxiety disorder (GAD). Duloxetine is also approved under the trade name Yentreve/Ariclaim for the diabetic peripheral neuropathic pain in adults and the treatment of stress urinary incontinence (SUI).

Major depressive disorder (MDD) has been identified as the fourth most disabling illness in the world. Of those individuals with an episode of MDD it has been indicated that 41% will have a second episode within a year, 59% within 2 years and 74% within 5 years.

Many available options exist for the treatment of mood disorders. The treatment of depression is commonly divided into three distinct phases. Specific objectives of each treatment phase provide a strategic map for managing these patients. The acute phase begins with the initial presentation of an episode and is designed to elicit at least a response as determined by a clinically significant reduction in symptoms. This is followed by a continuation phase designed to prevent a relapse of the most recent episode. Continuation therapy of at least 6 months is now recommended. Complete symptom remission can occur in either the acute or continuation phase, and full recovery is defined as a sustained period of remission lasting several months. The final phase is maintenance treatment, which has as its goal the prevention of a new acute episode (a recurrence) of major depressive disorder. Maintenance treatment has specifically been recommended for any patient who has had three or more major depressive episodes in the past 5 years.

This Type II variation was initially seeking approval for extending the indication of duloxetine to include prevention of recurrence of major depressive episodes, among patients with MDD who had responded to duloxetine. The MAH proposed to amend sections 4.1, 4.2 and 5.1 of the SPC.

2. Non-clinical aspects

No new non-clinical data was submitted as part of this variation and all documentation concerning the new claimed therapeutic indication 'Prevention of Recurrence of Major Depressive Episodes' is supported by clinical data.

An updated Environmental Risk Assessment (ERA) conducted in accordance with Article 8 of Directive 2001/83/EC as amended, was provided in this application.

The updated ERA included a Phase I and II risk assessment. The $PEC_{surfacewater}$ was refined using sales forecasts and metabolism as allowed by the Guideline on the ERA of Medicinal Products for Human Use (EMEA/CHMP/SWP/4447/00). Physical-chemical properties and fate characteristics indicated that duloxetine will not persist or accumulate in the aqueous, sediment or soil environmental compartments. This ERA considers all the uses of duloxetine including proposed indication and assumes that the discharge of duloxetine following therapeutic use to the sewage system is the main route of entry into the environment.

However, the calculations for $PEC_{wastewater}$ and the refined $PEC_{surfacewater}$ could not be followed in the documentation, and the MAH was asked to describe the parameters more in detail. The PEC calculations were clarified by the MAH. In the recalculation of $PEC_{surfacewater}$ after refinement of F_{pen} the maximum daily dose should be used instead of average daily dose as used in the refinement of F_{pen}. However, the PEC/PNEC ratios will still be below 1 and 0.1.

The overall conclusion on the ERA of duloxetine was not changed. The CHMP agreed with this conclusion.

3. Clinical aspects

3.1. Clinical efficacy

The extension of indication applied for is based on the findings from Study F1J-MC-HMDI (HMDI), which is the first study specifically designed to investigate the efficacy of duloxetine in the prevention of recurrence of depression (as defined by the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revised (DSM-IV-TR)).

HMDI is a long term, randomised, double-blind, placebo-controlled, Phase 3 study aimed to assess whether the prophylactic treatment with duloxetine in the maintenance phase can reduce the risk of depressive recurrences. Study HMDI was a multicentre study carried out in Germany, France, Italy, Russia, Sweden and the US.

No new information regarding pharmacokinetic or pharmacodynamic aspects was provided by the MAH.

Objectives
The primary objective of this study was to assess the efficacy of duloxetine 60 mg to 120 mg once daily (QD) compared with placebo in the prevention of depressive recurrences, as measured by time to recurrence, among patients with recurrent MDD who had responded to duloxetine during a 4- to 10-week acute treatment period and a 24-week continuation treatment period.

The secondary objectives of this study were:

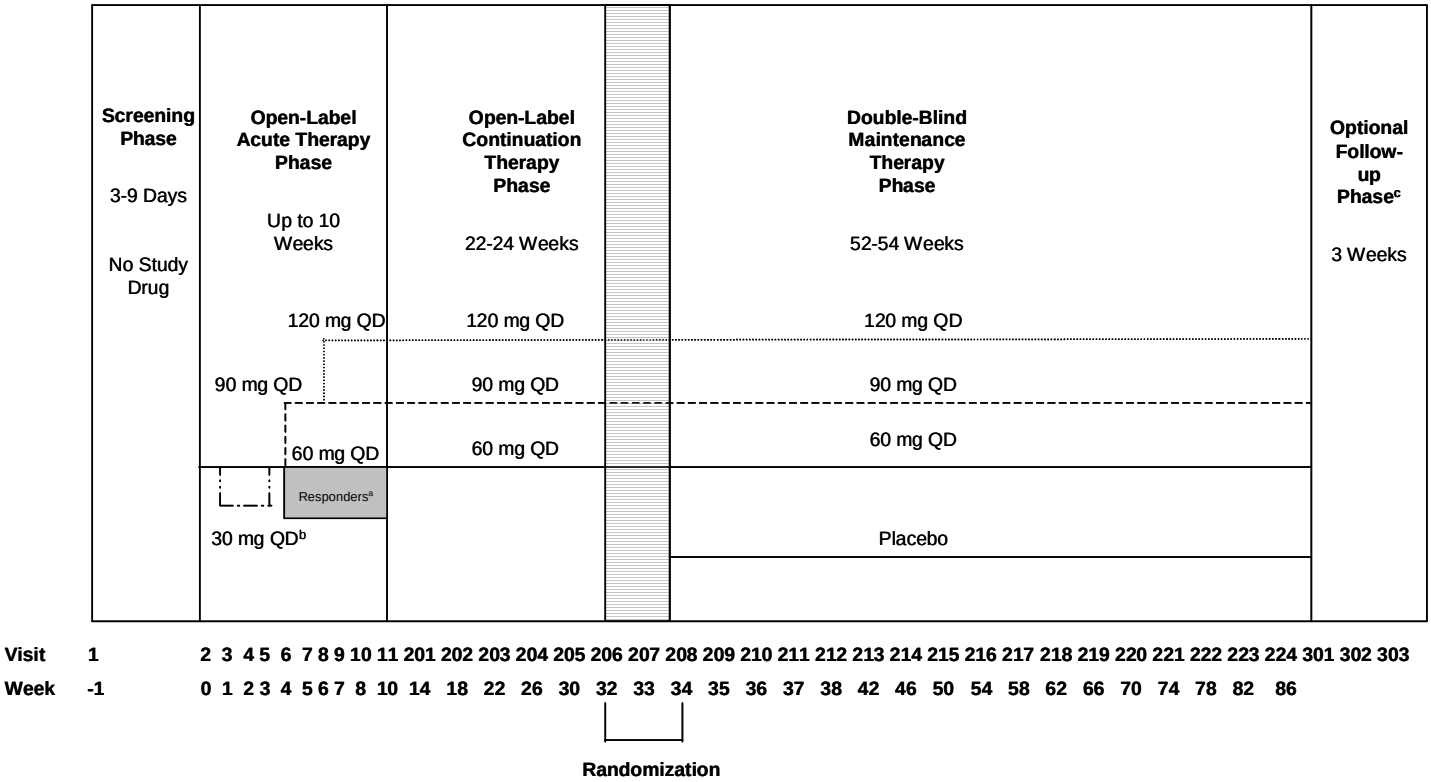
1. To evaluate the efficacy of maintenance treatment with duloxetine compared with placebo as measured by several other efficacy outcomes

