London, 4 July 2005
Product name: **Cymbalta**
Procedure number: EMEA/H/C/572/II/03

SCIENTIFIC DISCUSSION

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1. Introduction

Cymbalta (duloxetine) hard capsules are currently authorised in the European Union for the following indication:

"Treatment of major depressive episodes"

The variation relates to an update of section 4.1 of the Summary of Product Characteristics (SPC) to add the indication "Diabetic Peripheral Neuropathic Pain (DPNP) in adults. In addition, consequential changes were made to sections 4.2, 4.4, 4.8 and 5.1 of the SPC. The relevant sections of the Package Leaflet (PL) were updated accordingly.

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.

Diabetes is the leading cause of neuropathy in the Western world, and neuropathy is the most common complication and greatest source of morbidity and mortality in diabetes patients. The primary risk factor for diabetic neuropathy is hyperglycaemia. The duration of diabetes also increases the risk of neuropathy, but the association between duration and prevalence may depend in part upon patient age, which itself is a risk factor. Cigarette smoking, alcohol consumption, hypertension, height, and hypercholesterolemia are all considered independent risk factors for diabetic neuropathy. Neuropathic pain can be defined as pain initiated or caused by primary lesion or dysfunction in the nervous system. They result from the damage to the nervous system leading to peripheral or central neuropathic pain. Patients affected by DPNP may benefit from duloxetine therapy.

2. Quality aspects

Not applicable.

3. Pre-clinical aspects

The maximum recommended clinical dose for DPNP is identical to that for major depressive disorder. The sections 4.6, 5.2 and 5.3 of the SPC that include nonclinical data remain unchanged and as approved.

The effect of duloxetine in the treatment of DPNP is linked to its capacity to dose-dependently increase extracellular levels of serotonin and noradrenaline in various brain areas of animals. Duloxetine normalised pain thresholds in several preclinical models of neuropathic and inflammatory pain, and attenuated pain behaviour in a model of persistent pain. The pain inhibitory action of duloxetine is believed to be a result of potentiation of descending inhibitory pain pathways within the central nervous system.

The following paragraph was proposed to be included in section 5.1 of the SPC in order to describe the activity of duloxetine in preclinical models of pain:

> *"Duloxetine normalised pain thresholds in several preclinical models of neuropathic and inflammatory pain and attenuated pain behaviour in a model of persistent pain. The pain inhibitory action of duloxetine is believed to be a result of potentiation of descending inhibitory pain pathways within the central nervous system."*

The CHMP considered the wording acceptable.

4. Clinical aspects

4.1 Clinical pharmacology

Not applicable.

4.2 Clinical efficacy and safety

4.2.1 Introduction

The efficacy of duloxetine in patients with diabetic neuropathic pain (DPNP) was evaluated in two randomised, placebo-controlled acute studies (Study HMAW-Acute and Study HMAV-Acute). Further safety data were provided in Study F1J-MC-HMBT (28-week, open-label, safety study) with the primary objective of gathering safety data in the treatment of painful symptoms associated with diabetic neuropathy, as well as Study F1J-MC-HMAW – Extension (52-week extension phase of Study HMAW) giving further safety data on duloxetine in comparison with routine care.

4.2.2 Clinical efficacy

A total of 475 and 334 patients in Study HMAW-Acute and HMAV-Acute, respectively, were randomly assigned to receive different dosage regimens of duloxetine or placebo.

The objectives of both studies were similar; to compare the efficacy of duloxetine in different doses with placebo on the reduction of pain severity in the acute treatment of patients who met criteria for painful diabetic neuropathy but did not meet DSM-IV criteria for major depression. Male or female outpatients at least 18 years of age with pain due to bilateral peripheral neuropathy caused by Type 1 or Type 2 diabetes mellitus were included in these studies. The pain must have begun in the feet, with relatively symmetrical onset. Daily pain should have been present for at least 6 months. The diagnosis must have been confirmed by a score of at least 3 on the Michigan Neuropathy Screening Instrument.

Study HMAW Acute

Study HMAW-Acute was a double-blind, randomised, placebo-controlled, study comparing duloxetine 20 mg QD, 60 mg QD, and 60 mg BID with placebo over 12 weeks of acute treatment in patients aged ≥18 years with DPNP. The study consisted of two periods; a 1- to 2-week screening phase during which patients were screened for eligibility and a 12-week period of double blind acute treatment.

