Decentralised Procedure

Public Assessment Report

Dutilox / Zatinex
30 / 60 mg magensaftresistente Hartkapseln

Duloxetine hydrochloride

DE/H/4174-4175/001-002/DC

Applicant: Optimal Regulatory Solutions, S.L.
Spain

Reference Member State	DE

TABLE OF CONTENTS

I. INTRODUCTION **4**
II. EXECUTIVE SUMMARY **4**
II.1 Problem statement **4**
II.2 About the product **4**
II.3 General comments on the submitted dossier **4**
II.4 General comments on compliance with GMP, GLP, GCP and agreed ethical principles **4**
III. SCIENTIFIC OVERVIEW AND DISCUSSION **4**
III.1 Quality aspects **4**
III.2 Non-clinical aspects **5**
III.3 Clinical aspects **5**
IV. BENEFIT RISK ASSESSMENT **8**

ADMINISTRATIVE INFORMATION

Proposed name of the medicinal product(s) in the RMS	Dutilox / Zatinex 30 / 60 mg magensaftresistente Hartkapseln
Name of the drug substance (INN name):	Duloxetine hydrochloride
Pharmaco-therapeutic group (ATC Code):	N06DX21
Pharmaceutical form(s) and strength(s):	Gastro-resistant capsules, hard 30; 60 mg
Reference Number(s) for the Decentralised Procedure	DE/H/4174-4175/001-002/DC
Reference Member State:	DE
Concerned Member States:	DE/H/4174/001-002/DC: AT, BE, NL, PL, RO DE/H/4175/001-002/DC: RO
Applicant (name and address)	Optimal Regulatory Solutions S.L. Via Augusta, 59 off.104, ES-08006 Barcelona, Spain

I. INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the application for *"Dutilox / Zatinex 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 application according to Art. 10.2(b) of Dir. 2001/83/EC generally complies with prevailing European regulatory requirements for dossiers of 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.

For manufacturing sites outside the Community, the RMS has accepted copies of current GMP Certificates of satisfactory inspection summary reports, issued by the inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those non-Community sites.

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

III. SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 Quality aspects

The information presented is acceptable and sufficient to guarantee the quality of for Duloxetine 30 mg and 60 mg gastro-resistant capsules.

Drug substance
Duloxetine is included in the European Pharmacopoeia 8th edition and also described in USP.
Valid Certificates of suitability are presented for Duloxetine Hydrochloride manufactured by proposed active substance manufacturers.

Drug Product
The development of the product has been described, the choice of excipients is justified and their functions explained.
The product specifications cover appropriate parameters for this dosage form. Validations of the analytical methods have been presented. Batch analysis has been performed on three pilot scale batches of 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. The

presented stability results show that all specified parameters are fulfilled under long term conditions for 24 months and accelerated conditions for 6 months. A shelf-life 24 months for Duloxetine 30 mg and 60 mg gastro-resistant capsules considered justified by stability data provided for capsules packed Alu/Alu blisters, PVC/PVDC-Alu blisters and Polyethylene plastic bottle with screw is accepted. Specific storage condition are proposed for each packaging material.

III.2 Non-clinical aspects

The pharmacological and toxicological properties of duloxetine are well known and have been satisfactorily summarised in the Non-clinical Overview. By reference to the corresponding sections of Module 3, the Non-clinical Overview briefly delineates that potential impurities, degradants and excipients are controlled in accordance with prevailing ICH recommendations and that valid Certificates of suitability are available for the two drug substance manufacturers (see Quality AR for further information). On request of the CMS RO, the Non-clinical Overview has been further complemented by safety pharmacology data from the original MAA of the reference product *"Cymbalta"*.

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 active substance and have been adequately harmonised with the currently approved product information of the reference product *"Cymbalta"* (EMEA/H/C/572-WS/490), which is acknowledged.

Environmental Risk Assessment (ERA)

Since *"Dutilox / Zatinex 30 / 60 mg magensaftresistente Hartkapseln"* is 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

Duloxetine hydrochloride is a serotonin and noradrenaline reuptake inhibitor (SNRI). It is given orally as hydrochloride although doses are expressed in terms of the base; duloxetine hydrochloride 33.75 mg is equivalent to about 30 mg of duloxetine.

The indication of duloxetine 30 and 60 mg is exactly in line with that of the originator Cymbalta which is indicated:

- Treatment of major depressive disorder.
- Treatment of diabetic peripheral neuropathic pain.
- Treatment of generalised anxiety disorder.

