COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Duloxetine Amarox 20 mg, 30 mg, 40 mg and 60 mg, hard gastro-resistant capsules

(duloxetine hydrochloride)

NL/H/4619/001-004/MR

Date: 21 December 2021

This module reflects the scientific discussion for the approval of Duloxetine Amarox 20 mg, 30 mg, 40 mg and 60 mg, hard gastro-resistant capsules. The procedure was finalised at 7 September 2021. 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 Amarox 20 mg, 30 mg, 40 mg and 60 mg, hard gastro-resistant capsules, from Amarox Pharma B.V.

The products are indicated in adults:
20 and 40 mg product

- for women for the treatment of moderate to severe Stress Urinary Incontinence (IUD).

30 and 60 mg product

- treatment of major depressive disorder, diabetic peripheral neuropathic pain and generalised anxiety disorder.

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 two innovator products: Yentreve 20 mg and 40 mg hard gastro-resistant capsules, which have been registered in the EEA by Eli Lilly Nederland B.V. since 11 August 2004 through a centralised procedure (EMEA/H/C/000545), and Cymbalta 30 mg and 60 mg, gastro-resistant capsules which have been registered since 2004 through a centralised procedure (EMEA/H/C/000572).

The concerned member states (CMS) involved in this procedure were Germany (all strengths), Sweden (30 mg and 60 mg products) and Spain (30 mg and 60 mg products).

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

II. QUALITY ASPECTS

II.1 Introduction

Duloxetine Amarox are hard gastro-resistant capsules, filled with white to off white colored pellets. The four different strengths can be distinguished by the colours of the cap and body, the imprints, and the capsule size.

- The 20 mg capsule has an opaque green cap and opaque green body, imprinted with ‘H’ on cap and ‘190’ on body.
- The 30 mg capsule has an opaque blue cap and opaque white body, imprinted with ‘H’ on cap and ‘191’ on body.

- The 40 mg capsule has an opaque blue cap and opaque orange body, imprinted with 'H' on cap and 'D3' on body with black ink.
- The 60 mg capsule has an opaque blue cap and opaque green body, imprinted with 'H' on cap and '192' on body.

Each capsule contains as active substance respectively 20 mg, 30 mg, 40 mg or 60 mg of duloxetine (as hydrochloride).

The hard gastro-resistant capsules are packed in Aluminium-Aluminium blisters.

The excipients are:

Capsule contents of all strengths – sugar spheres (containing maize starch and sucrose) Hypromellose (E464), crospovidone, talc, sucrose, carboxy methyl ethyl cellulose, povidone, titanium dioxide (E171), macrogol (E1521) and polysorbate 80 (E433)

Capsule shell

- 20 mg - gelatine, titanium dioxide (E171), sodium laurilsulfate, iron oxide yellow (E172) and indigo carmine (E132)
- 30 mg - gelatine, titanium dioxide (E171), sodium laurilsulfate and indigo carmine (E132)
- 40 mg - gelatine, titanium dioxide (E171), sodium laurilsulfate, indigo carmine (E132), iron oxide yellow (E172) and iron oxide red (E172)
- 60 mg - gelatine, titanium dioxide (E171), sodium laurilsulfate, indigo carmine (E132) and iron oxide yellow (E172)

Printing (edible) ink

- 20 mg - shellac (E904), propylene glycol, black iron oxide (E172) and potassium hydroxide
- 30 mg - shellac (E904), propylene glycol and yellow iron oxide (E172)
- 40 mg - shellac (E904), propylene glycol, black iron oxide (E172) and potassium hydroxide
- 60 mg - shellac (E904), propylene glycol, potassium hydroxide and titanium dioxide (E171)

The excipients and packaging are usual for this type of dosage form.
The four capsule strengths are dose proportional with regard to duloxetine.

II.2 Drug Substance

The active substance is duloxetine hydrochloride, an established active substance described in the European Pharmacopoeia (Ph.Eur.). The active substance is sparingly soluble in water. The substance exhibits polymorphism. The molecule contains one chiral centre and the drug substance is the S-isomer.

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. The specification is including additional requirements for in-house impurity A, powder X-ray diffraction, particle size and microbiology. Batch analytical data demonstrating compliance with this specification have been provided for two batches.

Stability of drug substance

The active substance is stable for 60 months if stored in a double polyethylene bag (outer black) placed in a polyethylene drum. 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 are explained.

The main development studies performed are characterisation of the reference product, formulation development and comparative dissolution studies. The bioequivalence (BE) study was performed with the 60 mg drug product. The batch used in the BE study contains the same bulk pellets and is manufactured in the same way as the future commercial batches. The BE batch is of sufficient size in relation to the intended commercial batch size. The reference batch was obtained in Germany. A biowaiver has been requested for the lower products strengths. The pharmaceutical development of the product has been adequately performed.

