CBG MEB

Public Assessment Report

Scientific discussion

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

(duloxetine hydrochloride)

NL/H/3305/001-004/DC

Date: 20 July 2018

This module reflects the scientific discussion for the approval of Onelar 20 mg, 30 mg, 40 mg and 60 mg gastro-resistant capsules, hard. The procedure was finalised on 8 February 2016. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

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
USP	United States Pharmacopoeia

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Onelar 20 mg, 30 mg, 40 mg and 60 mg gastro-resistant capsules, hard, from Medochemie Limited.

The 20 mg and 40 mg product is indicated in adult women for the treatment of:
- moderate to severe Stress Urinary Incontinence (SUI)

The 30 mg and 60 mg product is indicated in adults for:
- treatment of major depressive disorder
- treatment of diabetic peripheral neuropathic pain
- treatment of generalised anxiety disorder

A comprehensive description of the indications and posology is given in the SmPC.

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Yentreve/Cymbalta 20 mg, 30 mg, 40 mg and 60 gastro-resistant capsules, hard (EU/1/04/280) which has been registered in Europe by a centralised procedure by Eli Lilly Nederland B.V. since 11 August 2004.

The concerned member states (CMS) involved in this procedure were:
20 mg and 40 mg – Cyprus, Croatia, Lithuania, Malta and Romania.
30 mg and 60 mg – Bulgaria, Cyprus, Czech Republic, Estonia, Greece, Croatia, Lithuania, Malta, Romania and Slovakia.

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

II. QUALITY ASPECTS

II.1 Introduction

Onelar 20 mg, 30 mg, 40 mg and 60 mg are hard gelatine gastro-resistant capsules filled with off white pellets.

- The 20 mg “size 4” capsules have a white body and turquoise cap. Each capsule contains 20 mg of duloxetine (as hydrochloride).
- The 30 mg “size 3” capsules have a white body and blue cap. Each capsule contains 30 mg of duloxetine (as hydrochloride).
- The 40 mg ‘size 2” capsules have a blue body and dark blue cap. Each capsule contains 40 mg of duloxetine (as hydrochloride).
- The 60 mg “size 0” capsules have a light grey body and pink cap. Each capsule contains 60 mg duloxetine (as hydrochloride).

The capsules are packed in PA/Al/PVC-Alu blisters and transparent PVC/PE/PVDC-Alu Blisters.

The excipients are:

Pellet Core - sugar spheres (sucrose, maize starch)
Pellet Coating - hypromellose 2910/5mPa·s, crospovidone Type A, sucrose, hypromellose acetate succinate, triethyl citrate (E1505), talc, macrogol 8000 and titanium dioxide
Capsule shell - titanium dioxide (E171), gelatine, patent blue V(E131), sodium laurilsulfate (30 mg, 40 mg and 60 mg strengths), carmoisine (E122) (30 mg, 40 mg strengths), erythrosine (60 mg strength), red iron oxide (E172) (60 mg strength) and black iron oxide (E172) (60 mg strength)

The different strengths of the product are 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. It is sparingly soluble in water, freely soluble in methanol and practically insoluble in hexane. Duloxetine hydrochloride exhibits polymorphism; Form A is consistently produced.

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 Ph.Eur.

Manufacturing process
CEPs have 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 is in line with the CEPs and meets the requirements of the monograph in the Ph.Eur. In addition, in-house methods are used for particle size and residual solvent determination. Batch analytical data demonstrating compliance with this specification have been provided for 4 batches (two batches per manufacturer).

Stability of drug substance
The active substance is stable for 24 months when stored under the stated conditions. Assessment thereof was part of granting the CEPs and has been granted by the EDQM. It is deemed acceptable that the claimed retest period is more stringent than the retest period mentioned in the CEPs.

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. A bioequivalence study has been performed with the 60 mg strength. For the 20 mg, 30 mg and 40 mg strengths a biowaiver was requested. Dissolution data of the biobatch of the test and reference product were compared in pH 6.8 after 2 hours in 0.1N HCl and in pH 4.5. These conditions are in accordance with the requirements as indicated in the guidance. The dissolution profiles were similar. The calculated f_2 values are above 50. The pharmaceutical development of the product has been adequately performed.

Manufacturing process
The manufacturing process comprises of the following phases: pellet preparation, drug coating, seal coating, enteric coating and over-coating, encapsulation and packaging. The manufacturing process has been validated according to relevant European/ICH guidelines. It is considered a non-standard manufacturing process. Process validation data on the product have been presented for three full scale batches of each strength in accordance with the relevant European guidelines.