The protocol-specified primary efficacy evaluation in this study was a comparison between the duloxetine 60 mg BID and placebo treatment groups after 12 weeks of treatment, using repeated measures analysis of the change from baseline in the primary efficacy analysis, the 24-hour average pain scale. Results from the repeated measures analysis were consistent with those from the mean change analysis.

Results from the primary efficacy measure show that doses of duloxetine 60 mg QD and 60 mg BID were statistically significantly better than placebo in the reduction of the severity of pain, which was seen from the first week after starting treatment to the end of the acute phase. No differences were seen between 60 mg BID and 60 mg QD or between 20 mg QD and placebo. The responders rate using a more strict criteria (50% reduction in pain severity) were 52%, 49%, 41% and 26% for duloxetine 60 mg BID, 60 mg QD, 20 mg QD and placebo, respectively, which were statistically significantly superior for the three dosage regimen of duloxetine compared with placebo.

Overall, results from secondary measures [Response Rates, The Brief Pain Inventory (BPI) – Severity and Interference, The Clinical Global Impressions of Severity (CGI-Severity),The Patient's Global Impressions of Improvement (PGI Improvement), The Sensory Portion of the Short-Form McGill Pain Questionnaire (SF-MPQ), Dynamic allodynia, The Beck Depression Inventory-II (BDI-II), the Beck Anxiety Inventory (BAI), and the HAMD17; Health Outcome Measures: The 36-item Short-Form Health Survey (SF-36), the Euro-Qol Questionnaire – 5 Day (EQ-5D)] were consistent with those from the primary endpoints, except for dynamic allodynia, most items of BPI-interference scale and BAI, BDI scores. Quality of life measures showed a statistically significant improvement in the body pain and mental health domain, with only numerical differences in the remaining aspects such as the physical and social functioning.

Study HMAV Acute

Study HMAV-Acute was a double-blind, randomized, placebo-controlled study comparing duloxetine 60 mg QD and 60 mg BID with placebo over 12 weeks of acute treatment in patients aged ≥18 years with DPNP.

The primary efficacy evaluation in this study was a comparison between the duloxetine 60 mg BID and placebo treatment groups after 12 weeks of treatment, using mean change analysis of the change from baseline in the primary efficacy analysis, the 24-hour average pain scale.

Consistently with the results of Study HMAW-Acute, duloxetine 60 mg QD and duloxetine 60 mg BID were both statistically significantly better than placebo at reducing the 24-hour average pain score in the mean change analysis in Study HMAV-Acute. Again, an analysis of the score using repeated measures showed duloxetine 60 mg QD and duloxetine 60 mg BID were statistically significantly better than placebo at reducing the score from one week after starting therapy to the end of the acute therapy phase. The rate of responders using the strict definition were 53%, 43% and 27% for duloxetine 60 mg BID, 60 mg QD and placebo groups, respectively.

Conclusions on efficacy

In the two pivotal studies, the difference for duloxetine 60 mg QD and 60 mg BID compared with placebo in pain reduction varied between 1.17 – 1.45, on a 0-10 Lickert scale. This difference is statistically significant ($p<0.001$). The statistical significance demonstrated for the primary endpoint was based on an ITT analysis for change from baseline to endpoint using LOCF.

The proposed dosage regimen is 60 mg once daily, which could be titrated up to 120 mg per day if an adequate pain relief, is not achieved. The dosage recommendation was supported by Study HMAVa in which the efficacy of duloxetine 60 mg once daily and 60 mg twice daily were consistently superior to placebo. The proposal to up-titrate to a maximum of 120 mg/day in those patients with an insufficient response was not clearly supported by these results, since 60 mg BID was not statistically significantly superior to 60 mg QD in any study. However, it is recognised that studies were not powered to show statistically significant differences between dosages. Duloxetine 120 mg/day was numerically superior to the lower dose for the primary endpoint and also for most of the secondary endpoints, including the responders' rate (for which a difference of up to 10% between dosages was seen). Therefore, it must be recognised that some patients might benefit from the highest dose.

The rate of response was also statistically significantly superior for duloxetine 60 mg BID and 60 mg QD compared with placebo (around 50% vs. 26% for duloxetine 60 mg BID/QD and placebo, respectively, using the strict criteria), which was also clinically relevant. About 30% of the patients reported no benefit of the active drug.

