CBG MEB

Public Assessment Report

Scientific discussion

Duloxetine Liconsa 30 mg and 60 mg, gastro-resistant capsules, hard

(duloxetine hydrochloride)

NL/H/3866/001-002/MR

Date: 24 October 2017

This module reflects the scientific discussion for the approval of Duloxetine Liconsa 30 mg and 60 mg, gastro-resistant capsules, hard. The procedure was finalised on 10 August 2017. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

ASMF	Active Substance Master File
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
ERA	Environmental Risk Assessment
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Duloxetine Liconsa 30 mg and 60 mg gastro-resistant capsules, hard, from Laboratorios Liconsa S.A.

The product is indicated for the treatment of:

- major depressive disorder
- diabetic peripheral neuropathic pain
- generalised anxiety disorder

Duloxetine Liconsa is indicated for adults.
A comprehensive description of the indications and posology is given in the SmPC.

This mutual recognition procedure concerns a generic application claiming essential similarity with the innovator product Cymbalta 30 mg and 60 mg gastro-resistant capsules, hard which has been registered in Europe by a centralised procedure (EU/1/04/296) by Eli Lilly Nederland BV since 17 December 2004. For data protection, reference is made to Ariclaim 30 mg and 60 mg gastro-resistant capsules hard which has been registered by centralised procedure EU/1/04/283 since 11 August 2004. Cymbalta and Ariclaim belong to the same global marketing authorisation.

The concerned member states (CMS) involved in this procedure were Denmark, Germany, Iceland, Ireland, Norway, Sweden and the United Kingdom.

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC.

II. QUALITY ASPECTS

II.1 Introduction

Duloxetine Liconsa 30 mg and 60 mg are hard gelatin gastro-resistant capsules. The 30 mg capsules are ink-printed in yellow with “DLX” on the opaque blue cap and “30 mg” on the opaque white body. Each capsule contains 30 mg of duloxetine as hydrochloride. The 60 mg capsules are ink-printed in white with “DLX” on the opaque blue cap and “60 mg” on the opaque green body. Each capsule contains 60 mg of duloxetine as hydrochloride.

The capsules are packed in PVC/PCTFE Aluminium foil blisters.

The excipients are:
capsule content – sugar spheres, maize starch, methacrylic acid-ethyl acrylate copolymer (1:1) dispersion 30% (Eudragit L30D55), hypromellose, sucrose, colloidal anhydrous silica, talc, triethyl citrate, plasacryl T20 (glyceryl monostearate, triethyl citrate, polysorbate 80, water).
capsule shell - titanium dioxide (E171), gelatine, FD&C Blue 2, water, and yellow iron oxide (E172) in the 60 mg capsules.
green ink - shellac, propylene glycol, potassium hydroxide, black iron oxide (E172) and yellow iron oxide (E172).
white ink - shellac, propylene glycol, sodium hydroxide, povidone and titanium dioxide (E171).

The capsule fill of the different strengths is fully dose proportional.

II.2 Drug Substance

The active substance is duloxetine hydrochloride, an established active substance described in the European Pharmacopoeia (Ph.Eur.). Duloxetine hydrochloride can be a white or almost white powder or white to light brownish coloured powder. The active substance is sparingly soluble in water and freely soluble in methanol, ethanol and chloroform and dimethyl sulfoxide. The solubility is not pH

dependent. Duloxetine exhibits polymorphism. The molecule contains one chiral centre and the drug substance is the S-isomer.

The CEP procedure is used for both manufacturers of the active substance. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the European Pharmacopoeia.

Manufacturing process
Since CEPs have been submitted, no details on the manufacturing process have been included.

Quality control of drug substance
The active substance specification is considered adequate to control the quality and is in line with the CEPs and meets the requirements of the monograph in the Ph. Eur. In addition, requirements are included for XRD, particle size and residual solvents. Batch analytical data demonstrating compliance with this specification have been provided for two full scale batches of each supplier.

Stability of drug substance
For both manufacturers, the active substance is stable for 5 years when stored under the stated conditions. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

II.3 Medicinal Product

Pharmaceutical development
The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines. The choice of excipients is justified and their functions explained. The main development studies performed are characterisation of the reference product, formulation development and comparative dissolution studies. For the 60 mg strength a bioequivalence study was performed, and for the 30 mg strength a biowaiver was requested. Sufficient comparative dissolution data of the two strengths have been provided. The dissolution profiles at pH 1.2 (HCl) for two hours followed by pH 6.8 (phosphate buffer), and at pH 4.5 phosphate buffer (2 hours) and pH 6.8 phosphate buffer demonstrate similarity. The pharmaceutical development of the product has been adequately performed.

Manufacturing process
The manufacturing process consists of drug loading of the sugar spheres, drug layer coating, sub coating, enteric coating, and filling of the capsules. The process has been validated according to relevant European/ICH guidelines. Process validation data on the product have been presented for three full-scale pellet batches in accordance with the relevant European guidelines. Process validation for full-scale finished product batches will be performed post authorisation.