2. To assess the efficacy of maintenance treatment with duloxetine compared with placebo on quality of life and health outcome measures

3. To evaluate the safety and tolerability of maintenance treatment with duloxetine compared with placebo.

Design and methods
Patients with an ongoing depressive episode who responded to duloxetine treatment during an initial 4- to 10-week open-label acute treatment period, and who continued to respond during a further 24-week open-label continuation treatment period were randomised to duloxetine or placebo for a 52-week double-blind maintenance phase (Figure 1).

Figure 1. Study design



Abbreviation: QD=once daily

a Patients who meet response criteria during Week 4 to Week 10 moved directly to the open-label continuation therapy phase.

b Patients who could not tolerate 60 mg QD may have decreased their doses to 30 mg QD during Week 1 to Week 3.

After an initial assessment period during which patients were screened for eligibility (screening phase) the study consisted of the following phases:

• Acute Phase — A 4- to-10-week acute treatment period during which all patients received open-label duloxetine, initially at a dose of 60 mg QD. In the event of non-response, the duloxetine 60 mg QD dose was to be increased to 90 mg QD at Visit 6 (Week 4), and a further dose increase to 120 mg QD would occur at Visit 8 (Week 6) in the event of continuing non-response. Patients meeting response criteria were eligible to enter the continuation phase of the study; those patients who failed to meet response criteria after 10 weeks of open-label treatment despite dose increases would be discontinued and were eligible to enter the optional follow-up phase.

Response Criteria (all must have been met):

- Had a 17-item Hamilton Depression Rating Scale ($HAMD_{17}$) total score of ≤9,
- Had a Clinical Global Impression-Severity (CGI-Severity) score of ≤2,
- Did not meet the DSM-IV criteria (Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition) for a major depressive episode (as assessed by the Mini International Neuropsychiatric Interview [MINI] depression module).

• Continuation Phase — A 24-week, open-label, treatment phase. Patients identified as having met response criteria to duloxetine during the acute therapy phase continued on the same dose of duloxetine during the continuation phase up until the randomisation visit. Patients and investigators were blinded to the exact visit at which randomisation occurred. At the randomisation visit, patients who continued to meet response criteria advanced to the maintenance phase. Those patients who failed to meet response criteria at the randomisation visit were to be discontinued from the study.

• Maintenance Phase — A 52-week, double-blind, placebo-controlled therapy phase. Patients were randomly assigned to receive either duloxetine at the same dose to which they had previously responded or placebo for 52 weeks or until they experienced a depressive recurrence. Due to the blinded nature of the randomisation visit, investigators and patients were informed that the maintenance phase was to be of 52 to 54 weeks' duration.

Recurrence Criteria: A patient was considered to have a depressive recurrence if they met any of the following three criteria:

- Had a CGI-Severity score of >4, and met DSM-IV criteria for MDD (as assessed by the MINI depression module) for at least 2 weeks, or
- Had three consecutive visits that met re-emergence criteria (see below) or 10 total re-emergence visits, or
- Discontinued due to lack of efficacy.

Patients identified as having a recurrence during the double-blind maintenance therapy phase had two options:

- Discontinue from the maintenance phase and participate in the optional follow-up phase, or
- Discontinue from the maintenance phase and the study overall and be managed at the discretion of the treating physician.

Re-emergence Criteria: Significant "re-emergence" of depressive symptoms was defined as having a CGI-Severity score of >4, but not necessarily meeting the DSM-IV criteria for MDD as assessed by the MINI depression module.

If re-emergence criteria were met, patients had weekly re-emergence visits until re-emergence criteria were no longer met. If a patient had three consecutive weekly re-emergence visits or a total of 10 re-emergence visits throughout the maintenance phase, the patient was considered to have had a depressive recurrence, was discontinued from the study and was eligible to enter the follow-up phase.

• Follow-Up Phase (Optional) — A 3-week follow-up phase to assess discontinuation-emergent adverse events (DEAEs) and other safety measures, during which the patients' dose of duloxetine was down-titrated in a double-blind fashion.

In this trial more stringent response criteria (a cut-off score on a validated scale) were required for patients to be eligible for maintenance treatment with respect to that suggested by the reference guideline ("NfG on Clinical Investigation of Medicinal Products in the Treatment of Depression" CPMP/EWP/518/97, Rev.1); i.e a 50% improvement on the usual rating scales. The proposed definition prevents from including patients (specially the severe ones) that by satisfying these criteria still show an excessively high $HAMD_{17}$ score to be considered a true responder.

This has probably led to an enrichment of the population with a selection of true responder patients (improving internal validity of the trial), but may limit the ability to extrapolate the results. This, together with the restrictive nature of the inclusion/exclusion criteria may limit the generalisation of the results.

According to the above-mentioned CHMP Guideline, 'recurrence' should have been defined in the protocol based on a validated scoring. In the present study 'recurrence' and 're-emergence' criteria are based on the investigator-based assessment (CGI-Severity) instead of a patient-based score ($HAMD_{17}$), which would have been much more preferable.

Although the patients were randomised after 28-34 weeks of treatment, a considerable number of patients might still be in their index episode due to the large variability of the natural course of major depression.

- **Study Participants**

Patients were outpatients of at least 18 years of age who met DSM-IV diagnostic criteria for recurrent MDD and who had experienced at least three episodes of depression, including the current episode, within the past 5 years. Patients had to have been in remission between episodes of depression, stable and off antidepressant medication for at least 2 months prior to the onset of the current episode. Patients had to have a $HAMD_{17}$ total score ≥18 at Visits 1 and 2, and a CGI-Severity ≥4 at Visits 1 and 2.

Patients were excluded from the study if they had

- any current Axis I disorder other than MDD, any previous psychotic disorder, any anxiety disorder within the past year, any Axis II disorder which, in the judgement of the investigator, would have interfered with compliance with the study protocol or had history of substance abuse or dependence within the past year
- demonstrated lack of response of the current episode of MDD to two or more antidepressant drugs, met criteria for treatment-resistant depression or were at serious suicidal risk
- electroconvulsive therapy (ECT) or transcranial magnetic stimulation (TMS) within the past year or had initiated or stopped psychotherapy within 6 weeks prior to enrolment
- serious medical illness or clinically significant laboratory abnormalities.