Hitherto there seems no way to identify responders or non-responders but to use the product ex juvantibus. If a response has not been achieved within 60 days, this seems to indicate a persistent non-response. The SPC states that the response should be evaluated after 2 months of treatment and that additional response after this time is unlikely.

Overall, results from secondary measures were consistent with those from the primary endpoints, except for dynamic allodynia, and some items of BPI-interference scale. Consistency between studies and between the repeated measure analysis and the mean change analysis were also demonstrated.

4.2.3 Clinical safety

The total duloxetine clinical trial safety database consisted of over 11000 patients in all indications. The primary DPNP data safety database comprised a total of 1074 patients who were exposed to duloxetine for the equivalent to 471.7 patient years. Among these patients, 484 had ≥6 months of exposure to duloxetine, and 158 had ≥12 months of exposure to duloxetine.

Nausea was the most frequently reported adverse event, occurring at the beginning of treatment and decreasing over time. The most common AEs were nausea (23.6%), somnolence (15.5%), dizziness (13.4%), insomnia (10.2 %), constipation (11.3 %). Diarrhoea, fatigue, dry mouth, and hyperhydrosis occurred in 5-10% of the duloxetine patients.

The safety profile of duloxetine in the claimed indication was similar, although numerically superior to that seen in other indications, with the only exception of somnolence for which a statistically significant difference were noted (reported in up to 23.9% in DPNP vs. 13.4% in other duloxetine-treated patients indications). This could be explained because the population enrolled in clinical development for DPNP was older, with higher concomitant medications and concurrent illnesses.

Nausea and diarrhoea tended to appear early in duloxetine treatment and subside quickly, whilst somnolence, dizziness, constipation and dry mouth decreased slightly over time and insomnia, fatigue and hyperhidrosis seemed to persist during treatment with duloxetine.

Most adverse events were reported as mild or moderate. Severe adverse events tended to be more commonly reported in females and in patients older than 75 years old. However, these were not considered of clinical relevance, and the data provided demonstrated that the safety profile of duloxetine in patients older than 75 years old was consistent to that seen in younger patients.

In the long-term studies, the incidence of TEAEs in duloxetine-treated patients was relatively low and confirmed the safety profile obtained in the short-term studies.

A total of 214 (19.9%) patients discontinued due to adverse events in the primary safety database. This was slightly higher than that seen in previous indications (9.5% vs. 13.9%), and maybe due to the higher proportion of elderly patients, more prone to suffer adverse events. The most frequently reported adverse events associated with discontinuation for all duloxetine treatment groups were nausea, dizziness, somnolence, and fatigue. A total of 135 (20.1%) patients discontinued due to AEs in the long-term DPNP dataset. The most frequently reported adverse events associated with discontinuation were consistent to that seen in the placebo-controlled studies.

When discontinuing duloxetine after more than 1 week of therapy, it is generally recommended that the dose be tapered over no less than 2 weeks before discontinuation in an effort to decrease the risk of discontinuation symptoms. As a general recommendation, the dose should be reduced by half or administered on alternate days during this period. The precise regimen followed should however take into account the individual circumstances of the patient, such as duration of treatment, dose at discontinuation.

As with other medicinal products with similar pharmacological action (antidepressants), isolated cases of suicidal ideation and suicidal behaviours have been reported during duloxetine therapy or early after treatment discontinuation. Adequate warning information on reported cases of suicidal ideation and behaviour with the use of duloxetine has been included in the SPC. The SPC also requests close supervision for patients who report any distressing thoughts or feelings at any time.

Overall the safety profile was as expected for a drug with this pharmacological profile. No unexpected, serious adverse events were detected in the extensive DPNP programme.

4.2.4 Changes to the SPC

The MAH made proposals for changes in sections 4.2, 4.4, 4.8 and 5.1 of the SPC in order to incorporate the DPNP indication. All other sections remain unchanged and as previously approved for Cymbalta.

Section 4.1

The MAH proposed to add the following wording for the new indication:

> *"Treatment of major depressive episodes.*
> *Treatment of diabetic peripheral neuropathic pain in adults."*

The CHMP considered the wording acceptable.