Manufacturing process

The manufacturing process has been validated according to relevant European/ICH guidelines. The process consists of drug loading of the sugar spheres, sub coating, enteric coating, film coating, filling in capsules and packaging. Process validation data on the

product have been presented for three full scale batches of each strength, as is required for non-standard processes.

Control of excipients

All excipients used comply with the requirements of their respective Ph.Eur. monographs. An in-house specification has been provided for carboxy methyl ethyl cellulose and the empty capsules. The specifications were acceptable, where relevant functionality related characteristics were included.

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 description, identification, average weight of filled capsules, average net fill content, lock length, water content, uniformity of dosage units (content uniformity), dissolution, assay, related substances, residual solvents, microbial limits and identification of the colorant. The release and shelf life limits are identical except for the limit for total impurities. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. The drug product specification is acceptable.

Satisfactory validation data for the analytical methods have been provided.

Batch analytical data from three full scale batches of each strength from the proposed production sites have been provided, demonstrating compliance with the release specification.

Stability of drug product

Stability data on the product have been provided for three full scaled batches stored in Al/Al blisters at 25°C/60% RH (12-36 months) and 40°C/75% RH (six months). The conditions used in the stability studies are according to the ICH stability guideline. The same results were observed in all capsule strengths at all conditions. No specific changes or patterns are noted in any of the parameters. Some changes are noted in water content. However, no significant changes are noted, all results remain well within specification. Dissolution is conform specification, the level impurities remains well below the limit. Assay results show little variability.

Based on the stability data provided, a shelf life of 36 months was granted for the drug products. No special storage conditions need to be included in the SmPC or on the label.

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

None of the materials used is of animal or human origin except for gelatine. Scientific data and/or certificates of suitability issued by the EDQM 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 Amarox 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 Amarox is 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

These products are generic formulations of Yentreve and Cymbalta which are 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 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 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 for the 60 mg strength, which are discussed below. A biowaiver is applied for the other strengths.

IV.2 Pharmacokinetics

The MAH conducted two bioequivalence studies in which the pharmacokinetic profile of the test products Duloxetine Amarox 60 mg, hard gastro-resistant capsules (Amarox Pharma B.V., the Netherlands) were compared with the pharmacokinetic profile of the reference product Cymbalta 60 mg hard gastro-resistant capsules (Eli Lilly Nederland B.V., the Netherlands):

- Study I - A bioequivalence study under fasted conditions with the 60 mg strength
- Study II - A bioequivalence study under fed conditions with the 60 mg strength

The study under fasted and fed conditions is performed to distinguish the effect of food on the absorption of deluxetine in the blood.

Biowaiver

The MAH requested a biowaiver for the 20 mg, 30 mg and 40 mg strengths, based on the *Guideline on the investigation of bioequivalence*. The following criteria for a biowaiver have been met: the products are manufactured by the same manufacturing process, the qualitative composition of the different strengths is the same and the composition of the strengths are quantitatively proportional. Furthermore, the provided in vitro dissolution studies were performed in accordance with the *Guideline on investigation of bioequivalence*. All three products show similar drug release profiles to the 60 mg strength.

In conclusion, conducting the two bioequivalence studies using the 60 mg strength is acceptable, and the results can be extrapolated to the other three, lower strengths. The biowaiver was granted.

Bioequivalence studies

The choice of the reference products

The choice of the reference product in both bioequivalence studies has been justified. The formula and preparation of the bioequivalence batches are identical to the formula proposed for marketing.

Analytical/statistical methods

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

Bioequivalence study I – 60 mg strength under fasting conditions

Design

An open label, single-dose, randomised, two-period, two-treatment, two-sequence, crossover comparitive bioequivalence study was carried out under fasted conditions in 56 healthy, male subjects, aged 19-43 years. Each subject received a single dose (60 mg) of one of the two duloxetine formulations. The tablet was orally administered with 240 ml water

after an overnight fast. There were two dosing periods, separated by a washout period of seven days.

Blood samples were collected pre-dose and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.33, 4.67, 5, 5.33, 5.67, 6, 6.33, 6.67, 7, 7.5, 8, 9, 10, 12, 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
Out of the 56 subjects, 52 subjects were eligible for pharmacokinetic analysis. One subject was withdrawn from the study due to adverse events (nausea and vomiting) during period II, one subject withdrew consent in period I and one did not check in for period II. The fourth subject was not included in the statistical description and analysis as that subject did show abnormal plasma concentration in the first period (did not show positive plasma concentrations after intake of the reference product).
The reasons for the dropouts are acceptable.