The initial criteria of selection intended to identify patients with a moderate to severe episode of depression ($HAMD_{17}$ total score ≥18 and CGI-Severity ≥4) and in which the rate of major depressive recurrences makes recommendable the maintenance treatment. The MINI, a standard diagnostic interview based on DSM-IV criteria, was used to establish the diagnosis and exclude other psychiatric illnesses.

No upper limit of age is established among the inclusion criteria. It would be expected that a group of elderly patients were finally included in the trial.

- **Treatments**

During the acute phase, patients were initially assigned to open-label duloxetine 60 mg orally QD. The dose was increased in the event of non-response during the acute phase. During the continuation phase, patients continued to take the dose to which they had responded in the acute phase. During the maintenance therapy phase, patients were randomly assigned in a 1:1 ratio within each site to either duloxetine (at the dose to which they previously responded) or placebo.

There was no dose escalation or de-escalation in the open-label continuation therapy phase or in the double-blind maintenance therapy phase.

Patients unable to tolerate the assigned dosage during the maintenance phase were discontinued from the study. Patients must have remained on this fixed dose of study drug throughout the maintenance phase without any allowed dose change during this period.

Patients should not have altered their courses of non-pharmacological therapies (holistic medicine, psychotherapy, physical therapy, peer support groups, light or photo therapy). Patients should also not have started any non-pharmacological therapies during the study's duration. Patients were allowed the episodic use of benzodiazepines or certain hypnotics during the study.

During the long-term period the patients received the recommended dose for the treatment of the acute episode. This is in line with the current recommendations.

The CHMP stated that comparison versus placebo can be considered standard. The indication of prevention of recurrence is only authorised for a limited number of antidepressants. It is likely however that in clinical practice, the treatment that showed to be effective in the acute and continuation phases will, in general be used in the maintenance phase. Therefore, the CHMP

concluded that virtually all available antidepressant could be a therapeutic alternative and noted that a third active control arm, though not necessary from a regulatory point of view, could have provided valuable information and improved the external validity of the results.

- **Outcomes/endpoints**

The primary efficacy variable was time to recurrence, which was defined as the number of days from randomisation to the visit at which the patient met the recurrence criteria during the maintenance phase.

The secondary efficacy variables according the secondary objectives of this study were:

a) To evaluate the efficacy of maintenance treatment with duloxetine compared with placebo as measured by:
    1. Recurrence rates
    2. Time to ≥50% worsening in the $HAMD_{17}$ and CGI-Severity ≥3
    3. Loss of response ($HAMD_{17}$ >9 and CGI-Severity >2) at any time
    4. $HAMD_{17}$ total score
    5. CGI-Severity scale
    6. Patient's Global Impressions of Improvement (PGI-Improvement) scale
    7. Hamilton Depression Rating Scale (HAMD) subscales
    8. Visual Analog Scale (VAS) for pain
    9. Symptom Questionnaire-Somatic Subscale (SQ-SS).

b) To assess the efficacy of maintenance treatment with duloxetine compared with placebo on quality of life and health outcome measures, as measured by the:
    - Sheehan Disability Scale (SDS)
    - 36-item Short-Form Health Survey (SF-36)
    - Resource Utilization and Hospitalization Module.

c) To evaluate the safety and tolerability of maintenance treatment with duloxetine compared with placebo as measured by:
    - Treatment-emergent adverse events (TEAEs)
    - Vital signs
    - Laboratory measurements
    - Arizona Sexual Experience Scale (ASEX).

- **Sample size**

In a fluoxetine recurrence-prevention study with a similar design (Gilaberte et al. 2001) the recurrence rates over 52 weeks for placebo- and fluoxetine-treated patients were 40% and 20%, respectively. It was also assumed that the time to recurrence and dropout both followed exponential distributions and that 25% of the patients in each treatment group would drop out by 52 weeks (1 year). Under these assumptions, a total of 257 randomised patients (randomly assigned with equal probability to the two treatment groups) were needed to have 90% power to detect 40% versus 20% recurrence rates over 52 weeks, using a log rank test at a two-sided significance level of .05. An accrual time of 0.001 weeks and 50% of time until 50% accrual were used.

It was anticipated that 70% of the patients enrolled in the acute phase of the study would respond and enter the continuation phase; 75% of the patients who entered the continuation phase would meet the randomisation criteria and would be randomly assigned. Therefore, if 490 patients were enrolled in the acute phase, then 257 would have been randomly assigned.

- **Randomisation and blinding**

All patients were assigned to take duloxetine during the acute therapy phase and during the open-label continuation therapy phase.

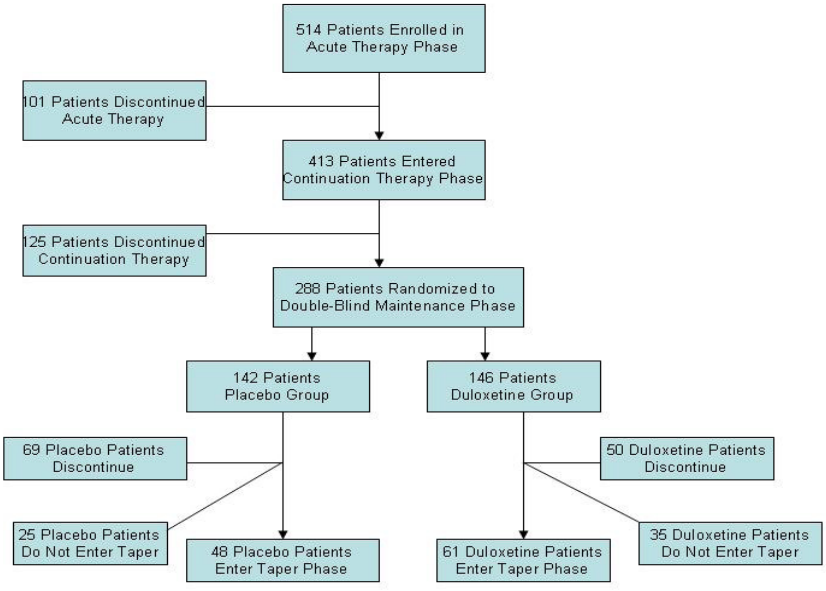
In the protocol, the length of the continuation phase was given as 22 to 24 weeks in order to keep investigators and patients blinded as to the exact timing of the randomisation visit. However, the randomisation visit occurred 24 weeks after treatment commenced in the continuation phase, and this information was supplied to Investigational Review Boards (IRBs) and regulatory authorities at the time of review. Assignment to treatment groups was determined by a computer-generated random sequence using an interactive voice response system (IVRS). All study drugs used were identical in colour, shape, smell, and taste.