Section 4.2

The MAH proposed to add the following wording:

> *"Diabetic Peripheral Neuropathic Pain:*
>
> *The starting and recommended maintenance dose is 60 mg daily with or without food. Dosages above 60 mg once daily, up to a maximum dose of 120 mg per day administered in evenly divided doses, have been evaluated from a safety perspective in clinical trials. The*

plasma concentration of duloxetine displays large inter-individual variability (see 5.2). Hence, some patients that respond insufficiently to 60 mg may benefit from a higher dose.

The medicinal product response should be evaluated after 2 months' of treatment. Additional response after this time is unlikely (see 5.1).

The therapeutic benefit should regularly (at least every three months) be reassessed."

Additionally, for clarity's sake, two subheaders were added to ensure that information relevant to each separate indication, as well as information that is relevant to both indications, is clearly understood by the prescribing physician: "Major Depressive Episodes", "Diabetic Peripheral Neuropathic Pain" .

The CHMP considered the wordings acceptable.

Section 4.4

The existing warning on suicide as per the currently approved Cymbalta SPC remains unchanged. The MAH proposed to add the following wording on suicide:

"Diabetic Peripheral Neuropathic Pain

As with other medicinal products with similar pharmacological action (antidepressants), isolated cases of suicidal ideation and suicidal behaviours have been reported during duloxetine therapy or early after treatment discontinuation. Physicians should encourage patients to report any distressing thoughts or feelings at any time.

For clarity subheaders were added for each indication.

The CHMP considered the wordings acceptable.

Section 4.8

The MAH proposed to subdivide the section by indication.

Following the initial assessment, it was considered that the section was too extensive and difficult to read and that data should be presented as of the ADRs that occurred with a frequency of ≥1% in both MDE and DPNP clinical trials and were reported significantly more often in patients taking duloxetine than placebo, or where the event was considered clinically relevant, as well as rewording common paragraphs to be applicable to both entities and only appear once in the section. Consequently, the MAH reorganised the section as follows:

"Tables 1 and 2 give the frequency of adverse reactions from placebo-controlled clinical trials in depression and diabetic neuropathic pain. The adverse reactions reported in these tables are those events that occurred in 1% or more of patients treated with duloxetine and were reported significantly more often in patients taking duloxetine than placebo, or where the event was considered clinically relevant.

The most commonly reported adverse reactions in patients with depression treated with CYMBALTA were nausea, dry mouth and constipation. However, the majority of common adverse reactions were mild to moderate, they usually started early in therapy, and most tended to subside even as therapy was continued. The most commonly observed adverse reactions in patients with diabetic neuropathic pain treated with CYMBALTA were: nausea; somnolence; dizziness; constipation and fatigue.

Table 1 ***Very Common Adverse Reactions (≥ 10%)***			
System Organ Class	***Adverse Reaction***	***CYMBALTA (N=1592) (%)***	***Placebo (N=1000) (%)***
Psychiatric disorders	*Insomnia*	*10*	*6*
Nervous system disorders	*Dizziness* *Somnolence*	*11* *10*	*5* *3*
Gastrointestinal disorders	*Nausea* *Dry mouth* *Constipation*	*22* *13* *12*	*7* *6* *4*
Table 2 ***Common Adverse Reactions (≥ 1%, < 10%)***			

System Organ Class	*Adverse Reaction*	*CYMBALTA (N=1592) (%)*	*Placebo (N=1000) (%)*
Metabolism and nutrition disorders	*Decreased Appetite Anorexia*	*6* *2*	*2* *<1*
Psychiatric disorders	*Decreased Libido* *Anorgasmia* *Middle insomnia*	*2* *2* *1*	*<1* *0* *<1*
Nervous system disorders	*Tremor* *Sedation* *Hypersomnia*	*3* *1 a* *1*	*1* *<1 a* *<1*
Eye disorders	*Vision blurred*	*3*	*1*
Vascular disorders	*Hot flush*	*2*	*1*
Respiratory, thoracic and mediastinal disorders	*Yawning*	*1*	*0*
Gastrointestinal disorders	*Diarrhoea* *Vomiting*	*8* *5*	*6* *3*
Skin and subcutaneous tissue disorders	*Increased Sweat* *Night sweats*	*7* *1*	*2* *<1*
Musculoskeletal and connective tissue disorders	*Muscle tightness*	*1*	*<1*
Reproductive system and breast disorders	*Erectile dysfunction** *Ejaculation disorder**	*5* *2*	*1* *<1*
General disorders and administration site conditions	*Fatigue* *Lethargy* *Feeling jittery*	*9* *1* *1*	*4* *<1* *<1*
Investigations	*Weight decreased*	*2*	*1*

