COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Duloxetine Liconsa 90 mg and 120 mg hard gastro-resistant capsules (duloxetine hydrochloride)

NL/H/5541/001-002/DC

Date: 6 March 2024

This module reflects the scientific discussion for the approval of Duloxetine Liconsa 90 mg and 120 mg hard gastro-resistant capsules. The procedure was finalised on 4 May 2023. 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
EMA	European Medicines Agency
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
RMS	Reference Member State
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 90 mg and 120 mg hard gastro-resistant capsules, from Laboratorios Liconsa S.A.

The product is indicated for: treatment of major depressive disorder and treatment of generalised anxiety disorder in adults.

A comprehensive description of the up-to-date indications and posology is given in the SmPC.

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC, which concerns a hybrid application.

In this decentralised procedure, essential similarity is proven between the new product and the innovator product Cymbalta 60 mg gastro-resistant capsules, which has been registered in the EEA via a centralised procedure (EMEA/H/C/000572).

The concerned member states (CMS) involved in this procedure were Belgium, Finland, Germany, Greece, Hungary, Italy, Luxembourg, Norway, Poland, Portugal, Spain and Sweden.

II. QUALITY ASPECTS

II.1 Introduction

Duloxetine Liconsa is a hard gastro-resistant capsule. The two strengths can be distinguished by the different size, colour and debossing of the tablets.

Duloxetine Liconsa 90 mg is a hard gelatine capsule approximately 21.7 mm with an opaque dark blue cap and opaque light blue body. Each capsule contains as active substance 90 mg of duloxetine.

Duloxetine Liconsa 120 mg is a hard gelatine capsule approximately 23.3 mm with an opaque dark blue cap and opaque blue body. Each capsule contains as active substance 120 mg of duloxetine.

The excipients are:
Capsule content: sugar spheres (sugar syrup, corn starch, sucrose), methacrylic acid-ethyl acrylate copolymer (1:1) dispersion 30%, hypromellose, sucrose, silica (colloidal anhydrous), talc, triethyl citrate, glyceryl monostearate, triethyl citrate and polysorbate 80.
Capsule shell: titanium dioxide (E171), gelatine, FCF - FD&C Blue 1 (brilliant blue FCF) (90 mg only), FD&C Blue 2 (indigo carmine) and yellow iron oxide (E172) (120 mg only).

The two tablet strengths are dose proportional.

The 90 mg capsules are packed in aluminium/aluminium (Alu/Alu) or polyvinylchloride/polychlorotrifluoroethylene-aluminium (PVC/PCTFE-Alu) blisters. The 120 mg gelatine capsules are packed in Alu/Alu blisters.

II.2 Drug Substance

The active substance is duloxetine hydrochloride, an established active substance described in the European Pharmacopoeia (Ph.Eur.), as well as the US Pharmacopoeia. The active substance is crystalline powder and is sparingly soluble in water. The stability during manufacture and storage should be established for one active substance form.

The CEP procedure is used for 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 Ph.Eur.

Manufacturing process

A CEP has been submitted; therefore 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 meets the requirements of the monograph in the Ph.Eur. and CEP. Batch analytical data demonstrating compliance with this specification have been provided for three full scale batches.

Stability of drug substance

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). The retest period for drug substance is not covered by the respective CEP. However, based on the provided stability data the retest period of 5 years is acceptable for drug substance.

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 development of the product has been described, the choice of excipients is justified and their functions explained. The polymorphic stability during manufacturing and storage has been demonstrated. The *in vitro* dissolution method and testing complementary to BE studies is acceptable. The discriminatory power has been adequately demonstrated. The biowaiver of

the additional strength is acceptable from a quality perspective. The pharmaceutical development of the product has been adequately performed.

Manufacturing process

The manufacturing process is a nonstandard process which involves coating, applying of layers, lubrication, filling and packaging. For each layer on the pellets the following steps are performed: preparation of suspension, spraying of suspension, drying and sieving. The manufacturing process has been validated according to relevant European guidelines. Process validation data on the product have been presented for three batches for each strength, in accordance with the relevant European guidelines.

Control of excipients

The excipients comply with Ph.Eur. requirements. 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 includes tests for appearance, identity, assay, uniformity of dosage units, dissolution, related substances, water content and microbiological quality. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. An adequate nitrosamines risk evaluation report has been provided. No risk for presence of nitrosamines in the drug product was identified.

Satisfactory validation data for the analytical methods have been provided.

Batch analytical data from three commercial scale batches from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product

Stability data on the product have been provided for three commercial scale batches per strength stored at 25°C/60% RH (24 months), 30°C/65% RH (12 months) and 40°C/75% RH (6 months) for each strength. The stability was tested in accordance with applicable European guidelines. The drug product is photostable. On basis of the data submitted, a shelf life was granted of 24 months. The labelled storage conditions are store below 30ºC and store in the original blister package in order to protect against moisture.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

Scientific data and/or certificates of suitability issued by the EDQM for gelatine have been provided and compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via medicinal products has been satisfactorily demonstrated.