Results

- **Participant flow**

A total of 514 patients with a moderate to severe episode of depression and history of major depressive recurrences (at least three episodes within the past 5 years) were enrolled into the open-label acute phase of the study. Responder patients (n=413; 80.5% of enrolled participants) followed treatment on the same dose of duloxetine for additional open-label 24 weeks (continuation phase) and those subjects who were still in response at the end of the period (n=288; 56% of initially recruited patients) were finally randomised to duloxetine (n= 146) or placebo (n= 142) for a long-term treatment (52-week maintenance phase). A total of 169 patients completed the maintenance phase of the study (73 [51.4%] patients in the placebo group and 96 [65.8%] patients in the duloxetine group). A total of 119 patients discontinued the double-blind maintenance phase of the study (69 [48.6%] placebo and 50 [34.2%] duloxetine). A total of 109 patients entered the optional taper phase (61 in the duloxetine group and 48 in the placebo group).

Figure 2. Patient disposition



Regarding the discontinuation of patients across the study, the most common cause was the patient decision (n=95, 18.48% of the recruited patients) followed by adverse events (AEs) (n=65; 13.22% of the enrolled population), mainly during the first phases of the trial, and recurrence (n= 59; 11.47%).

These figures (number of drop-outs and reasons for discontinuation) are roughly similar to those reported during the originally submitted trials conducted with duloxetine for the authorization of short-term treatment of depression.

The MAH made efforts to minimise the effect of randomisation as a trigger element of an excessive number of drop outs. Patients were not aware of the precise moment of randomisation, and the real assignment took place up to 2 weeks after the expected date. Whereas this procedure can reduce the patient and physician concerns of having been moved to placebo it does not prevent the risk of relapsing (e.g. potential "slow responder" patients) if the short-term treatment would have been insufficiently long to achieve a complete response. In fact 29% of the discontinuation occurred in the placebo group in the maintenance phase and took place 8-16 weeks after randomisation, mainly due to recurrences. This cast doubts about the, at least partially, relapsing (instead of recurrence) prevention nature of the trial.

In an effort to address the debate around the clear delineation of an episode as a new recurrence rather than a relapse of the initial episode, Eli Lilly Nederland B.V. conducted a number of post-hoc analyses with patients most clearly "between episodes" and out of the index episode (i.e. those in sustained remission throughout the continuation phase) to clarify the nature of the recurrence episodes. The latter subset of patients showed clear evidence of efficacy. As it could be foreseen, the difference between placebo and active treatment increased over time in this subgroup. Therefore, a long-term benefit could be reasonably expected in those patients who achieved remission during the depressive episode, and it should be reflected in the product information accordingly.

As noted by the CHMP, and as expected, most benefit was derived by those patients with a maintenance phase baseline $HAMD_{17}$ score <7. Based on these findings, the MAH agreed with the CHMP recommendation that it is important to clarify for prescribers that patients who respond to treatment initially are more likely to continue to respond in the long-term.

The CHMP considered the issue resolved provided that this information is reflected in the SPC.

- **Baseline data**

Most patients were female (69.8%) and most patients were Caucasian (98.1%). The average age of patients was 47.6 years and the ages ranged from 18 to 79. Approximately 2/3 of patients were enrolled in EU countries. The mean $HAMD_{17}$ score was 23.07 and the mean CGI-Severity score was 4.49 at baseline. The average age at the first episode of depression was 33 years of age. The average duration of the current depressive episode was approximately 4 months and the average number of previous depressive episodes was 4.22.

The CHMP stated that the population initially enrolled in the study may be considered as representative for the target moderately depressive population. The patients randomised in the maintenance phase of the study presented similar characteristics. The average duration of the last episode was about 25 and 30 weeks in the placebo and duloxetine group, respectively.

The minimum and/or maximum values for some of the characteristics of past and current episodes indicate that a number of odd patients have been included (e.g. duration of current episode 72 months, number of previous episodes 71, time interval between episodes 0 months). The MAH was asked to clarify the issue. Following the responses from the MAH, the CHMP agreed that the odd values seem to be the result of some clerical errors and they did not have any impact on the results or the conclusions.

A total of 430 (83.7%) out of the 514 recruited patients had previously received one or more drug treatment for depression, whereas 16.3% (n=84) had never been treated. Apparently there were no patients previously treated with duloxetine. Patients that finally entered the maintenance phase showed similar figures (previously treated: placebo arm 86.6%; duloxetine arm 83.6%; naïve patients: placebo arm 13.4%, duloxetine arm 16.4%). A total of 354 patients (68.9%) were recruited in the EU, and 160 were enrolled in Russia and the US.

- **Numbers analysed**

Efficacy analyses were performed in each phase of the study: acute therapy (4 to 10 weeks), continuation therapy (24 weeks), and double-blind maintenance therapy (52 weeks). All 288 randomised patients (146 duloxetine, 142 placebo) in the double-blind maintenance therapy phase were included in the primary efficacy analysis.

A surprisingly lower rate of compliance (defined as the patient had taken between 80 and 120% of capsules prescribed) was observed by the CHMP in the duloxetine arm (72%) during the double-blind period with respect to placebo (84.5%) and to previous phases (>83%). Two-fold duloxetine patients (n=41) compared to placebo (n=21) appeared to have been non-compliant. Only 9 out of these 62 non-compliant patients finally figured as discontinued due to a protocol violation without any alternative explanation of the remaining 53 subjects. As the number and imbalance of the figures could have a potential impact on the results, the MAH was requested to provide further clarification.

Further to this request, the MAH detailed the extent of non-compliance among the 62 non-compliant patients. Most of the non-compliance reported was due to a single visit deviation. This was foreseen in the protocol and it did not drive the patients to discontinue. The analyses performed by the MAH on the remaining cases did not reveal a relevant impact on the results. Taking this information into account, the CHMP considered the issue resolved.

- **Outcomes and estimation**

Primary endpoint

Time to a depressive recurrence was significantly longer in patients treated with duloxetine compared with patients treated with placebo (p<.001).

Duloxetine started to separate from placebo after day 28, which corresponds to the time at which duloxetine tapering to placebo was complete. The separation of duloxetine from placebo increased over time until day 280. The persistent separation of duloxetine from placebo supports the long-term effect of duloxetine in preventing recurrence of depression on continued treatment.

The efficacy results for the analysis of time to recurrence are significant (p<.001) for the log-rank test, as well as the log-rank test controlling for country and the log-rank test controlling for investigator.

Furthermore, the investigator by treatment interaction term is not significant, indicating that, relative to placebo, duloxetine prolongs time to recurrence even after adjustment for potential country or investigator effects.

Secondary endpoints

- *Recurrence Rate:* There was a significant difference between treatment groups in the recurrence rate at anytime during the maintenance therapy phase of the study (p<.001). Over the course of the 52-week study 68 new depressive episodes were recorded, 33.1% in the placebo group and 14.4% in patients receiving duloxetine.

With respect to the criteria of recurrence 51 (75%) episodes (35 in the placebo patients and 16 in the duloxetine group) fulfilled CGI/DSM-IV criteria (patients satisfied DSM-IV criteria for MDD as assessed by the MINI and CGI-Severity Score ≥ 4). In a total of 17 (25%) episodes (12 in the placebo group and 5 in the duloxetine group) the qualifier was the discontinuation of the patients due to lack of efficacy. None of the recurrences satisfied the re-emergence criteria (3 consecutive visits or a total of 10 visits where CGI-Severity score ≥ 4 and does not satisfy DSM-IV criteria as assessed by the MINI).