* *Adjusted for gender (N Males = Duloxetine 660, Placebo 375)*

a *Values rounded from a frequency of 1.3% (duloxetine) and 0.6% (placebo)*

In clinical trials of duloxetine in patients with diabetic neuropathic pain, small but statistically significant increases in fasting blood glucose were observed in duloxetine-treated patients compared to placebo at 12 weeks and routine care at 52 weeks. The increase was similar at both time points and was not considered clinically relevant. Relative to placebo or routine care, mean HbA_{1c} values were stable, there was no mean weight gain, mean lipid concentrations (cholesterol, LDL, HDL, triglycerides) were stable, and there were no differences in incidence of serious and non-serious diabetes-related adverse reactions.

Electrocardiograms were obtained from 1139 duloxetine treated patients and 777 placebo-treated patients in 8-week clinical trials in major depressive disorder, and from 528 duloxetine-treated and 205 placebo-treated patients with diabetic neuropathic pain in clinical trials lasting up to 13-weeks. The heart rate-corrected QT interval in duloxetine-treated patients did not differ from that seen in placebo-treated patients. No clinically significant differences were observed for QT, PR, QRS, or QTcB measurements between duloxetine-treated and placebo-treated patients."

The CHMP considered the wordings acceptable.

Section 5.1

The final ATC code (Other antidepressants N06AX21) was added.

For clarity subheaders were added for each indication. The MAH proposed to add three paragraphs describing the results of clinical trials in DPNP.

"Diabetic Peripheral Neuropathic Pain: The efficacy of duloxetine as a treatment for diabetic neuropathic pain was established in 2 randomised, 12-week, double-blind, placebo-controlled, fixed dose studies in adults (22 to 88 years) having diabetic neuropathic pain for at least 6 months. Patients meeting diagnostic criteria for major depressive disorder were excluded from these trials. The primary outcome measure was the weekly mean of 24-hour average pain, which was collected in a daily diary by patients on an 11-point Likert scale.

In both studies, duloxetine 60 mg once daily and 60 mg twice daily significantly reduced pain compared with placebo. The effect in some patients was apparent in the first week of treatment. The difference in mean improvement between the two active treatment arms was not significant. At least 30% reported pain reduction was recorded in approximately 65% of duloxetine treated patients versus 40% for placebo. The corresponding figures for at least

50% pain reduction were 50% and 26% respectively. Clinical response rates (50% or greater improvement in pain) were analysed according to whether or not the patient experienced somnolence during treatment. For patients not experiencing somnolence, clinical response was observed in 47% of patients receiving duloxetine and 27% patients on placebo. Clinical response rates in patients experiencing somnolence were 60% on duloxetine and 30% on placebo. Patients not demonstrating a pain reduction of 30% within 60 days of treatment were unlikely to reach this level during further treatment.

Although data from a one-year open label study offer some evidence for longer-term efficacy, no conclusive efficacy data for treatments longer than 12 weeks duration are available from placebo-controlled studies."

In addition, the MAH proposed to include the following paragraph describing the activity of duloxetine in preclinical models of pain:

"Duloxetine normalised pain thresholds in several preclinical models of neuropathic and inflammatory pain and attenuated pain behaviour in a model of persistent pain. The pain inhibitory action of duloxetine is believed to be a result of potentiation of descending inhibitory pain pathways within the central nervous system."

The CHMP considered the wordings acceptable.

4.2.5 Changes to the PL

Section 1

The MAH proposed to include the DPNP indication and description of the disease state and time to onset of action:

"You have been given CYMBALTA to treat your depression or to treat a condition called diabetic neuropathic pain.

Neuropathic pain is a medical condition in which the pain is commonly described as burning, stabbing, stinging, shooting or aching or like an electric shock. There may be loss of feeling in the affected area, or sensations such as touch, heat, cold or pressure may cause pain."

