Decentralised Procedure

Public Assessment Report

Duloxgamma / Duloxetin AAA-Pharma
30 / 60 mg magensaftresistente Hartkapseln

Duloxetine hydrochloride

DE/H/4026-27/001-002/DC

Applicants:
Wörwag Pharma GmbH & Co. KG /
AAA-Pharma GmbH, Germany

Reference Member State	DE

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ADMINISTRATIVE INFORMATION

Proposed name of the medicinal product(s) in the RMS	Duloxgamma / Duloxetin AAA-Pharma 30 / 60 mg magensaftresistente Hartkapseln
Name of the drug substance (INN name):	Duloxetine (as hydrochloride)
Pharmaco-therapeutic group (ATC Code):	N06AX21
Pharmaceutical form(s) and strength(s):	Gastro-resistant capsules, hard 30; 60 mg
Reference Number(s) for the Decentralised Procedure	DE/H/4026-27/001-002/DC
Reference Member State:	DE
Concerned Member States:	**DE/H/4026/001-002/DC:**BG, CZ, EE, HU, LV, PL, RO, SK HR and LT withdrawn **DE/H/4027/001-002/DC:** LU
Applicant (name and address)	**DE/H/4026/001-002/DC:** Wörwag Pharma GmbH & Co. KG Calwer Str.7, D-71034 Böblingen, Germany **DE/H/4027/001-002/DC:** AAA-Pharma GmbH Calwer Str. 7, 71034 Böblingen, Germany

I. INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the application for *"Duloxgamma / Duloxetin AAA-Pharma 30 / 60 mg magensaftresistente Hartkapseln"*, in the treatment of major depressive disorder, diabetic peripheral neuropathic pain and generalised anxiety disorder in adults, is approved.

II. EXECUTIVE SUMMARY

II.1 Problem statement

N/A

II.2 About the product

Duloxetine is a serotonine and noradrenaline reuptake inhibitor that weakly interferes with dopamine reuptake and does not exert significant affinity on histaminergic, dopaminergic, cholinergic and adrenergic receptors. Duloxetine is indicated for the treatment of major depressive disorder, diabetic peripheral neuropathic pain and generalised anxiety disorder in adults.

II.3 General comments on the submitted dossier

This decentralised application according to Art. 10.1 of Dir. 2001/83/EC concerns a generic version of duloxetine. The originator product is *"Ariclaim 30 and 60 mg hard gastro-resistant capsules"* registered by Eli Lilly Nederland B.V. since 11th August 2004 across the EU as treatment of diabetic peripheral neuropathic pain in adults. On the same date, Eli Lilly Nederland B.V. received a centralised MA for *"Yentreve 20 and 40 mg hard gastro-resistant capsules"* for the therapy of moderate to severe stress urinary incontinence in adult women. Subsequently, Eli Lilly Nederland B.V. also obtained a centralised MA for the European reference product *"Cymbalta 30 and 60 mg hard gastro-resistant capsules"* as treatment of major depressive disorder, diabetic peripheral neuropathic pain and generalised anxiety disorder in adults on 17th December 2004. Hence, data protection has expired.

The MAA generally follows prevailing European regulatory requirements for essentially similar medicinal products.

II.4 General comments on compliance with GMP, GLP, GCP and agreed ethical principles

The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture and assembly of this product.

For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

GMP active substance

Regarding the statement on GMP for the active substance a statement/declaration is provided from the manufacturer(s) responsible for manufacture of the finished product and batch release situated in the EU.

III. SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 Quality aspects

The chemical-pharmaceutical documentation and Quality Overall Summary in relation to *Duloxgamma / Duloxetin AAA-Pharma 30 / 60 mg magensaftresistente Hartkapseln* are of sufficient quality in view of the present European regulatory requirements.

Drug substance

Duloxetine is included in the European Pharmacopoeia 8th edition and also described in USP.

There are four nominated sources of the active substance in the dossier. Three have been granted a Ph. Eur. Certificate of Suitability. For the fourth manufacturer is the information on the synthesis and control of the active substance presented in an Active Substance Master File (ASMF). The route of synthesis is described. The structure of duloxetine hydrochloride has been confirmed by spectroscopic analyses. The proposed drug substance specification is acceptable. However, a test to

confirm polymorphic form should be included in the active substance specification. The analytical test methods have been described and validated. Satisfactory batch analysis data of batches of duloxetine hydrochloride have been presented. Stability studies have been performed with the drug substance. No significant changes in any parameters were observed.

The ASMF for duloxetine hydrochloride has been assessed by the national competent Authority of the United Kingdom (UK/H/5866+5868/001-002).

The re-test period included in the CEP for manufacturer A is 36 months. Based on the data available, retest period of 12 months is proposed by the ASMF holder. For drug substance supplied by manufacturer B, a re-test-period of 5 years with the storage condition " Preserve in tight, light resistant containers, store at 25°C, excursions permitted between 15°C and 30°C" is acceptable. The re-test period of 54 months for manufacturer C is justified by stability data.

Drug Product
The development of the product has been described, the choice of excipients is justified and their functions explained. The range for production scale batch size has been defined.
The product specifications cover appropriate parameters for this dosage form. Validations of the analytical methods have been presented. Batch analysis has been performed 30 mg and 60 mg duloxetine gastro-resistant hard capsules. The batch analysis results show that the finished products meet the specifications proposed.
The description and choice of container closure system is in accordance with relevant EU-directives. The conditions used in the stability studies are according to the ICH stability guideline and a shelf-life of 18 month is supported by the provided 12 month stability data.