Time-to-event analysis showed that at each time point, the recurrence rate was always higher in the placebo group than in the duloxetine group, though differences appear to keep constant beyond 3 months. However, patients discontinuing prior to a potential recurrence seemed to have been censored at the time of discontinuation.

When an alternative analysis counting all discontinuing patients as failures was presented on request, a statistically significant difference was still shown. Nevertheless, the difference between duloxetine and placebo became less pronounced.

The CHMP stated that, in line with CHMP Guideline requirements, a pre established cut-off value of a validated scale would have been preferable as key (more objective and patient-based) method of assignment of recurrence.

- *Loss of Response*: There was a significant difference between treatment groups in the proportion of patients meeting criteria for loss of response at any time during the maintenance therapy phase of the study (46.5% for patients randomised to placebo versus 30.1% for patients randomised to duloxetine; p=.003).

- *$HAMD_{17}$ Total Score, CGI-Severity Score, VAS for Pain, and SQ-SS - Mean Changes from Baseline to Endpoint:* There was a significant difference between treatment groups in change in $HAMD_{17}$ total score and in CGI-Severity score during the maintenance therapy phase of the study (p<.001).

There was no significant difference between treatment groups in mean change from baseline to endpoint on the VAS for overall pain. There were no significant differences between treatment groups for mean changes from baseline to endpoint for SQ-SS.

- *PGI-Improvement*: There was a significant difference between treatment groups in PGI-Improvement means at endpoint during the maintenance therapy phase of the study (p<.001).

Results of the repeated measures analyses at the final visit were consistent with the last-observation-carried-forward (LOCF) analyses.

In general, secondary outcome measures support the results of the primary analysis.

Health Outcomes/Quality-of-Life Evaluation

- *Sheehan Disability Scale (SDS)*: There was a significant difference between treatment groups in the mean change from baseline to endpoint during the maintenance therapy phase of the study in the SDS global score (p=.029), SDS – work/school item (p=.022), and SDS – family life/home responsibilities item (p=.021).

- *36-item Short-Form Health Survey (SF-36)*: There was a statistically significant difference between treatment groups in the SF-36 mean changes from baseline to endpoint during the maintenance therapy phase of the study for the mental component summary (p=.002), for role limitations due to physical problems (p=.029), for role limitations due to emotional problems (p=.003), and for mental health (p=.001).

- **Dose**

Patients who continued on the duloxetine dose of 60, 90 or 120 mg QD to which they had responded during the open-label acute and the continued phase of Study HMDI appeared to have comparable recurrence rates during the double-blind maintenance phase irrespective of dose (recurrence rate at dose of 60 mg QD was 12.5% (8 of 64 patients); recurrence rate at dose of 90 mg QD was 15.6% (7 of 45 patients); recurrence rate at dose of 120 mg QD was 16.2 % (6 of 37 patients)).

Patients in the open-label 24-week continuation phase also appeared to have comparable response rates irrespective of dose (response rates at dose of 60 mg QD was 70.9% (124 of 175 patients); response rate at dose of 90 mg QD was 68.0% (87 of 128 patients); response rate at dose of 120 mg QD was 70.0 % (77 of 110 patients)).

Based on this analysis the MAH considered that there are no significant differences among the doses to support the selection of a specific one. The CHMP agreed with this approach.

In addition, the MAH proposed to update section 4.2 of the SPC to reflect that higher doses can be taken once daily, in line with the recently approved posology for the generalized anxiety disorder (GAD) indication. Indeed, in Study HMDI, similarly to many of the more recent duloxetine studies, doses were administered as 60, 90 or 120 mg once daily, with all doses showing similar safety profiles compared to earlier studies in which the highest doses were administered as 60mg twice daily. This proposal was endorsed by the CHMP.

- **Analysis of Time to Depressive Recurrence by Subgroup**

In the subgroups of age, gender, origin (race), number of previous episodes of depression, number of previous drugs used to treat depression, and baseline $HAMD_{17}$, no statistically significant treatment-by-subgroup interactions were observed.
The within-strata comparisons of time to depressive recurrence across treatment groups using log-rank test showed statistical superiority of duloxetine over placebo for the larger stratum in all subgroups.

Derived from this subgroup analysis the MAH stated that there is no evidence of inconsistency in the main measure of efficacy (time to recurrence) according to age, sex, race determinants or some relevant features of the condition. Admittedly, no clear sign of lack of efficacy can be concluded from it but it seems to be rather due to the low size (and imbalance) of some categories.

The MAH was requested to discuss the lack of efficacy when deterioration was defined as HAMD ≥ 18 (i.e. deterioration defined based on objective and depression specific criteria). Although efficacy was demonstrated for patients with HAMD ≥ 15, there are doubts about the rationale for the *post-hoc* choice of cut-off point. The concern was that various cut-off points were examined and only the significant one (i.e. HAMD≥15) was presented.

Further to this request, the MAH explained that the use of two *post-hoc* cut-off values for the $HAMD_{17}$ was based on external guidance ($HAMD_{17}$ ≥18 from the CHMP and $HAMD_{17}$ ≥15 from an independent clinical expert). However, both analyses were presented in full and using both cut-off values the duloxetine-treated patients had a significantly longer time to depressive recurrence compared with placebo, the primary outcome of the study. Recurrence rate was lower for duloxetine versus placebo using both HAMD cut-off values and in the case of $HAMD_{17}$ ≥15 this was statistically significant.

The clarifications provided by the MAH with respect to the selection of cut-off values used for definition of deterioration were considered satisfactory by the CHMP.

Overall conclusions on clinical efficacy

Study HMDI forms the basis to support the efficacy of duloxetine in the prevention of depressive recurrences. The main reasons for discontinuation of patients along the study were the patient decision (18.5% of the recruited patients) followed by AEs (13%) and recurrence (11.5%).

Recurrence criteria were mainly driven by physician-based criteria (CGI-Severity score ≥ 4 with or without satisfying DSM-IV criteria for MDD). Most of the recurrences causing discontinuation satisfied both criteria. It should be remarked that a validated scale (more objective and patient-based) method of assignment of recurrence would have been preferable. Lack of efficacy was also considered as additional criterion, and it was fulfilled by 25% of patients who experienced a recurrence episode.

The MAH has made efforts to minimise the effect of randomisation as a trigger element of an excessive number of drop outs. Patients were not aware of the precise moment of randomisation, and the real assignment took place up to 2 weeks after the expected date. Whereas this procedure could reduce the patient and physician concerns of having been moved to placebo it does not prevent the risk of relapsing if the short-term treatment would have been insufficiently long to achieve a complete response. As explained earlier, 29% of the discontinuation occurred in the placebo group in the maintenance phase and took place 8-16 weeks after randomisation, mainly due to recurrences, and this casts doubts about the, at least partially, relapsing (instead of recurrence) prevention nature of the trial.