"Cymbalta starts to work in most people with depression within two weeks of starting treatment. Your doctor may continue to give you Cymbalta when you are feeling better to prevent your depression from returning. The effect of Cymbalta may be noticeable in many patients with diabetic neuropathic pain within 1 week of treatment."

The CHMP considered the wordings acceptable.

Section 4

The MAH proposed to include the following additional side effects for the DPNP population:

"Very common ≥10%) side effects with CYMBALTA may include feeling sick (nausea), dry mouth and constipation, dizziness, tiredness, and trouble sleeping.

Common (≥1 and <10%) side effects may include diarrhoea, being sick (vomiting), tiredness, lethargy, tremor, blurred eyesight, lack appetite or decrease in appetite, weight loss, dizziness, difficulty sleeping, feeling sleepy, increased sweating or night sweats, hot flushes, sexual problems (including problems getting an erection, changes in ejaculation, less sex drive, not being able to have an orgasm).

A few men have experienced some difficulty in starting to pass urine."

The CHMP considered the wording acceptable.

5. Overall conclusions and benefit/risk assessment

Efficacy

The efficacy of duloxetine in patients with diabetic neuropathic pain (DPNP) was evaluated in two randomised, placebo-controlled studies (Study HMAW-Acute and Study HMAV-Acute) in patients with painful diabetic neuropathy, during a 12-week acute therapy phase.

Male or female outpatients at least 18 years of age with pain due to bilateral peripheral neuropathy for at least 6 months, caused by Type 1 or Type 2 diabetes mellitus were included in these studies. Patients meeting diagnostic criteria for major depressive disorder were excluded from these trials. The primary outcome measure was the weekly mean of 24-hour average pain, which was collected in a daily diary by patients on an 11-point Likert scale.

In both studies, duloxetine 60 mg once daily and 60 mg twice daily significantly reduced pain compared with placebo. The effect in some patients was apparent in the first week of treatment. The difference in mean improvement between the two active treatment arms was not significant. At least 30% reported pain reduction was recorded in approximately 65% of duloxetine treated patients versus 40% for placebo. The corresponding figures for at least 50% pain reduction were about 50% and 26% respectively.

Safety

The duloxetine database consisted of over 11,000 patients in all indications. The primary safety database comprises a total of 1074 patients who were exposed to duloxetine over the course of both acute and long-term treatment in Studies HMAW, HMAV-Acute, and HMBT, equivalent to 471.7 patient years of exposure. Duloxetine is a drug with highly variable pharmacokinetics and many factors affect the systemic exposure (gender, age, renal and hepatic function, smoking status, CYP2D6 status, drug-drug interactions)

Adverse reactions occurred significantly more often in the duloxetine than in the placebo group, nausea (23.6%), being the most frequently reported adverse event. Other common adverse reactions were somnolence (15.5%), dizziness (13.4%), insomnia (10.2 %), constipation (11.3 %). Diarrhoea, fatigue, dry mouth, and hyperhydrosis occurred in 5-10% of the duloxetine patients. Nausea and diarrhoea tended to appear early in duloxetine treatment and subside quickly, whilst somnolence, dizziness, constipation and dry mouth decreased slightly over time and insomnia, fatigue and hyperhidrosis seemed to persist during treatment with duloxetine.

A total of 214 (19.9%) patients discontinued due to adverse events in the primary safety database. This was slightly higher than that seen in previous indications (9.5% vs. 13.9%), and maybe due to the higher proportion of elderly patients, more prone to suffer adverse events. The adverse event most frequently leading to discontinuation of patients was nausea.

In conclusion, the safety profile of duloxetine did not identify any unexpected serious adverse reaction, which would cause special concern.

Benefit/risk assessment

The MAH has provided evidence of efficacy of duloxetine as a treatment for diabetic neuropathic pain through two 2 randomised, 12-week, double-blind, placebo-controlled, fixed dose studies in adult diabetic neuropathic pain. In the two studies, duloxetine 60 mg once daily and 60 mg twice daily significantly reduced pain compared with placebo.

Although some concerns remain, in particular the lack of adequate demonstration of maintenance of the effect of duloxetine in diabetic peripheral neuropathy, the tolerability profile of duloxetine seems acceptable. Therefore, duloxetine may have a place in the treatment of diabetic peripheral neuropathic pain in adults, and the CHMP concluded that there was a positive benefit/risk in DPNP.