III.2 Non-clinical aspects

The pharmacological and toxicological properties of duloxetine are well known and have been comprehensively summarised based on publicly available information in the Non-clinical Overview. Unfortunately, the Non-clinical Overview has been widely compiled by direct copying from different scientific references (abstracts, EPAR etc.), which leads to a repetition of information instead of providing an integrated critical assessment as outlined in the European Dir. 2001/83/EC. At least, the structure recommended by NTA Vol. 2B has been followed and the paragraphs have been logically interconnected. Moreover, an evaluation of excipients and potential impurities has been included. Although the scientific quality of the Non-clinical Overview could be improved, the document is therefore accepted.

The instructions on use of the compound during pregnancy and lactation and the preclinical safety data contained in the proposed SmPC and PL, respectively, essentially reflect the characteristics of the substance and have been adequately harmonised with the currently approved product information of the reference product *"Cymbalta"* (EMEA/H/C/572/PSUSA/1187).

Environmental Risk Assessment (ERA)
Since *"Duloxgamma / Duloxetin AAA-Pharma 30 / 60 mg magensaftresistente Hartkaspeln"* are intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.3 Clinical aspects

Pharmacokinetics
Two pivotal bioequivalence studies (EudraCT 2014-000150-10, Study code: D+C/07/13 and EudraCT 2014-000487-18, Study code: D+C/02/14) has been conducted comparing Duloxetine 60 mg hard gastro-resistant capsules with the reference medicinal product Cymbalta 60 mg gastro-resistant capsules under fasting and fed conditions, both meeting the criteria for bioequivalence.

A full study report has been provided. According to EMA Guidance (CPMP/EWP/QWP/1401/98 Rev.1 Cor**), for drugs with linear pharmacokinetics, the bioequivalence study should in general be conducted at the highest strength, which is fulfilled.

No further studies were required with the 30 mg strength as Duloxetine has linear pharmacokinetics and as in that case it is not always necessary to perform bioequivalence on all strengths as long as conditions as set out in the general biowaiver criteria of section 4.1.6. Strength to be investigated of the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98m Rev. 1/Corr**) are met. Meanwhile, revision of the clinical dossier (clinical overview) was done and within the clinical module the Applicant provide further data of the qualitative and quantitative composition of the test product.

Based on obtained results of the bioequivalence studies it can be concluded that the tested formulations confirm adequacy of in vivo performance in comparison to reference product and by that adequacy of composition and manufacturing process of product under development.

Pharmacodynamics / Clinical efficacy / Clinical safety
N/A

Legal Status
For prescription only

User Testing
The Package Leaflet for Duloxgamma 30/60 mg hard-gastro-resistant capsules had been user tested and achieved a satisfactory result according to the guideline criteria.
The 1st round of testing showed that, for each question, at least 90% of 10 participants were able to find the correct information, and at least 90% of participants were able to answer it correctly.
The 2nd round of testing showed that, for each question, at least 90% of another 10 participants were able to find the correct information, and at least 90% of participants were able to answer it correctly.
Based on quantitative and qualitative results from the first and second rounds, there were no revisions to the PL after the two rounds.
The results of this test indicate that the PL is well structured and organised, easy to understand, easy to navigate and written in a comprehensible manner. The test shows that the PL is readable and the users are able to act upon the key safety messages that it contains.

Summary Pharmacovigilance system
The Applicant/Proposed Future MAH has submitted a signed Summary of the Applicant's/Proposed Future MAH's Pharmacovigilance System. Provided that the Pharmacovigilance System Master File fully complies with the new legal requirements as set out in the Commission Implementing Regulation and as detailed in the GVP module, the RMS considers the Summary acceptable.

Risk Management Plan
The following summaries of safety concerns were listed.

Summary of safety concerns	
Important identified risks	• Hepatic risks • Suicidality • Hyperglycemia • Stevens-Johnson Syndrome • Gastrointestinal Tract Bleeding • Serotonin syndrome
Important potential risks	• Cardiovascular events including those with concomitant use of NSAIDs • Upper gastrointestinal tract (UGIT) bleeding event with concomitant use of NSAIDs • Renal Failure

Important potential risks	• Characterization of the safety and tolerability of duloxetine in pediatric patients was previously considered missing • Prospective data about potential risks of exposure to duloxetine during Pregnancy • Characterization of drug utilization in unapproved indications and populations • Safety of duloxetine in elderly patients ≥ 75 years old with concomitant NSAIDs use • Long-term safety data in chronic pain patients

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to duloxetine.

There are no additional risk minimisation measures and no additional pharmacovigilance activities.

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the RMS;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time, but via different procedures.

Periodic Safety Update Report (PSUR)
With regard to PSUR submission, the MAH should take the following into account:
- PSURs shall be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal. Marketing authorisation holders shall continuously check the European medicines web-portal for the DLP and frequency of submission of the next PSUR.
- For medicinal products authorized under the legal basis of Article 10(1) or Article 10a of Directive 2001/83/EC, no routine PSURs need to be submitted, unless otherwise specified in the EURD list.
- For medicinal products that do not fall within the categories waived of the obligation to submit routine PSURs by the revised pharmacovigilance legislation, the MAH should follow the DLP according to the EURD list.

IV. BENEFIT RISK ASSESSMENT

The application contains an adequate review of published clinical data and the studies provided by the applicant are in favour of bioequivalence. The application is approved.
For intermediate amendments see current product information.