London, 22 November 2007
Product Name : **Ariclaim**
Procedure No: **EMEA/H/C/000552/II/0024**

SCIENTIFIC DISCUSSION

1. Introduction

Ariclaim (duloxetine) hard capsules was authorised in the European Union for women for the indication of *"Treatment of moderate to severe Stress Urinary Incontinence (SUI)" in* August 2004.

The MAH submitted this variation to update the section 4.1 of the Summary of Product Characteristics (SPC) to add the indication *"Diabetic Peripheral Neuropathic Pain (DPNP) in adults*".

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. Non-Clinical aspects

2.1. Toxico-pharmacological aspects

No new non-clinical data that change the toxico-pharmacological profile of duloxetine have been submitted.

The effect of duloxetine in the treatment of DPNP has been studied in animals. 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.

An environmental risk assessment that has been conducted in accordance with Article 8 (ca) and (g) of Directive 2001/83/EC as amended was provided. A Phase II Ecotoxicity Assessment has been conducted. There was no evidence that the therapeutic use of duloxetine hydrochloride in Europe and its subsequent discharge to sewage treatment plants will have negative consequences for the environment.

3. Clinical aspects

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 HMAVa-Acute). Further safety data as well as long-term efficacy 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.

The MAH declared that the two clinical studies presented in this submission were conducted in accordance with the Good Clinical Practice.

3.1 Clinical efficacy

A total of 475 and 334 patients in Study HMAW-Acute and HMAVa-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[1] criteria for major depression. The *study population* included in the studies were 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. 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.

All analyses were conducted on an intent-to-treat (ITT) basis, meaning that data were analysed by the treatment groups to which patients were randomly assigned. All randomly assigned patients were included in patient baseline characteristic summaries, while all randomly assigned patients with a baseline and at least one post-baseline value were included in the efficacy analyses.

Study HMAW Acute

Study HMAW-Acute was a double-blind, randomised, placebo-controlled, study comparing duloxetine 20 mg QD (once daily), 60 mg QD and 60 mg BID (twice daily) 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 that 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, BDIII 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.

[1] *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (1994).

Study HMAVa Acute

Study HMAVa-Acute was a double-blind, randomised, 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. 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 HMAVa-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.

Bioequivalence

All strengthsare capsules which contain the same pellets of duloxetine in different amount, therefore these capsules are proportional and no problems of bioequivalence between these capsules are expected. This means that 20 mg plus 40 mg is equivalent to 60 mg, thus corresponds to the recommending dose for the DPNP indication.

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 the 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 medicinal product.

Hitherto there was 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.

3.2 Clinical safety

The total duloxetine clinical trial safety database consisted of over 11,000 patients in all indications.
The primary DPNP safety database consists of two studies in the development plan which were primarily designed to evaluate the safety of duloxetine over long-term administration. The extension phase of Study HMAW compared duloxetine 60 mg BID with routine care over 52 weeks of treatment, while in Study HMBT, duloxetine 60 mg BID and 120 mg QD were administered open-label over 28 weeks of treatment.

Patient exposure and demographics
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. The demographic characteristics of the treatment groups and databases were generally consistent. Patients in the primary safety database were of both genders but predominantly Caucasian men aged between 20 and 88 years. The higher prevalence of males in these studies is likely related to the fact that patients with depression, which is more common in females, were excluded. However, enough females were included in the database to allow for an adequate safety assessment.

Deaths
In the entire clinical program involving over 11,000 individuals 29 deaths were reported. The reported deaths are what might be expected from these patient populations and do not suggest medicinal product toxicity. Cardiac-related deaths were the most frequent and appear to be related to underlying heart disease and patients' advancing age. There was no evidence of deaths related to QT prolongation.

Adverse events
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 population enrolled in clinical development for DPNP were 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, etc.

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 casesof 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.

With the exception of hepatic enzymes, small and clinically insignificant changes in laboratory analytes were seen across the databases, with very few instances of potentially clinically significant abnormal laboratory values. Small increases in mean values for aspartate transaminase (AST), alanine transaminase (ALT), and alkaline phosphatase (ALKPH) were seen, but these were not accompanied by clinical symptoms in the vast majority of patients, and there is little to suggest that duloxetine alone is likely to be the cause of significant hepatotoxicity. Duloxetine has been shown to be associated with a mild, transient elevation of ALT and AST. These elevations were not dose related and not associated with adverse events. Rarely, patients taking duloxetine while consuming large amounts of alcohol have been found to have significant elevations of ALT and AST, as well as elevated bilirubin. No patients have died as a result of liver failure or sustained permanent liver injury.

The safety profile in various demographic groups was found to be similar. Although there were younger patients than older and more males than females, there were sufficient numbers in the smaller groups to allow for robust conclusions.

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

4 Pharmacovigilance

Risk Management Plan

The MAH referred to the Risk Management Plan submitted to the EMEA/CHMP in October 2006.

The CHMP, having considered the data submitted in the application, is of the opinion that no additional risk minimisation activities are required beyond those included in the product information.

5 Overall Conclusions and Benefit/Risk assessment

Ariclaim contains duloxetine hydrochloride. Duloxetine is a combined serotonin and noradrenaline reuptake inhibitor. Ariclaim has been approved in the European Union for the treatment of Severe Urinary Incontinence.

The efficacy of duloxetine in the new DPNP indication has been examined in clinical studies of patients with DPNP in doses up to 60 mg BID. Strong evidence in support of the effectiveness of duloxetine in both oncedaily (60 mg QD) and twice-daily (60 mg BID) dosing regimens has been demonstrated in two adequate and well-controlled clinical studies: HMAVa - Acute and HMAW - Acute.

In both studies, duloxetine was statistically significantly superior to placebo in improvement of the a priori-declared primary outcome measure, the 24-hour average pain score. In addition, duloxetine was statistically significantly superior to placebo in demonstrating response and sustained response on the 24-hour average pain score, which is a clinical relevant measure of pain relief.

In terms of safety, the absence of serious idiosyncratic toxicity in the development of duloxetine. There was no evidence to suggest that deaths in the clinical study program were associated with use of duloxetine and no clear pattern in the incidence or nature of serious adverse events (SAEs) to suggest systemic drug toxicity. Systematic review of possible cardiovascular effects, including blood pressure changes and changes in QTc intervals, did not reveal any noteworthy impact or safety hazard. Nausea is the most frequently reported adverse event, usually occurring at the beginning of treatment and decreasing quickly over time. Small increases in mean values for the hepatic enzymes were seen, but these were not accompanied by clinical symptoms in the vast majority of patients, and there is little to suggest that duloxetine alone is likely to be the cause of significant hepatotoxicity. The issue of the hepatic reactions may be closely monitored. In the long-term studies, the incidence of TEAEs in duloxetine-treated patients was low and comparable to routine care; no event occurred significantly more often in duloxetine treated patients than in those patients treated with routine care. Therefore, there is no evidence of additional tolerability concerns with chronic duloxetine dosing.

Based on the CHMP review of safety and efficacy, the CHMP considers that the benefit-risk for duloxetine dihydrochloride indicated in *'Diabetic Peripheral Neuropathic Pain (DPNP) in adults'*, is favourable and recommended the variation to the marketing authorisation.