The CHMP considered that this variation to incorporate the indication “Diabetic Peripheral Neuropathic Pain (DPNP) in adults” was acceptable and that the following wordings should be implemented in the SPC with corresponding changes to the PL:

Section 4.1 of the SPC

"Treatment of major depressive episodes.
Treatment of diabetic peripheral neuropathic pain in adults."

Section 1 of the PL

"You have been given CYMBALTA to treat your depression or to treat a condition called diabetic neuropathic pain.

Neuropathic pain is a medical condition in which the pain is commonly described as burning, stabbing, stinging, shooting or aching or like an electric shock. There may be loss of feeling in the affected area, or sensations such as touch, heat, cold or pressure may cause pain."

"Cymbalta starts to work in most people with depression within two weeks of starting treatment. Your doctor may continue to give you Cymbalta when you are feeling better to prevent your depression from returning. The effect of Cymbalta may be noticeable in many patients with diabetic neuropathic pain within 1 week of treatment."

Section 4.2 of the SPC

"Diabetic Peripheral Neuropathic Pain: The starting and recommended maintenance dose is 60 mg daily with or without food. Dosages above 60 mg once daily, up to a maximum dose of 120 mg per day administered in evenly divided doses, have been evaluated from a safety perspective in clinical trials. The plasma concentration of duloxetine displays large inter-individual variability (see 5.2). Hence, some patients that respond insufficiently to 60 mg may benefit from a higher dose.

The medicinal product response should be evaluated after 2 months' of treatment. Additional response after this time is unlikely (see 5.1).

The therapeutic benefit should regularly (at least every three months) be reassessed."

Section 4.4 of the SPC

"Diabetic Peripheral Neuropathic Pain: As with other medicinal products with similar pharmacological action (antidepressants), isolated cases of suicidal ideation and suicidal behaviours have been reported during duloxetine therapy or early after treatment discontinuation. Physicians should encourage patients to report any distressing thoughts or feelings at any time.

Section 4.8 of the SPC

"Tables 1 and 2 give the frequency of adverse reactions from placebo-controlled clinical trials in depression and diabetic neuropathic pain. The adverse reactions reported in these tables are those events that occurred in 1% or more of patients treated with duloxetine and were reported significantly more often in patients taking duloxetine than placebo, or where the event was considered clinically relevant.

The most commonly reported adverse reactions in patients with depression treated with CYMBALTA were nausea, dry mouth and constipation. However, the majority of common adverse reactions were mild to moderate, they usually started early in therapy, and most tended to subside even as therapy was continued. The most commonly observed adverse reactions in patients with diabetic neuropathic pain treated with CYMBALTA were: nausea; somnolence; dizziness; constipation and fatigue.

Table 1 ***Very Common Adverse Reactions (≥ 10%)***			
System Organ Class	***Adverse Reaction***	***CYMBALTA (N=1592) (%)***	***Placebo (N=1000) (%)***
Psychiatric disorders	*Insomnia*	*10*	*6*
Nervous system disorders	*Dizziness* *Somnolence*	*11* *10*	*5* *3*
Gastrointestinal disorders	*Nausea* *Dry mouth* *Constipation*	*22* *13* *12*	*7* *6* *4*
Table 2			

Common Adverse Reactions (≥1%, < 10%)			
System Organ Class	***Adverse Reaction***	***CYMBALTA (N=1592) (%)***	***Placebo (N=1000) (%)***
Metabolism and nutrition disorders	*Decreased Appetite* *Anorexia*	*6* *2*	*2* *<1*
Psychiatric disorders	*Decreased Libido* *Anorgasmia* *Middle insomnia*	*2* *2* *1*	*<1* *0* *<1*
Nervous system disorders	*Tremor* *Sedation* *Hypersomnia*	*3* *1 a* *1*	*1* *<1 a* *<1*
Eye disorders	*Vision blurred*	*3*	*1*
Vascular disorders	*Hot flush*	*2*	*1*
Respiratory, thoracic and mediastinal disorders	*Yawning*	*1*	*0*
Gastrointestinal disorders	*Diarrhoea* *Vomiting*	*8* *5*	*6* *3*
Skin and subcutaneous tissue disorders	*Increased Sweat* *Night sweats*	*7* *1*	*2* *<1*
Musculoskeletal and connective tissue disorders	*Muscle tightness*	*1*	*<1*
Reproductive system and breast disorders	*Erectile dysfunction** *Ejaculation disorder**	*5* *2*	*1* *<1*
General disorders and administration site conditions	*Fatigue* *Lethargy* *Feeling jittery*	*9* *1* *1*	*4* *<1* *<1*
Investigations	*Weight decreased*	*2*	*1*