Control of excipients
All excipients comply with the requirements of their respective Ph. Eur. Monographs. An in-house specification has been provided for plasacryl and the capsules. These specifications are acceptable.

Quality control of drug product
The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification is based on the relevant monograph in the Ph.Eur. and includes tests for description, identification, assay, uniformity of dosage units (content uniformity), dissolution, degradation products, water content and microbial limits. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. Satisfactory validation data for the analytical methods have been provided. Batch analytical data from three pilot scaled batches of each strength from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product
Stability data on the product has been provided three full scaled batches stored in PVC/PCTFE/Al blister at 25°C/60% RH (18-24 months) and 40°C/75% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. No specific changes or patterns are noted in any of the parameters. A photostability study was carried out on the finished product in the proposed package. It was concluded that the 30 mg and 60 mg capsules formulations are not sensitive to light.
Based on the stability data provided the proposed shelf life of 36 months can be granted for the drug product. No storage conditions are required.

Specific measures for the prevention of the transmission of animal spongiform encephalopathies
There are no substances of ruminant animal origin present in the product except for gelatine. CEPs have been provided for each gelatine supplier.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Duloxetine Liconsa has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product. No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Duloxetine Liconsa 30 mg and 60 mg are 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.2 Discussion on the non-clinical aspects

This product is a generic formulation of Cymbalta, which is available on the European market. Reference is made to the preclinical data obtained with the innovator product. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. Therefore, the member states agreed that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

Duloxetine is a well-known active substance with established efficacy and tolerability.
A clinical overview has been provided, which is based on scientific literature. The overview justifies why there is no need to generate additional clinical data. Therefore, the member states agreed that no further clinical studies are required.

For this generic application, the MAH has submitted two bioequivalence studies, which are discussed below.

IV.1 Pharmacokinetics

The MAH conducted two bioequivalence studies in which the pharmacokinetic profile of the test product Duloxetine Liconsa 60 mg (Laboratorios Liconsa S.A., Spain) is compared with the pharmacokinetic profile of the reference product Cymbalta 60 mg gastro-resistant capsules (Eli Lilly Nederland BV, NL). For both studies the same test and reference products were used. One study was

conducted under fed and one under fasted conditions. This approach is appropriate considering a delayed-release formulation that can be taken with or without food.

The choice of the reference product in the bioequivalence studies is accepted, as it has been registered through a centralised procedure. The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Biowaiver

A biowaiver for the additional 30 mg strength has been granted, based on the following:

- The two strengths are manufactured in same facility using same manufacturing process
- The qualitative composition is the same
- The composition of the strengths is quantitatively proportional
- Linear pharmacokinetics across the strengths
- Comparative dissolution between the two strengths.

Comparative dissolution testing was performed between the biobatch 60 mg and the additional strength of 30 mg under the conditions: pH 1.2 (HCl) for two hours followed by pH 6.8 (phosphate buffer) and pH 4.5 (acetate buffer) for two hours followed by pH 6.0. Under the first condition, the dissolution profiles were comparable for the two strengths. Initially, the second condition was not met due to a high variability with the first measuring point. Therefore, no comparison could be made based on the f2 values. The MAH provided additional data of a dissolution study using similar pH but a different medium, namely: pH 4.5 (phosphate buffer) for 2 hours followed by pH 6.8 (phosphate buffer). In the pH 4.5 phosphate buffer the variability was minor when compared to the pH 4.5 acetate buffer. This adequately demonstrated that the high variability is due the buffer medium and not the pH or drug product. Based on these conclusions, the biowaiver for the 30 mg capsules is considered acceptable.

Bioequivalence studies

Bioequivalence study I - Fasted conditions

Design

A single-dose, randomised, open-label, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 40 healthy male subjects, aged 18-42 years. Each subject received a single dose (60 mg) of one of the 2 duloxetine formulations. The capsule was orally administered after an overnight fast. There were 2 dosing periods, separated by a washout period of 12 days.

Blood samples were collected pre-dose and at 1, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 8, 10, 12, 16, 24, 36, 48 and 60 hours after administration of the products.

The design of the study is acceptable. The wash-out period of 12 days is long enough to prevent carry-over effects as this is more than 5 times duloxetine's mean half-life of 12 hours (range 8-17 hours). The sampling schedule is considered adequate to estimate the pharmacokinetic parameters.

Analytical/statistical methods

The analytical method has been adequately validated and is considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Results

Ten subjects were withdrawn due to adverse events and on medical grounds. Two subjects made a voluntary withdrawal by not reporting back for the second period. One subject was excluded from analysis due to having zero plasma concentrations at all time points in the second period. Therefore, a total of 27 subjects were eligible for pharmacokinetic analysis.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of duloxetine under fasted conditions.