Pharmacokinetics

To support the application, the Applicant has submitted *two* bioequivalence studies in healthy volunteers, one under fasting conditions and one study in fed state:

One Open Label, Randomized, 2-Period, 2-Treatment, 2-Sequence, Crossover, Single-Dose Bioequivalence Study of Duloxetine (as hydrochloride) 60mg Delayed Release Capsule (Estevia , Spain) versus Cymbalta® 60mg Hard Gastro-Resistant Capsule containing Duloxetine (as hydrochloride) 60mg (Reference, Lilly SA, Spain) in Healthy Human Volunteers under Fasting Condition (DLN-P0-600), and

one Open Label, Randomized, 2-Period, 2-Treatment, 2-Sequence, Crossover, Single-Dose Bioequivalence Study of Duloxetine (as hydrochloride) 60mg Delayed Release Capsule (Test, Estevia, Spain) versus Cymbalta® 60mg Hard Gastro-Resistant Capsule containing Duloxetine (as hydrochloride) 60mg (Reference, Lilly SA, Spain) in Healthy Human Volunteers under Fed Condition (DLN-P0-601).

The number of BE studies for a delayed release dosage form complies with the guidance (EMA/CPMP/EWP/280/96 Corr1), which is one fasting and one fed study.

All studies have been operated in Canada and conducted in accordance with ethical principles

outlined in the Declaration of Helsinki and ICH – GCP guidelines. All the procedures in these studies were carried out as per local regulatory requirements, Guideline on the investigation of Bioequivalence CPMP/QWP/EWP/1401/98 Rev.1, January 2010 and in-house standard operating procedures.

The acceptance criteria for bioequivalence concerning duloxetine 60 mg gastro-resistant hard capsules were met in both studies. Bioequivalence has been demonstrated.

No separate studies were performed for the other dose strength of the generic duloxetine gastro-resistant hard capsules.

Waiver of strength has been applied for. The results of the of the 60 mg strength can be extrapolated to the 30strength according to conditions in the Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev. 1/Corr** and Guideline on the pharmacokinetic and clinical evaluation of modified release dosage forms (EMA/ CPMP/EWP/280/96 Corr 1).

Pharmacodynamics
No pharmacodynamic studies have been presented.

Clinical efficacy and safety
No new clinical studies to support efficacy and safety of *Dutilox / Zatinex 30 / 60 mg magensaftresistente Hartkapseln* have been provided.

DE/H/4174/001-002/DC:
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.

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Legal Status
Prescription only

User Testing
Readability has been adequately demonstrated.

Risk Management Plan
DE/H/4174/001-002/DC:

Summary of safety concerns	
Important identified risks	• Cardiovascular events: SOC: Cardiac disorders (PTs: Tachycardia, Arrhythmia supraventricular) & SOC: Vascular disorders (PT: Hypertensive crisis) • Hepatobiliary disorders: SOC: Hepatobiliary disorders (PTs: Hepatitis, Liver injury, Hepatic failure, Jaundice) & SOC: Investigations (PT: Hepatic enzyme increased) • SOC: Metabolism and nutrition disorders (PT: Hyperglycaemia) • SOC: Nervous system disorder (PT: Serotonin syndrome) • SOC: Psychiatric disorders (PTs: Suicidal ideation, Suicidal Behaviour) • SOC: Skin and subcutaneous tissue disorders (PT: Stevens-Johnson syndrome) • SOC: Vascular disorders (PT: Haemorrhage)*:* Use in children and adolescents under 18 years of age for the treatment of major depressive disorder. SOC: Psychiatric disorders (PTs: Suicidal ideation, Suicidal Behaviour)
Important potential risks	• SOC: General disorders and administration site conditions (PT: Drug interaction) • Persistent pulmonary hypertension of the newborn after exposure in-utero • Reproductive toxicity
Missing information	• Use in children and adolescents under 18 years of age for the treatment of diabetic peripheral neuropathic pain, generalized anxiety disorder and stress urinary incontinence. • Use in elderly patients • Use in patients with renal impairment

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

DE/H/4175/001-002/DC:

Summary of safety concerns	
Important identified risks	• Hepatic risks: SOC: Hepatobiliary disorders (PTs: Hepatitis, Liver injury, Hepatic failure, Jaundice) & SOC: Investigations (PT: Hepatic enzyme increased) • Suicidality: SOC: Psychiatric disorders (PTs: Suicidal ideation, Suicidal Behaviour) • Hyperglycaemia: SOC: Metabolism and nutrition disorders (PT: Hyperglycaemia) • Stevens-Johnson syndrome: SOC: Skin and subcutaneous tissue disorders (PT: Stevens-Johnson syndrome) • Gastrointestinal tract bleeding: SOC: Gastrointestinal disorders. • Serotonin syndrome: SOC: Nervous system disorder (PT: Serotonin syndrome)
Important potential risks	• Cardiovascular events including those with concomitant use of NSAIDs (including myocardial infarction, heart failure, and stroke) • Upper gastrointestinal tract (UGIT) bleeding events with concomitant use of NSAIDs • Renal Failure
Missing information	• Characterization of the safety and tolerability of duloxetine in paediatric 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

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

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 for the 60 mg strength and extrapolation to the lower strength is considered justified.
The application is approved. For intermediate amendments see current product information.