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 is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment was 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 was made to the preclinical data obtained with the innovator product. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which was 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 hydrochloride is a well-known active substance with established efficacy and tolerability. A clinical overview has been provided, which is based on scientific literature. The member states agreed that no further clinical studies are required, besides the three bioequivalence studies, which are discussed below.

IV.2 Pharmacokinetics

The MAH conducted three bioequivalence studies in which the pharmacokinetic profile of the test product Duloxetine Liconsa 90 mg and 120mg hard gastro-resistant capsules (Laboratorios Liconsa S.A., Spain) was compared with the pharmacokinetic profile of the reference product Cymbalta 60 mg gastro-resistant capsule (Eli Lilly Nederland BV, Netherlands).

The choice of the reference product in the bioequivalence study has been justified by comparison of dissolution study results and composition. The formula and preparation of the bioequivalence batch was identical to the formula proposed for marketing.

Biowaiver

The following general requirements must be met where a waiver for additional strength is claimed, according to the EMA Bioequivalence guideline:

a. the pharmaceutical products are manufactured by the same manufacturing process,
b. the qualitative composition of the different strengths is the same,
c. the composition of the strengths are quantitatively proportional, i.e. the ratio between the amount of each excipient to the amount of active substance(s) is the same for all strengths (for immediate release products coating components, capsule shell, colour agents and flavours are not required to follow this rule),
d. appropriate *in vitro* dissolution data should confirm the adequacy of waiving additional *in vivo* bioequivalence testing.

The dissolution was investigated according to the EMA Bioequivalence guideline. Two dissolution media were used: 2h in pH 4.5 solution and 1.5h in pH 6.8 solution, and 2h in HCl 0.1N + 1.5h in pH 6.8 solution. The experiments showed similarity between the 120 mg and 90 mg strength. The test product (120 mg) is considered bioequivalent to the reference product Cymbalta (2x 60 mg). A biowaiver is claimed for the 90 mg strength.

Bioequivalence studies

Study 1 – 120 mg strength under fasting conditions

Design

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover, open label, balanced bioequivalence study was carried out under fasted conditions in 48 healthy male subjects, aged 25-44 years. The study was conducted in three groups. Each subject received a single dose of one of the two duloxetine hydrochloride formulations (120 mg Duloxetine Liconsa or 2x 60 mg Cymbalta). The tablet was orally administered with 240 mL water after an overnight fast of at least 10 hours. There were two dosing periods, separated by a washout period of 8 days for group I and II, and 13 days for group III.

Blood samples were collected pre-dose and at 1, 2, 3, 4, 4.5, 5, 5.5, 6, 6.5, 7, 7.5, 8, 8.5, 9, 10, 11, 12, 13, 14, 16, 24, 36, 48 and 72 hours after administration of the products.

The design of the study is acceptable.

Duloxetine may be taken without reference to food intake. From the literature it is known that food does not interact with the absorption of duloxetine with clinical significance. The bioequivalence study under fasting conditions is in accordance with CPMP/EWP/QWP/1401/98 Note for Guidance on the investigation of bioavailability and bioequivalence.

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
A total of 48 subjects were enrolled in the study. 48 subjects were dosed in Period I. 17 subjects dropped out due to adverse events (16 vomiting and 1 upper abdominal pain). One subject withdrew on his own accord. One subject failed to report to Period II. 29 subjects were eligible for pharmacokinetic analysis.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of duloxetine, 120 mg under fasted conditions.

Treatment N=29	**AUC_{0-t} (ng.h/mL)**	**$AUC_{0-\infty}$ (ng.h/mL)**	**C_{max} (ng/mL)**	**t_{max} (h)**
Test	2268 ± 861	2397 ± 944	99 ± 31	6.00 (3.00 – 12.00)
Reference	2394 ± 907	2513 ± 977	113 ± 39	6.00 (4.50 – 13.00)
***Ratio (90% CI)**	0.95 (0.90 – 1.01)	0.96 (0.90 – 1.01)	0.89 (0.84 – 0.95)	-

$AUC_{0-\infty}$	Area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t}	Area under the plasma concentration-time curve from time zero to t = 72 hours
C_{max}	Maximum plasma concentration
t_{max}	Time after administration when maximum plasma concentration occurs
CI	Confidence interval

**ln-transformed values*

Study 2 – 120 mg strength under fed conditions
Design
A single-dose, randomised, two-period, two-treatment, two-sequence, crossover, open label, balanced bioequivalence study was carried out under fed conditions in 72 healthy male subjects, aged 25-44 years. The study was conducted in three groups. After an overnight fasting of at least 10 hours, a single (1 x 120 mg capsule Duloxetine Liconsa or 2 x 60 mg Cymbalta) dose was administered to the subjects at 30 minutes after serving the standardised high-fat & high-calorie breakfast (252 g carbohydrates, 523 g fat and 150 g protein) with 240 mL of water. A single dose of 1 mL of dimenhydrinate solution for injection (50 mg/mL) was administered intramuscularly (IM) to the subjects approximately 30-45 minutes prior to dosing and at approximately 3 hours after dosing in each period for the prevention of nausea and vomiting induced by study drug. There were two dosing periods, separated by a washout period of 8 days for group I and II, and 7 days for group III.

