LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Duloxetin Actavis
(duloxetine hydrochloride)

SE/H/1467/01-02/DC

This module reflects the scientific discussion for the approval of Duloxetin Actavis. The procedure was finalised on 2015-06-09. For information on changes after this date please refer to the module 'Update'.

Postadress/Postal address: P.O. Box 26, SE-751 03 Uppsala, SWEDEN
Besöksadress/Visiting address: Dag Hammarskjölds väg 42, Uppsala
Telefon/Phone: +46 (0)18 17 46 00 Fax: +46 (0)18 54 85 66
Internet: www.mpa.se E-mail: registrator@mpa.se

I. INTRODUCTION

The application for Duloxetin Actavis, 20 mg and 40 mg, gastro-resistant capsule, hard, is a generic application made according to Article 10(1) of Directive 2001/83/EC. The applicant, Actavis Group PTC ehf applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and BG, PL and SI as concerned member states (CMS).

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is Yentreve® 20 mg, gastro-resistant capsule, hard, authorised in EU 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 UK with Eli Lilly Nederland B.V. as marketing authorisation holder.
Please note that Yentreve and Cymbalta belong to the same global MA.

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

Bioequivalence was evaluated in two single-dose, two-way crossover studies, one under fasting and one under fed conditions. This is adequate for a delayed-release formulation.

Study 2533/11 was conducted in 36 healthy volunteers, comparing Duloxetine 60 mg, gastro-resistant capsule with Cymbalta, 60 mg, gastro-resistant capsule under fasting conditions. The study was conducted at Lotus Labs Pvt. Ltd., Bangalore, India between 29th August and 9th September 2012. Blood samples were collected pre-dose and up to 72 hours post-dose. The study design is considered acceptable. Plasma concentrations of duloxetine were determined with an adequately validated LC-MS/MS method. 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%.

Study 2534/11 was conducted in 36 healthy volunteers, comparing Duloxetine 60 mg, gastro-resistant capsule with Cymbalta, 60 mg, gastro-resistant capsule under fed conditions (high-fat meal). The study was conducted at Lotus Labs Pvt. Ltd., Bangalore, India between 29th August and 9th September 2012. Blood samples were collected pre-dose and up to 72 hours post-dose. The study design is considered acceptable. Plasma concentrations of duloxetine were determined with an adequately validated LC-MS/MS method. 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%.

Based on the submitted bioequivalence studies under fasting and fed conditions, Duloxetine 60 mg, gastro-resistant capsule (not applied for in the current application) is considered bioequivalent with Cymbalta, 60 mg, gastro-resistant capsule. From a pharmacokinetic point of view, absence of studies with the applied strengths 20 mg and 40 mg is acceptable, as the pharmacokinetics of duloxetine is linear (or possibly slightly non-linear with a more than proportional increase in plasma concentrations with increasing dose).

Bioequivalence has been satisfactorily demonstrated for the 60 mg capsule and the results can be extrapolated to the applied 20 mg and 40 mg strengths.

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, 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 Actavis, 20 mg and 40 mg, gastro-resistant capsule, hard .

Safety specification

Summary table of safety concerns as approved in RMP

Important identified risks	*Hepatic risks* *Suicidality* *Hyperglycaemia* *Steven-Johnson Syndrome* *Gastro-intestinal tract bleeding*
Important potential risks	*Cardiovascular events including those with concomitant use of NSAIDs (including myocardial infarction, heart failure, and stroke)* *Renal failure*
Missing information	*Prospective data about potential risks of exposure to duloxetine during pregnancy* *Use of duloxetine 120mg in elderly patients*

Pharmacovigilance Plan

Routine pharmacovigilance is suggested and no additional pharmacovigilance activities are proposed by the applicant, which is endorsed.

Risk minimisation measures

Routine risk minimisation is suggested and no additional risk minimisation activities are proposed by the applicant, which is endorsed.

Summary of the RMP

The RMP is approved.

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.

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 English.
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 benefit/risk ratio is considered positive and Duloxetin Actavis, 20 mg and 40 mg, gastro-resistant capsule, hard, is 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 Actavis, 20 mg and 40 mg, gastro-resistant capsule, hard, was positively finalised on 2015-06-09.

LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

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)

Postadress/Postal address: P.O. Box 26, SE-751 03 Uppsala, SWEDEN
Besöksadress/Visiting address: Dag Hammarskjölds väg 42, Uppsala
Telefon/Phone: +46 (0)18 17 46 00 Fax: +46 (0)18 54 85 66
Internet: www.mpa.se E-mail: registrator@mpa.se