* *Adjusted for gender (N Males = Duloxetine 660, Placebo 375)*

a *Values rounded from a frequency of 1.3% (duloxetine) and 0.6% (placebo)*

In clinical trials of duloxetine in patients with diabetic neuropathic pain, small but statistically significant increases in fasting blood glucose were observed in duloxetine-treated patients compared to placebo at 12 weeks and routine care at 52 weeks. The increase was similar at both time points and was not considered clinically relevant. Relative to placebo or routine care, mean HbA_{1c} values were stable, there was no mean weight gain, mean lipid concentrations (cholesterol, LDL, HDL, triglycerides) were stable, and there were no differences in incidence of serious and non-serious diabetes-related adverse reactions.

Electrocardiograms were obtained from 1139 duloxetine treated patients and 777 placebo-treated patients in 8-week clinical trials in major depressive disorder, and from 528 duloxetine-treated and 205 placebo-treated patients with diabetic neuropathic pain in clinical trials lasting up to 13-weeks. The heart rate-corrected QT interval in duloxetine-treated patients did not differ from that seen in placebo-treated patients. No clinically significant differences were observed for QT, PR, QRS, or QTcB measurements between duloxetine-treated and placebo-treated patients."

Section 4 of the PL

"Very common (≥10%) side effects with CYMBALTA may include feeling sick (nausea), dry mouth and constipation, dizziness, tiredness, and trouble sleeping.

Common (≥1 and <10%) side effects may include diarrhoea, being sick (vomiting), dry mouth, tiredness, lethargy, tremor, blurred eyesight, lack appetite or decrease in appetite, weight loss, dizziness, difficulty sleeping, feeling sleepy, increased sweating or night sweats, hot flushes, sexual problems (including problems getting an erection, changes in ejaculation, less sex drive, not being able to have an orgasm).

A few men have experienced some difficulty in starting to pass urine."

Section 5.1 of the SPC

"Diabetic Peripheral Neuropathic Pain: The efficacy of duloxetine as a treatment for diabetic neuropathic pain was established in 2 randomised, 12-week, double-blind, placebo-controlled, fixed dose studies in adults (22 to 88 years) having diabetic neuropathic pain for at least 6 months. Patients meeting diagnostic criteria for major depressive disorder were

excluded from these trials. The primary outcome measure was the weekly mean of 24-hour average pain, which was collected in a daily diary by patients on an 11-point Likert scale.

In both studies, duloxetine 60 mg once daily and 60 mg twice daily significantly reduced pain compared with placebo. The effect in some patients was apparent in the first week of treatment. The difference in mean improvement between the two active treatment arms was not significant. At least 30% reported pain reduction was recorded in approximately 65% of duloxetine treated patients versus 40% for placebo. The corresponding figures for at least 50% pain reduction were 50% and 26% respectively. Clinical response rates (50% or greater improvement in pain) were analysed according to whether or not the patient experienced somnolence during treatment. For patients not experiencing somnolence, clinical response was observed in 47% of patients receiving duloxetine and 27% patients on placebo. Clinical response rates in patients experiencing somnolence were 60% on duloxetine and 30% on placebo. Patients not demonstrating a pain reduction of 30% within 60 days of treatment were unlikely to reach this level during further treatment.

Although data from a one-year open label study offer some evidence for longer-term efficacy, no conclusive efficacy data for treatments longer than 12 weeks duration are available from placebo-controlled studies."

"Duloxetine normalised pain thresholds in several preclinical models of neuropathic and inflammatory pain and attenuated pain behaviour in a model of persistent pain. The pain inhibitory action of duloxetine is believed to be a result of potentiation of descending inhibitory pain pathways within the central nervous system."

The MAH has implemented the above-mentioned changes in the SPC and the PL.

6. Conclusion

On 26 May 2005 the CHMP considered this Type II variation to be acceptable and agreed on the amendments to be introduced in the Summary of Product Characteristics and Package Leaflet.