Complementary secondary measurements (such as reduction in $HAMD_{17}$ total score, CGI-Severity score or PGI-Improvement) support the results of the primary analysis.

It is noticeable that the relevant differences in terms of recurrences were established between days 50 to 100 post-randomisation. After that point little benefit seems to be added, both arms behaving similarly. Whether these findings support the concerns about the true recurrence nature of the trial or raise additional doubts on the real long-term effect of duloxetine deserve further discussion. A third arm (active control) could have provided a valuable reference on this issue.

The short duration of the trial (1-year maintenance treatment, when longer duration would have been preferable as being closer to clinical practice and regulatory recommendations) does not allow elucidating if some additional gain can be further expected.

There were additional issues of relevance in the analysis and interpretation of the results. First, the fact that twice as many duloxetine patients compared to placebo appeared to have been non compliant. The MAH created a protocol to deal with these circumstances but some discrepancies were observed between non compliant patients and the rate of discontinuation derived from this reason during the maintenance period.

As requested by the CHMP, the MAH conducted several *post-hoc* analyses to identify the true nature of the recurrence episodes. In general these new results showed a similar trend to that originally described in the primary analysis; however some of these results cast doubts about the robustness of the primary analysis:

- the potential confounding factor of discontinuation symptoms after randomisation on early recurrence has been reasonably excluded
- a reduced magnitude of the difference between placebo and duloxetine is revealed when recurrence episodes were analysed according to the baseline severity of the index episode
- likely duloxetine showed to be less efficacious in the prevention of recurrences in the subgroup of patients in which response to duloxetine was not optimal. The potential dilution of the effect in more moderate responders to the acute episode also raises additional concerns.

The subset analyses of patient fulfilling different remission criteria did not solve the question whether recurrence or relapse prevention had been demonstrated. Since the patients are on treatment, remission might be due to treatment rather than a “true” remission. The crucial issue remained: the duration of an MDD episode is very variable with a mean of about 6 months and in the pivotal study the mean duration of the most recent previous episode was about 25 to 30 weeks. Thus, it is most likely that a substantial part of the patients were still in their index episode at the time of randomisation, and the study cannot discriminate between recurrence and relapse prevention. An appropriate design to demonstrate recurrence prevention would have been to study patients with a known propensity of recurrence and randomise when they have been in remission and off treatment for a certain time period.

The data originally provided by the MAH showed that the recurrence rate did not evenly distribute in time, with most occurring between 50 to 100 days. The long term benefit of the preventive effect beyond three months of treatment appeared doubtful. These survival curves behaviour were replicated in most of post-hoc analysed now submitted, contrary to other antidepressants, where the curves diverge over the course of the study. Only when patients on sustained response or functional remission at randomisation were considered this progressive separation could be observed. This subgroup represents less than 60% of the primary subset which could jeopardise the extrapolability of this *post-hoc* analysis.

3.2. Clinical safety

Patient exposure

All 514 patients enrolled in the acute therapy phase of the study were included in the safety analyses. The mean duration of exposure was 39.81 days for patients in the acute therapy phase and 154.44 days for patients in the continuation therapy phase. The mean duration of exposure was higher for patients randomised to duloxetine than patients randomised to placebo during the maintenance phase of the study.

The 260 patients treated ≥ 6 months (171 with duloxetine) and 125 patients treated ≥12 months (68 with duloxetine) provided a long-term safety database. Although it could be considered insufficient itself to support a chronic indication, the long-term safety characterisation of duloxetine was also sustained by the safety data from the already approved use in the treatment of major depressive episodes. This database comprises a total of 2418 patients studied over the course of both acute and open label long-term treatment (52 weeks), and further 533 patients exposed to 60mg QD duloxetine in the relapse prevention study HMBC (for 26 weeks). Similarly, the use in other indications could add valuable information to the general profile of the drug.

An indeterminate subgroup of elderly patients was included in the study submitted with this procedure (where only the number of patients older than 55 years is available). Apart from the issue of efficacy, the analysis in the elderly is also relevant from the safety perspective.

Adverse events (AE)

A total of 67.9% duloxetine patients reported at least one Treatment-emergent adverse event (TEAE) during the open-label acute therapy phase. The most frequently occurring TEAEs during the open-label acute therapy phase included nausea (29.2%), headache (15.4%), dry mouth (14.8%), and hyperhidrosis (14.8%).

A total of 59.1% duloxetine patients reported at least one TEAE during the *open-label continuation therapy* phase. The most frequently occurring TEAEs during the open-label continuation phase of the study included headache (9.4%), nasopharyngitis (6.3%) and hyperhidrosis (6.1%).

A total of 62.7% of placebo-treated patients and 61.0% of duloxetine –treated patients (p=.809) reported an AE during the double-blind maintenance phase of the study. The most frequently occurring TEAEs during the maintenance phase of the study (occurring in >5% of duloxetine patients) included back pain (8.9% duloxetine and 4.9% placebo), headache (8.9% duloxetine and 7.7% placebo), and fatigue (5.5% duloxetine and 2.8% placebo). No TEAEs were reported statistically significantly more frequently in one treatment group or the other during the maintenance phase.

During the taper phase of the study, a total of 8.3% placebo and 23.0% duloxetine patients (p=.067) reported at least one discontinuation-emergent AE (DEAE).

Table HMDI.12.3. Treatment-Emergent Adverse Events Occurring in at Least 5% of Patients in any Study Phase by Preferred Term
All Randomized Patients

	Acute Phase	Continuation Phase	Maintenance Phase		Taper/DC Phase	
	Duloxetine (N=514)	Duloxetine (N=413)	Placebo (N=142)	Duloxetine (N=146)	Placebo (N=48)	Duloxetine (N=61)
Adverse Events	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Patients with ≥ 1 AE	349 (67.9)	244 (59.1)	89 (62.7)	89 (61.0)	4 (8.3)	14 (23.0)
Nausea	150 (29.2)	5 (1.2)	7 (4.9)	6 (4.1)	0	1 (1.6)
Headache	79 (15.4)	39 (9.4)	11 (7.7)	13 (8.9)	0	0
Dry mouth	76 (14.8)	11 (2.7)	1 (0.7)	4 (2.7)	0	0
Hyperhidrosis	76 (14.8)	25 (6.1)	2 (1.4)	7 (4.8)	0	0
Fatigue	60 (11.7)	10 (2.4)	4 (2.8)	8 (5.5)	0	0
Constipation	48 (9.3)	13 (3.1)	1 (0.7)	0	0	0
Dizziness	41 (8.0)	10 (2.4)	9 (6.3)	5 (3.4)	1 (2.1)	1 (1.6)
Diarrhea	38 (7.4)	18 (4.4)	4 (2.8)	2 (1.4)	0	0
Vomiting	28 (5.4)	5 (1.2)	2 (1.4)	2 (1.4)	0	0
Insomnia	27 (5.3)	14 (3.4)	9 (6.3)	7 (4.8)	0	0
Decreased appetite	26 (5.1)	1 (0.2)	0	0	0	0
Nasopharyngitis	16 (3.1)	26 (6.3)	11 (7.7)	9 (6.2)	0	1 (1.6)
Back pain	10 (1.9)	19 (4.6)	7 (4.9)	13 (8.9)	0	1 (1.6)

Abbreviations: AE = adverse event, DC = discontinuation, N = number of enrolled patients in treatment phase, n = number of patients in this category.
Source: Tables HMDI.14.3.1.1 through HMDI.14.3.1.3

In general, the safety profile in the long term treatment can be considered similar to that described in the short-term administration. After several weeks of treatment a lower incidence is observed (tolerance phenomena) compared to the initially reported AE rate.

