LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Duloxetin DOC Generici
(duloxetine hydrochloride)

SE/H/1453/01-02/DC

Applicant: DOC Generici Srl

This module reflects the scientific discussion for the approval of Duloxetin DOC Generici. The procedure was finalised on 2015-05-11. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

The application for Duloxetin DOC Generici, 30 mg and 60 mg, gastro-resistant capsule, hard, is a generic application made according to Article 10(1) of Directive 2001/83/EC. The applicant, DOC Generici Srl, apply through the Decentralised Procedure with Sweden acting as reference member state (RMS) and IT as concerned member state (CMS).

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is Yentreve, 20 and 40 mg, gastro-resistant capsule, hard, authorised in the union (central procedure) since 2004, with Eli Lilly Nederland B.V. as marketing authorisation holder.
The reference product used in the bioequivalence study is Cymbalta, 60 mg, gastro-resistant capsule, hard, from Spain (member state of source) with Eli Lilly Nederland B.V. as marketing authorisation holder.

For approved indications, see the Summary of Product Characteristics.

For recommendations to the marketing authorisation not falling under Article 21a/22 of Directive 2001/83 and conditions to the marketing authorisation pursuant to Article 21a or 22 of Directive 2001/83/EC to the marketing authorisation, please see section VI.

II. QUALITY ASPECTS

II.1 Drug Substance

The structure of the drug substance has been adequately proven and its physico-chemical properties are sufficiently described.

The manufacture of the drug substance has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

The drug substance specification includes relevant tests and the limits for impurities and degradation products have been justified. The analytical methods applied are suitably described and validated.

Stability studies confirm the retest period.

II.2 Medicinal Product

The medicinal product is formulated using excipients listed in section 6.1 in the Summary of Product Characteristics.

The manufacturing process has been sufficiently described and critical steps identified.

The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.

Stability studies have been performed and data presented support the shelf life and special precautions for storage claimed in the Summary of Product Characteristics, sections 6.3 and 6.4.

III. NON-CLINICAL ASPECTS

III.1 Discussion on the non-clinical aspects

Since this product has been shown to be essentially similar and refer to a product approved based on a full application with regard to preclinical data, no further such data have been submitted or are considered necessary.

IV. CLINICAL ASPECTS

IV.1 Pharmacokinetics

Duloxetine is administered as a single enantiomer. Duloxetine is well absorbed after oral administration with a C_{max} occurring 6 hours post dose. Food delays the time to reach the peak concentration from 6 to 10 hours and it marginally decreases the extent of absorption (approximately 11%). These changes do not have any clinical significance and therefore there are no restrictions with respect to food in the SmPC of the originator. The elimination half-life of duloxetine ranges from 8 to 17 hours (mean of 12 hours). According to the EPAR of Cymbalta there is an apparent slight non-linear behaviour and more-than-proportional increase in plasma concentration across the duloxetine dosage range of 40 mg/day to 120 mg/day. Nevertheless, the magnitude of the deviation from strictly linear pharmacokinetic behaviour is small. In a study by Zhao et al, linear pharmacokinetics was observed within the range 30-90 mg (Zao et al 2009).

Bioequivalence was evaluated in two single-dose, two-way crossover studies, one in the fed state and one in the fasted state. This is adequate for a delayed-release formulation. Both studies were performed at Algorithme Pharma Inc., Mount-Royal, Quebec, Canada. Both studies compared Duloxetine, 60 mg, gastro-resistant capsules with Cymbalta, 60 mg, gastro-resistant capsules. Blood samples were collected pre-dose and up to 60 hours post-dose. Plasma concentrations of duloxetine were determined with an adequately validated LC/MS/MS method.

The study in the fasted state was conducted in 32 healthy volunteers between 28th October and 17th November 2010. The study design is considered acceptable. For AUC_{0-t} and C_{max} the 90% confidence interval for the ratio of the test and reference products fell within the conventional acceptance range of 80.00-125.00%.

The study in the fed state was conducted in 32 healthy volunteers between 28th October and 15th November 2010. The study design is considered acceptable. The provided meal was a high-fat high-calorie meal according to the definition in the Guideline on the investigation of Bioequivalence (CHMP/QWP/EWP/1401/98 Rev. 1) For AUC_{0-t} and C_{max} the 90% confidence interval for the ratio of the test and reference products fell within the conventional acceptance range of 80.00-125.00%.

From a pharmacokinetic point of view, absence of studies with the additional strength 30 mg is acceptable, as the pharmacokinetics of duloxetine is linear (or possibly slightly non-linear with a mote than proportional increase in plasma concentrations with increasing dose).

Based on the submitted bioequivalence studies, Duloxetine gastro-resistant capsules are considered bioequivalent with Cymbalta gastro-resistant capsules.

IV.2 Discussion on the clinical aspects

Since this product has been shown to be essentially similar and refer to a product approved based on a full application with regard to clinical efficacy/safety data, no further such data have been submitted or are considered necessary.

IV.3 Risk Management Plan

The MAH has submitted a risk management plan (RMP), 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 Duloxetin DOC Generici.

The submitted RMP has been updated in accordance with the reference product and the listed ongoing safety concerns below with routine risk minimisation measures are considered approvable.

Summary of safety concerns:

Important identified risks
1. Hepatic risks
2. Suicidality
3. Hyperglycemia
4. Stevens-Johnson Syndrome
5. Gastrointestinal Tract Bleeding

Important potential risks
7. Cardiovascular events including those with concomitant use of NSAIDs (including myocardial infarction, heart failure, and stroke)
8. Renal Failure

Missing information
10. Prospective data about potential risks of exposure to duloxetine during pregnancy
11. Safety of duloxetine in elderly patients ≥75 years old with concomitant NSAIDs use.

Pharmacovigilance Plan

Not applicable as the application is made for generic product.

V. USER CONSULTATION

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The language used for the purpose of user testing the PIL was Spanish.
The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality of the generic product, Duloxetin DOC Generici, is found adequate. There are no objections to approval of Duloxetin DOC Generici, from a non-clinical and clinical point of view. Bioequivalence between the test and reference product has been adequately demonstrated. The product information is acceptable.
The application is therefore recommended for approval.

List of recommendations not falling under Article 21a/22 of Directive 2001/83 in case of a positive benefit risk assessment

N/A

List of conditions pursuant to Article 21a or 22 of Directive 2001/83/EC

N/A

VII. APPROVAL

The Decentralised procedure for Duloxetin DOC Generici, 30 mg and 60 mg, gastro-resistant capsule, hard, was positively finalised on 2015-05-11.

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Public Assessment Report – Update

Scope	Procedure number	Product Information affected	Date of start of the procedure	Date of end of procedure	Approval/ non approval	Assessment report attached
						Y/N (version)

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