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, 11, 12, 13, 14, 16, 24, 36, 48 and 72 hours after administration of the products.

The design of the study is acceptable.

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
A total of 72 subjects enrolled in the study. Five subjects withdrew due to adverse events (vomiting). One subject withdrew due to injury and another four dropped out due to protocol deviation. Three subjects withdrew for personal reasons. Two subjects did not report to period II. 57 subjects were eligible for pharmacokinetic analysis.

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of duloxetine, 120 mg under fed conditions.

Treatment N=57	**AUC_{0-t} (ng.h/mL)**	**$AUC_{0-\infty}$ (ng.h/mL)**	**C_{max} (ng/mL)**	**t_{max} (h)**
Test	2524 ±1572	2688 ± 1828	118 ± 64	7.00 (3.00 – 13.00)
Reference	2490 ± 1491	2645 ± 1712	125 ± 71	6.50 (3.00 – 13.00)
***Ratio (90% CI)**	0.99 (0.95 – 1.04)	0.99 (0.95 – 1.04)	0.93 (0.86 – 1.00)	-

$AUC_{0-\infty}$	Area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t}	Area under the plasma concentration-time curve from time zero to t = 72 hours
C_{max}	Maximum plasma concentration
t_{max}	Time after administration when maximum plasma concentration occurs
CI	Confidence interval

**ln-transformed values*

Study 3 - 120 mg strength under fasting conditions, sprinkled on apple sauce
Design
A single-dose, randomised, two-period, two-treatment, two-sequence, crossover, open label, balanced bioequivalence study was carried out under fasted conditions in 60 healthy male subjects, aged 25-44 years. The study was conducted in two groups. After an overnight fasting of at least 10 hours each subject received a single dose (120 mg) of one of the two duloxetine hydrochloride formulations. The entire content of one capsule (120 mg) of the test product was sprinkled on a teaspoonful (approximately 5 grams) of room temperature apple sauce, and the reference product (2x 60 mg) was administered normally with 240 mL of water. A single dose of 1 mL of dimenhydrinate solution for injection (50 mg/mL) was administered intramuscularly (IM) to the subjects approximately 30-45 minutes prior to dosing and at approximately 3 hours after dosing in each period for the prevention of nausea and vomiting induced by study drug. There were two dosing periods, separated by a washout period of 7 days for group I and 9 days for group II. The dosing interval between doses was 9 days for group I and 7 days for group II.

Blood samples were collected pre-dose and at 1, 2, 3, 4, 4.5, 5, 5.5, 6, 6.5, 7, 7.5, 8, 8.5, 9, 10, 11, 12, 13, 14, 16, 24, 36, 48 and 72 hours after administration of the products.

The design of the study is acceptable.

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
60 subjects enrolled in the study. Four subject dropped out due to adverse events (vomiting and abdominal pains. One subject withdrew due to personal reasons and one subject was dropped due to protocol deviation. 54 subjects were eligible for pharmacokinetic analysis.

Table 3. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of duloxetine, 120 under fasted conditions.

Treatment N=54	**AUC_{0-t} (ng.h/mL)**	**$AUC_{0-\infty}$ (ng.h/mL)**	**C_{max} (ng/mL)**	**t_{max} (h)**
Test	2197 ± 1253	2323 ± 1404	103 ± 44	6.00 (4.50 – 11.00)
Reference	2249 ± 1539	2398 ± 1785	103 ± 50	6.50 (4.50 – 12.00)
***Ratio (90% CI)**	1.00 (0.95 – 1.05)	1.00 (0.95 – 1.05)	1.01 (0.95 – 1.06)	-

$AUC_{0-\infty}$	Area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t}	Area under the plasma concentration-time curve from time zero to t = 72 hours
C_{max}	Maximum plasma concentration
t_{max}	Time after administration when maximum plasma concentration occurs
CI	Confidence interval

**ln-transformed values*

Conclusion on (three) bioequivalence studies:
The 90% confidence intervals calculated for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence studies Duloxetine Liconsa 120 mg is considered bioequivalent with Cymbalta, 2x 60 mg.

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.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 Duloxetine Liconsa.

Table 4. Summary table of safety concerns as approved in RMP

Important identified risks	Suicidality
Important potential risks	None
Missing information	None

The member states agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information. Specific follow-up forms are in place for the safety concern “Suicidality”.

IV.4 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 three 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 (PL) 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 test consisted of: a pilot test with two participants, followed by two rounds with 10 participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. The results show that the PL 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 90 mg and 120 mg hard gastro-resistant capsules have a proven chemical-pharmaceutical quality and are generic forms of Cymbalta 60 mg gastro-resistant capsules. Cymbalta is a well-known medicinal product with an established favourable efficacy and safety profile.

Bioequivalence has been shown to be in compliance with the requirements of European guidance documents.

The Board followed the advice of the assessors.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted,

considered that essential similarity has been demonstrated for Duloxetine Liconsa with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 4 May 2023.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

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