Discontinuation

A total of 86 out of 514 patients discontinued due to AE, remarkably in the early weeks of the study. During the 4- to 10-week acute therapy phase of the study, 34 (6.6%) patients in the duloxetine group 60-120 mg QD discontinued the study due to an AE. During the 24-week continuation therapy phase of the study, 25 (6.1%) patients in the duloxetine group 60-120 mg QD discontinued the study due to an AE. During the 52-week maintenance phase of the study, 3 (2.1%) of patients in the placebo group and 6 (4.1%) patients in the duloxetine group 60-120 mg QD discontinued the study due to an AE. There were no significant differences between patients in the placebo group vs duloxetine for patients who discontinued due to an AE (p=.501).

The most frequently reported AEs reported as reasons for discontinuation were nausea (1.6% during the acute therapy phase and 0.2% during the continuation therapy phase) and vomiting (1.0% during the acute therapy phase and 0.2% during the continuation therapy phase).

Serious adverse events and deaths

- **Deaths**

One patient died during the open-label acute therapy phase of the study. This was a 27-year-old male patient who committed suicide 28 days after receiving the first dose of study drug (duloxetine 60 mg QD). The patient had a history of depression/mental disorders since 1996, but no prior history of suicide acts, ideation or gestures. He was not on concomitant medication during the study period. Death was not considered related to study treatment by the investigator.

According to the information stated in the SPC of duloxetine, suicide or suicide-related events could be expectable among the safety events of the drug. In addition to the above described complete suicide two other patients reported suicide attempts along the first 36 weeks of the trial (1 during the acute phase, 1 during the continuation phase). The assessment of suicidal behaviour associated with duloxetine is comprised in the Risk Management Plan as an identified risk under monitoring.

- **Serious adverse events (SAEs)**

During the 4- to 10-week acute therapy phase of the study, 6 (1.2%) patients in the duloxetine group 60-120 mg QD experienced at least one SAE. During the 24-week continuation therapy phase of the study, 13 (3.1%) patients in the duloxetine group 60-120 mg QD experienced at least one SAE. During the 52-week maintenance phase of the study, 4 (2.8%) of patients in the placebo group and 7 (4.8%) patients in the duloxetine group 60-120 mg QD (p=.541) experienced at least one SAE. There was no trend or pattern in the SAEs.

Laboratory findings

- **Chemistry Analytes**

The most frequently occurring abnormal laboratory values during the acute therapy phase included high creatine phosphokinase (CPK, 31 [7.2%]), high ALT (26 patients [6.1%]), and high cholesterol (25 patients [5.7%]).

The most frequently occurring abnormal laboratory values during the continuation therapy phase included high CPK (33 patients [9.5%]) and low bilirubin, (27 patients [7.1%]).

The most frequently occurring abnormal laboratory values during the maintenance therapy phase included high ALT (14 [13%] placebo and 19 [16%] duloxetine) and high CPK (17 [16%] placebo and 16 [14%] duloxetine). There was a significant difference between treatment groups during the maintenance therapy phase of the study for abnormal laboratory values for high total bilirubin (3.88% placebo and 0% duloxetine; p=.025).

Two patients discontinued the study due to abnormal laboratory values. During the acute therapy phase of the study, one patient discontinued due to thrombocytopenia. During the maintenance phase of the study, one patient, who was randomised to duloxetine, discontinued the study due to hepatic enzymes increased.

This study provides new data on long-term comparison versus placebo, although the number of exposed patients was limited. In principle the laboratory abnormalities observed have already been described for other approved indications and no new safety signal is raised.

- **Vital signs, weight and electrocardiogram**

There were no significant differences between treatment groups during the maintenance therapy phase of the study for mean change from baseline to endpoint in vital signs (pulse, systolic blood pressure, diastolic blood pressure, or weight).

During the continuation phase of the study, one patient discontinued the study due to hypertension and one patient discontinued the study due to weight increased. During the maintenance phase of the study, one patient, who was randomised to duloxetine, discontinued the study due to blood pressure increased.

Electrocardiograms

There was a significant difference between placebo and duloxetine treatment in mean change from baseline to endpoint for heart rate during the maintenance therapy phase of the study (p<.001). The mean change from baseline to endpoint was a decrease of 5.24 bpm for patients randomised to placebo and an increase of 0.42 bpm for patients randomised to duloxetine.

There was a significant difference between placebo and duloxetine treatment for the mean change from baseline to endpoint for PR interval during the maintenance therapy phase of the study (p=.030). The mean change from baseline to endpoint was an increase of 3.55 msec for patients randomised to placebo and an increase of 0.12 msec for patients randomised to duloxetine.

There was no significant difference between treatment groups for the mean change from baseline to endpoint for QRS interval during the maintenance phase of the study.

There was a significant difference between placebo and duloxetine treatment for the mean change from baseline to endpoint for QT interval during the maintenance therapy phase of the study (p=.004). The mean change from baseline to endpoint was an increase of 11.57 msec for patients randomised to placebo and an increase of 2.57 msec for patients randomised to duloxetine.

Although there were significant differences between treatment groups in the mean change from baseline to endpoint for ECG variables, the mean changes were small and were not considered clinically relevant.

The persistent increase in systolic blood pressure was expected from the pharmacological actions and previous clinical experiences of duloxetine and do not warrant any changes to the current safety information in the SPC. However, the CHMP was of the view that the significant differences in ECG values between the duloxetine and placebo groups during the maintenance phase of the study HDMI should be presented by using Friedericia's correction formula before any conclusion could be made regarding the effect on QT. Furthermore, the CHMP requested that the table be completed by including the SD, P25, P50 and P75 for all parameters.

Using Fridericia's correction (QTcF), there was no statistically significant difference between placebo- and duloxetine-treated patients with respect to mean change in QT interval (p =.985).

Results from analysis of QT interval, including Fridericia's and Bazette's corrections, were included in the HMDI clinical study report initially submitted. The CHMP concluded that there were no safety concerns remaining and considered the issue to be solved.

Special population – elderly

Only 55 patients ≥ 65 years (26 on duloxetine 60 mg, 17 on duloxetine 90 mg and 12 patients on 120 mg) were enrolled in the study, 14 of which were treated with duloxetine during the 52-week maintenance phase. According to the data recorded, the safety profile in the elderly population (including SIADH or dizziness-related AEs) does not seem distinctly worse than in the adult group. The paucity of AEs reported due to the small size of this age subgroup does not allow reaching any sound conclusion in this respect.