Treatment N=27	**AUC_{0-t}** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h
Test	708 ± 347	38.5 ± 17	6.0 (5.0 – 8.2)
Reference	727 ± 291	41.5 ± 17	6.5 (4.5 – 10.0)
***Ratio (90% CI)**	0.94 (0.87 – 1.02)	0.90 (0.82 – 0.99)	--
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 concentration			

**ln-transformed values*

Safety
Twelve adverse events (AEs) were reported by 11 subjects (7 after test product, 4 after reference product and 1 after post-study assessment) during the conduct of the study. All AEs were mild in nature except for the maculopapular rash (1 subject) and diarrhea (1 subject), which were moderate in nature. All the subjects were followed up until AE resolution.

Bioequivalence study II - Fed conditions
Design
A single-dose, randomised, open-label, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fed conditions in 43 healthy male subjects, aged 21-41 years. Each subject received a single dose (60 mg) of one of the 2 duloxetine formulations. The tablet was orally administered with 250 ml water within 30 minutes after being served a high fat and high calorie vegetarian breakfast. There were 2 dosing periods, separated by a washout period of 10 days.

Blood samples were collected pre-dose and at 1, 2, 3, 4, 5, 5.5, 6, 6.5, 7, 7.5, 8, 8.5, 9, 9.5, 10, 12, 16, 24, 36, 48 and 60 hours after administration of the products.

The design of the study is acceptable. The wash-out period is long enough in view of duloxetine's mean half-life of 12 hours. The sampling schedule is adequate. The breakfast consisted approximately of 150, 250, and 500-600 kcal from protein, carbohydrate, and fat, respectively. The high fat, high calorie breakfast is in accordance to that recommended in the bioequivalence guideline (i.e. high fat of approximately 50 percent of total caloric content of the meal and high-calorie of approximately 800 to 1000 kcal).

Analytical/statistical methods
The analytical method has been adequately validated and is considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Results
One subject was withdrawn from the study due to medical grounds, two subjects quit the study on their own accord and two violated the protocol deviation (positive test result for alcohol consumption between the two periods). Therefore, 38 subjects were eligible for pharmacokinetic analysis.

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of duloxetine under fed conditions.

Treatment N=38	**AUC_{0-t}** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h
Test	1032 ± 441	58.1 ± 23	8.5 (5.5 – 10.0)
Reference	889 ± 364	49.7 ± 16	8.5 (5.0 – 16.0)

***Ratio (90% CI)**	1.15 (1.08 – 1.21)	1.14 (1.05 – 1.24)	--
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 concentration			

**ln-transformed values*

Safety
Six adverse events (AEs) were reported by 3 subjects during the conduct of the study (giddiness, dizziness, headache). All AEs were reported in Period-I and were reported in subjects after administration of reference product. All AEs were mild in nature and all the subjects were followed up until AE resolution. The causality assessment was judged as possibly related to the study drug administered for all the AEs.

Conclusion on bioequivalence studies:
The 90% confidence intervals calculated for AUC_{0-t} and C_{max} for the studies under fed and fasted conditions are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence studies Duloxetine Liconsa is considered bioequivalent with Cymbalta.

The MEB has been assured that the bioequivalence studies have been conducted in accordance with acceptable standards of Good Clinical Practice (GCP, see Directive 2005/28/EC) and Good Laboratory Practice (GLP, see Directives 2004/9/EC and 2004/10/EC).

IV.2 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 Duloxetine Liconsa.

- Summary table of safety concerns as approved in RMP

Important identified risks	- Suicidal thoughts and behavior - Hepatic risks - Gastrointestinal tract bleeding - Hyperglycemia - Stevens-Johnson syndrome
Important potential risks	- Cardiovascular events including those with concomitant use of NSAIDs (including myocardial infarction, heart failure and stroke) - Upper gastrointestinal tract bleeding events with concomitant use of NSAIDs - Renal failure
Missing information	- Elderly patients ≥ 75 years old with concomitant use of NSAIDs - Prospective data about potential risks of exposure to duloxetine during pregnancy - Characterization of the safety and tolerability of duloxetine in pediatric patients

The member states agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

IV.3 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Cymbalta. No new clinical studies were conducted. The MAH demonstrated through

bioequivalence studies that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of this reference product. Risk management is adequately addressed. This generic medicinal product can be used instead of the reference 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.
A group of potential users was asked 14 questions that were formulated addressing the key safety issues and 4 general questions addressing the general impression (design and lay-out) of the leaflet. At least 90% of the participants were able to answer 90% of all questions correctly. Therefore, no amendment of the package leaflet was considered necessary.
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

Duloxetine Liconsa 30 mg and 60 mg gastro-resistant capsules, hard have a proven chemical-pharmaceutical quality and are generic forms of Cymbalta. Cymbalta 30 mg and 60 mg gastro-resistant capsules, hard are well-known medicinal products with an established favourable efficacy and safety profile.

Bioequivalence has been shown to be in compliance with the requirements of European guidance documents, both under fasting and fed conditions.

The Board followed the advice of the assessors. Duloxetine Liconsa was authorized in the Netherlands on 9 March 2016.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The concerned member states, on the basis of the data submitted, mutually recognised the MEB's evaluation for marketing authorisation. Essential similarity has been demonstrated for Duloxetine Liconsa with the reference product. The mutual recognition procedure was finalised with a positive outcome on 10 August 2017.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

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