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

Treatment N=52	**AUC_{0-t} (ng.h/ml)**	**$AUC_{0-\infty}$ (ng.h/ml)**	**C_{max} (ng/ml)**	**t_{max} (h)**
Test	1183 ± 538	1245 ± 584	62.7 ± 23.6	5.0 ± 1.15
Reference	1178 ± 492	1231 ± 528	65.0 ± 25.2	5.0 ± 0.97
***Ratio (90% CI)**	0.99 0.94 - 1.04	--	0.97 0.92 - 1.03	--
CV (%)	16.2	--	--	--

$AUC_{0-\infty}$ 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 hours
C_{max} maximum plasma concentration
CI confidence interval
t_{max} time for maximum concentration
CV coefficient of variation

**ln-transformed values*

Bioequivalence study II – 60 mg strength under fed conditions

Design

An open label, single-dose, randomised, two-period, two-treatment, two-sequence, crossover comparitive bioequivalence study was carried out under fasted conditions in 48 healthy male subjects, aged 20-43 years. Each subject received a single dose (60 mg) of one of the two duloxetine formulations. After an overnight fasting of 10 hours, a standard non-vegetarian, high-calorie, high-fat breakfast in total was provided to the study subjects 30 minutes prior to scheduled dosing time. The breakfast consisted of bread and butter, egg omelette with butter, French fries, whole milk with sugar and chicken tikka with garnish, alltogether good for 918.70 kcal. The tablet was orally administered with 240 ml water. There were two dosing periods, separated by a washout period of seven days.

Blood samples were collected pre-dose and at 1, 2, 3, 4, 5, 6, 7, 7.5, 8, 9, 9.5, 10, 10.5, 11, 12, 13, 14, 16, 18, 24, 36, 48.00 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

Out of the 48 subjects, 44 subjects were eligible for pharmacokinetic analysis. One subject withdrawn due to adverse events (nausea and vomiting) during period I, and two subjects did not check in for period II. The fourth subject was not included in the statistical description and analysis as that subject did show abnormal plasma concentration in the first period (did not show positive plasma concentrations after intake of the reference product).
The reasons for the dropouts are acceptable.

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

Treatment N=44	**AUC_{0-t}** (ng.h/ml)	**$AUC_{0-\infty}$** (ng.h/ml)	**C_{max}** (ng/ml)	**t_{max}** (h)
Test	1357 ± 679	1440 ± 787	67.4 ± 25.3	7.5 ± 2.2
Reference	1325 ± 628	1406 ± 716	72.2 ± 26.6	6.0 ± 1.3
***Ratio (90% CI)**	1.02 0.96 - 1.08	0.93 0.87 - 0.99	--	--
CV (%)	15.7	17.3	--	--

$AUC_{0-\infty}$	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 hours
C_{max}	maximum plasma concentration
CI	confidence interval
t_{max}	time for maximum concentration
CV	coefficient of variation

**ln-transformed values*

Conclusion on bioequivalence studies

The pharmacokinetic variables are comparable between both treatments. For both 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 Amarox 60 mg, hard gastro-resistant capsules are considered bioequivalent with Cymbalta 60 mg hard gastro-resistant capsules under both fasting and fed conditions.

The MEB has been assured that the bioequivalence study has 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 Amarox.

Table 3. 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.

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator products Yentreve and Cymbalta. No new clinical studies were conducted. The MAH demonstrated through bioequivalence studies that the pharmacokinetic profile of the 60 mg product is similar to the pharmacokinetic profile of the reference product Cymbalta. A biowaiver was granted for the 20 mg, 30 mg and 40 mg strengths. Risk management is adequately addressed. These generic medicinal products can be used instead of the reference products.

V. USER CONSULTATION

A user consultation with target patient groups on the package leaflets (PL) has been performed on the basis of two bridging reports. For the 20 mg and 40 mg strengths, reference has been made to the centrally authorised PL of Yentreve 20 mg and 40 mg, hard gastro-resistant capsules (EMEA/H/C/000545) for content, and the PL of Levetiracetam Hetero 750 mg film-coated tablets for layout (German Marketing Autorisation number Zul.Nr.83762.00.00-83765.00.00). For the 30 mg and 60 mg strengths, reference has been made to the centrally authorised PL of Cymbalta 30 mg and 60 mg hard gastro-resistant capsules (EMEA/H/C/000572) for content, and the PL of Levetiracetam Hetero 750 mg film-coated tablets for layout. Both bridging reports submitted by the MAH have been found acceptable; bridging is justified for both content and layout of the leaflets.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Duloxetine Amarox 20 mg, 30 mg, 40 mg and 60 mg, hard gastro-resistant capsules have a proven chemical-pharmaceutical quality and are generic forms of Yentreve 20 mg and 40 mg, hard gastro-resistant capsules and Cymbalta 30 mg and 60 mg hard gastro-resistant capsules. Yentreve and Cymbalta are both 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.

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 Amarox with the reference product, and have therefore granted a marketing authorisation. The mutual recognition procedure was finalised with a positive outcome on 7 September 2021.

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