LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report

Scientific discussion

Duloxetin Teva B.V.
(duloxetine hydrochloride)

SE/H/1884/01-02/DC

This module reflects the scientific discussion for the approval of Duloxetin Teva B.V. The procedure was finalised on 2019-07-30. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

The application for Duloxetin Teva B.V., gastro-resistant capsule, hard, 20 mg and 40 mg, is a generic application made according to Article 10(1) of Directive 2001/83/EC. The applicant, Teva B.V. Netherlands, applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and DE as concerned member state (CMS) for both SE/H/1883/01-02/DC and SE/H/1884/01-02/DC.

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is Yentreve, gastro-resistant capsule, hard, 20 mg and 40 mg 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 gastro-resistant capsule, hard, 60 mg authorised in the Union since 2004, with Eli Lilly Nederland B.V. as marketing authorisation holder.

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

To support the marketing authorisation application the applicant has conducted two bioequivalence studies, one under fasting and one under fed conditions. This is adequate for a delayed-release formulation.

The applied product is a hydroxypropyl methylcellulose (HPMC) capsule and the product tested in the bioequivalence studies was a gelatine capsule. The change in capsule shell was approved in a variation application for the parent DCP of this application (SE/H/1467/001-002/DC) based on dissolution data. The use of the gelatine capsule formulation in the bioequivalence studies is considered acceptable also in this application and the bioequivalence studies are representative for the applied HPMC capsule formulation.

Pharmacokinetic properties of the active substance
Absorption: The absolute oral bioavailability of duloxetine ranged from 32 % to 80 % (mean of 50 %). 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.

Linearity: 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 (Zhao et al 2009).

Elimination: The elimination half-life of duloxetine ranges from 8 to 17 hours (mean of 12 hours).

Study 2533/11
Methods
This was a single-dose, two-way crossover study conducted in 36 healthy volunteers, comparing Duloxetine 60 mg, gastro-resistant capsule with Cymbalta, 60 mg, gastro-resistant capsule under fasting conditions. Blood samples for concentration analysis were collected pre-dose and up to 72 hours post-dose. Plasma concentrations of duloxetin were determined with an LC-MS/MS method. Analysis of variance (ANOVA) was performed on the log-transformed data for AUC_{0-t} and C_{max}. The study was conducted between 29th August and 9th September 2012.

Results
The results from the pharmacokinetic and statistical analysis are presented in

Table **1** below.

Table 1. Study 2533/11: Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range) for duloxetine under fasting conditions, n=28.

Treatment	**AUC_{0-t}** **ng*h/ml**	**C_{max}** **ng/ml**	**t_{max}** **h**
Test	**799.68 ± 371.80**	**43.70 ± 20.39**	**6.25** **3.00-9.00**
Reference	**805.56 ± 408.79**	**43.63 ± 19.63**	**6.00** **4.50-7.50**
***Ratio (90% CI)**	**100.44** **(93.76-107.59)**	**99.21** **(91.65-107.39)**	**-**
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours **C_{max}** maximum plasma concentration **t_{max}** time for maximum plasma concentration			

**calculated based on ln-transformed data*

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
Methods
This was a single-dose, two-way crossover study 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). Blood samples for concentration analysis were collected pre-dose and up to 72 hours post-dose. Plasma concentrations of duloxetin were determined with an LC-MS/MS method. Analysis of variance (ANOVA) was performed on the log-transformed data for AUC_{0-t} and C_{max}. The study was conducted between 29th August and 9th September 2012.

Results
The results from the pharmacokinetic and statistical analysis are presented in Table 2 below.

Table 2. Study 2534/11: Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range) for duloxetine under fed conditions, n=31.

Treatment	**AUC_{0-t}** **ng*h/ml**	**C_{max}** **ng/ml**	**t_{max}** **h**
Test	**1017.74 ± 462.76**	**52.47 ± 21.22**	**9.00** **6.00-16.00**
Reference	**976.96 ± 381.53**	**52.37 ± 20.16**	**7.50** **4.00-12.00**
***Ratio (90% CI)**	**102.19** **(94.79-110.17)**	**99.84** **(91.56-108.87)**	**-**
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours **C_{max}** maximum plasma concentration **t_{max}** time for maximum plasma concentration			

**calculated based on ln-transformed data*

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%.

Bioequivalence studies have been submitted for the 60 mg strength. A biowaiver was sought for the strengths 20 mg, 30 mg and 40 mg.

Discussion and overall conclusion
The bioequivalence studies and its statistical evaluation were in accordance with accepted standards for bioequivalence testing, as stated in the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr). The bioanalytical methods were adequately validated.

Absence of studies with the strengths 20 mg, 30 mg and 40 mg is acceptable, as all conditions for biowaiver for additional strength, as described in the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr) are fulfilled and since the pharmacokinetics of duloxetine is linear (or possibly slightly non-linear with a more than proportional increase in plasma concentrations with increasing dose).

Based on the submitted bioequivalence studies, Duloxetin Teva B.V. is considered bioequivalent with Cymbalta.

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 Teva B.V (SE/H/1884/01-02/DC).

Safety specification
The MAH has submitted the version 5.0 RMP dated 07/09/2018 and proposed the following summary safety concerns:

List of important risks and missing information	
Important identified risks	• Hepatic risks • Suicidality • Hyperglycaemia • Stevens-Johnson Syndrome • Gastrointestinal 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 120 mg in elderly patients

The summary of safety specification is in line with the most recent version of the reference products Cymbalta and Yentreve.

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.
The applicant states that the safety information in the proposed product information is aligned to the reference medicinal product, this is acceptable.

Summary of the RMP
The submitted Risk Management Plan (version 5.0 signed 07/09/2018) is considered acceptable.

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 quality of the generic product, Duloxetin Teva B.V., is found adequate. There are no objections to approval of Duloxetin Teva B.V. from a non-clinical nor clinical point of view. Bioequivalence between the test and reference product has been adequately demonstrated.

The benefit risk of this product is positive and 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/EC 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 Teva B.V. 20 mg and 40 mg gastro-resistant capsule, hard, was positively finalised on 2019-07-30.

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Public Assessment Report – Update

Procedure number*	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse

*Only procedure qualifier, chronological number and grouping qualifier (when applicable)

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