Regarding safety in the elderly, the MAH was requested to discuss RMP strategies to monitor the safety of use such as specific review in PSURs. The CHMP stated that in particular the incidence of dizziness, falls and fractures should be monitored as the RMP estimates that the incident of postural hypotension in the elderly is between 20-50%.

Further to this request from the CHMP, Lilly proposed to include a review of safety in the elderly in the next PSUR 9 (submission due 1st October 2009). Previous PSURs contained a review of data in the elderly population, but the incidence of events was compared to the full dataset (i.e. both non-elderly and elderly groups) rather than just the non-elderly population. In PSUR 9, Lilly proposed to separate elderly and non-elderly groups to specifically compare case count and frequency of reactions for elderly compared to non-elderly. Incidence of dizziness, falls, fractures and postural hypotension will be examined by inclusion as specific terms. The CHMP agreed with this proposal. RMP v.5 was reviewed together with PSURs 7 and 8, submitted in parallel. An RMP which is due for an update around December 2009 will also be updated with the above-mentioned information.

Arizona Sexual Experience (ASEX) Scale

During the study effects upon sexual parameters were examined using the ASEX scale. During the maintenance therapy phase, there were no significant differences between duloxetine and placebo for any ASEX scale items in terms of means at baseline, endpoint, or in the change from baseline to endpoint.

4. Overall conclusions on clinical safety

The 260 patients treated ≥ 6 months (171 with duloxetine) and 125 patients treated ≥12 months (68 with duloxetine) provide a long-term safety database. Although it could be considered insufficient in itself to support a chronic indication, the long-term safety characterisation of duloxetine is also sustained by the safety data from the already approved use in the treatment of major depressive episodes. This database comprises a total of 2418 patients studied over the course of both acute and open label long-term treatment (52 weeks), and further 533 patients exposed to 60mg QD duloxetine in the relapse prevention study HMBC (for 26 weeks). Similarly, the use in other indications could add valuable information to the general profile of the drug.

The safety profile in the long term treatment can be considered similar to that described in the short-term administration. No new safety signal is raised. After several weeks of treatment a lower incidence of adverse events is observed (tolerance phenomena) compared to those initially reported.

Risk Management Plan (RMP)
The RMP 5 has been reviewed together with PSURs 7 and 8, which were submitted in parallel. In general, the safety profile in the long term treatment can be considered similar to that described in the short-term administration.

The MAH committed to performing the studies and additional pharmacovigilance activities detailed in the Pharmacovigilance Plan, as agreed in version 5 of the Risk Management Plan (RMP) and any subsequent updates of the RMP agreed by the CHMP.

As per the CHMP Guideline on Risk Management Systems for medicinal products for human use, the updated RMP should be submitted at the same time as the next Periodic Safety Update Report (PSUR).

In addition, an updated RMP should be submitted
- When new information is received that may impact on the current Safety Specification, Pharmacovigilance Plan or risk minimisation activities
- Within 60 days of an important (pharmacovigilance or risk minimisation) milestone being reached
- At the request of the EMEA

Proposed changes to the Product Information (new information in **bold underlined**, deleted information in ~~strikethrough~~)

SPC

4.1 Therapeutic indications

Treatment of major depressive ~~episodes~~ **disorder**.
Treatment of diabetic peripheral neuropathic pain in adults.
Treatment of generalised anxiety disorder.

4.2 Posology and method of administration

[…]

Therapeutic response is usually seen after 2-4 weeks of treatment.
After consolidation of the antidepressive response, it is recommended to continue treatment for several months, in order to avoid relapse**. In patients responding to duloxetine, and with a history of repeated episodes of major depression, further long-term treatment at a dose of 60 to 120 mg/day could be considered.**

[…]

5.1 Pharmacodynamic properties

[...]

In a relapse prevention study, patients responding to 12-weeks of acute treatment with open-label Cymbalta 60 mg once daily were randomised to either Cymbalta 60 mg once daily or placebo for a further 6-months. Cymbalta 60 mg once daily demonstrated a statistically significant superiority compared to placebo (p=0.004) on the primary outcome measure, the prevention of depressive relapse, as measured by time to relapse. The incidence of relapse during the 6-months double-blind follow-up period was 17% and 29% for duloxetine and placebo, respectively.

During 52 weeks of placebo-controlled double blind treatment, duloxetine-treated patients with recurrent MDD had a significantly longer symptom free period (p<.001) compared with patients randomized to placebo. All patients had previously responded to duloxetine during open-label duloxetine treatment (28 to 34 weeks) at a dose of 60 to 120 mg/day. During the 52-week placebo-controlled double blind treatment phase 14.4% of the duloxetine-treated patients and 33.1% of the placebo-treated patients experience a return of their depressive symptoms (p<.001).

[...]

Sections 4.2, 4.4 and 5.1 of the SPC were updated to reflect the new approved indication.

The CHMP agreed with the MAH that no updates to the Package Leaflet were needed.

5. Benefit risk assessment

In the treatment of major depressive episodes (MDE), the efficacy of duloxetine at doses of 60 mg/day to 120 mg/day has been demonstrated in a number of large-scale, double-blind, placebo-controlled clinical studies. Duloxetine has also been shown to be effective in the prevention of depressive relapse at a dose of 60 mg QD.

The currently approved indication therefore states “Treatment of major depressive episodes”. In order to specifically assess whether treatment with duloxetine following an initial response would reduce the risk of depressive recurrences, the present Study HMDI utilised a 52-week double-blind maintenance therapy period to compare the time to recurrence for duloxetine treated patients with that of placebo treated patients.

However, it can be questioned whether the study has an appropriate design for studying recurrence prevention. Patients were initially treated for an acute episode of major depression and randomised after 28-34 weeks of treatment. The natural course of major depression is known to be very variable and for the patients in study HMDI the average duration of the last episode prior to inclusion was about 25 and 30 weeks in the placebo and duloxetine group, respectively. Thus part of the patients might have been in their index episode at the time of randomisation, and it is not possible to say whether deterioration after randomisation is due to a relapse of the index episode or a recurrence.

Further clarifications provided by the MAH in order to identify the nature of the remissions and the qualification of recurrences suggest that patients properly responding to the acute treatment phase with duloxetine would obtain greater benefit from the long-term treatment than patients being switched to placebo. This population in which an effect of long-term treatment has been robustly demonstrated should be the one to be reflected in the product information accordingly.

The safety profile of duloxetine in the long term treatment of depressive patients can be considered similar to that described in the short-term administration. No new safety signals have been raised.

Treatment of major depressive episode refers to the acute treatment of a depression episode. In relation to the indication, long-term treatment of depressive disorder, as a wider concept, is accepted rather than the treatment of a specific episode. In order to reflect the outcome of the study, and taking into account the above-mentioned information, the CHMP agreed that the indication should be modified to read 'treatment of major depressive disorder'.