LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Duloxetine Orion
(duloxetine hydrochloride)

SE/H/1441/01-02/DC

This module reflects the scientific discussion for the approval of Duloxetine Orion. The procedure was finalised on 2015-06-18. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

The application for Duloxetine Orion, 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, Orion Corporation, applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and DK and FI 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, 40 mg, gastro-resistant capsule, hard authorised in the Union 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.

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, which is adequate for a delayed-release formulation.

Study 230-10 was conducted in 48 healthy volunteers, comparing Duloxetine Orion 60 mg, gastro-resistant capsule with Cymbalta, 60 mg, gastro-resistant capsule under fasting conditions. 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 231-10 was conducted in 48 healthy volunteers, comparing Duloxetine Orion 60 mg, gastro-resistant capsule with Cymbalta, 60 mg, gastro-resistant capsule under fed conditions (high-fat meal). 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, Duloxetine Orion, 60 mg, gastro-resistant capsule is considered bioequivalent with Cymbalta, 60 mg, gastro-resistant capsule under fasting and fed conditions.

For a multiple unit delayed-release formulation establishing bioequivalence at one strength only is sufficient provided that the formulations contain identical beads or pellets and that the dissolution profiles are similar. This was the case for Duloxetine Orion. Studying the highest strength is adequate considering that the pharmacokinetics is linear (or possibly slightly non-linear with a more-than-proportional increase in plasma concentration with increasing doses).

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 Orion.

Safety specification

Summary table of safety concerns as approved in RMP

Important identified risks	*Hepatic risks* *Suicidality* *Hyperglycaeamia* *Stevens-Johnsson Syndrome* *Gastrointestinal track 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 120 mg 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 Risk Minimisation Plan

Summary of Safety Concerns and Planned Risk Minimisation Activities as approved in RMP

Safety concern	***Routine risk minimisation***	***Additional risk minimisation activities***
Important identified risks Important identified risks: □ Hepatic risks □ Suicidality □ Hyperglycaemia □ Stevens-Johnson Syndrome □ Gastrointestinal tract	Information given in SmPC sections 4.2, 4.3, 4.4, 4.5, 4.8, 5.1 and 5.2. Other routine risk minimisation measures: □ Prescription only medicine	None proposed

bleeding	□ Close monitoring through routine pharmacovigilance	
Important potential risks □ Cardiovascular events including those with concomitant use of NSAIDs (including myocardial infarction, heart failure and stroke) □ Renal failure	Information given in SmPC sections 4.2, 4.3, 4.4, 4.8 and 5.2. Other routine risk minimisation measures: □ Prescription only medicine □ Close monitoring through routine pharmacovigilance	None proposed
Missing information □ Prospective data about potential risks of exposure to duloxetine during pregnancy □ Safety of duloxetine 120 mg in elderly patients	Information given in SmPC sections 4.2, 4.4, 4.6, 5.1 and 5.2. Other routine risk minimisation measures: □ Prescription only medicine □ Close monitoring through routine pharmacovigilance	None proposed

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

A user consultation with target patient groups on the package leaflet (PL) has been performed on the basis of a bridging report making reference to Cymbalta (EMEA/H/C/000572) as approved in the centralised variation procedure EMEA/H/C/000572-WS/0513. The applicant has proposed a bridging to several of their layouts and describes Orion's standard page layout. The RMS considers the description of standard layout and design positive and well-founded.

The bridging report submitted by the applicant has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The benefit/risk ratio is considered positive and Duloxetine Orion, 30 mg and 60 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 Duloxetine Orion, 30 mg and 60 mg, gastro-resistant capsule, hard was positively finalised on 2015-06-18.

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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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