Control of excipients
All excipients comply with the requirements of their respective Ph.Eur. monographs. An in-house specification has been provided for hard gelatine capsules. Hypromellose acetate succinate is tested according to the United States Pharmacopoeia (USP) monograph. 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, average weight, identification, dissolution, water content, assay, uniformity of dosage units by content uniformity, related substances and microbial control. The shelf-life specification is identical to the release specification except the limit for water

content. 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 3 batches of each strength from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product
Stability data have been provided for a sufficient amount of batches per strength stored at 25°C/60% RH (long term), 30ºC/75% RH (intermediate) and 40°C/75% RH (accelerated). The conditions used in the stability studies are according to the ICH stability guideline. Production scale batches packed in PA/ALU/PVC-Alu blisters were stored for 12 months at long term and 6 months at accelerated conditions. Production scale batches packed in PVC/PE/PVDC-Alu blisters were stored for 18 months at long term and 6 months at accelerated conditions.
Based on the available stability data a shelf life of 24 months is granted when packed in PA/ALU/PVC-Alu blisters, without any special storage conditions. A shelf life of 12 months is granted, packed in PVC/PE/PVDC-Alu blisters and with storage condition: “Store below 30ºC in the original packing in order to protect from moisture”. It is demonstrated that the drug product is photostable.

Specific measures concerning 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 Onelar 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 Onelar 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

This product is a generic formulation of Yentreve 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.2 Pharmacokinetics

The MAH conducted two bioequivalence studies in which the pharmacokinetic profile of the test product Onelar 60 mg gastro-resistant hard capsules (Medochemie Limited, Cyprus) is compared with the pharmacokinetic profile of the reference product Cymbalta 60 mg gastro-resistant hard capsules (Eli Lilly Nederland B.V., The Netherlands). 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
The choice of the reference product in the bioequivalence studies is accepted. The use of Cymbalta as a reference product is acceptable as it was registered through a centralised procedure and is part of the same global marketing authorisation as Yentreve. The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Biowaiver
A biowaiver for the additional 20 mg, 30 mg and 40 mg strengths has been granted, based on the following:

- The strengths are manufactured by the same manufacturing process
- The qualitative composition of the different strengths is the same
- The composition of the strengths is quantitatively proportional
- Satisfactory comparative dissolution between strengths was provided

The MAH has provided comparative dissolution data of the biobatch of the test and reference product in pH 6.8 after two hours in 0.1N HCl and in pH 4.5. The f_2 calculations showed similarity (>50). Comparison of the 20 mg, 30 mg and 40 mg with the 60 mg product (biobatch), show the same results; the f_2 calculations support the findings that dissolution for all strengths is similar to the biobatch.

Bioequivalence studies

Bioequivalence study I - Fasted conditions
Design
A single-dose, randomised, open-label, two-treatment, two-period, two sequence, cross-over bioequivalence study was carried out under fasted conditions in 72 healthy male (n=28) and female (n=44) subjects, aged 18-57 years. Each subject received a single dose (60 mg) of one of the 2 duloxetine formulations. The capsule was orally administered with 200 ml water after an overnight fasting of at least 8 hours. There were 2 dosing periods, separated by a washout period of 7 days.

Blood samples were collected at pre-dose and at 1, 2, 3, 4, 5, 5.5, 6, 6.5, 7, 8, 9, 9.5 10, 10.5, 11, 12, 14, 18, 24, 36, 48 and 72 hours after administration of the products.

The design of the study is acceptable. Subjects using drugs which can modify CYP1A2 and CYP2D6 enzymes were excluded. This is agreed as duloxetine is extensively metabolised by CYP1A2 and CYP2D6.

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
Six subjects discontinued the study due to adverse events. 66 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=66	AUC_{0-t} ng.h/ml	C_{max} ng/ml	t_{max} h
Test	424 ± 301	24.9 ± 16	6.5 (3.0 - 11.0)
Reference	427 ± 303	26.5 ± 15	5.0 (2.0 - 9.0)
***Ratio (90% CI)**	0.99 (0.93 – 1.05)	0.93 (0.87 - 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*

Bioequivalence study II - Fed conditions

Design

A single-dose, randomised, open-label, two-treatment, two-period, two sequence, cross-over bioequivalence study was carried out under fed conditions in 44 healthy male (n=25) and female (n=19) subjects, aged 18-53 years. Each subject received a single dose (60 mg) of one of the 2 duloxetine formulations. The tablet was orally administered with 200 ml water 30 minutes after being served a standard high-fat, high-calories breakfast (1 slice of bread, 2 boiled eggs, 10 g butter, 1 bacon slice, 125 g French fries, 250 ml whole milk). There were 2 dosing periods, separated by a washout period of 7 days.

Blood samples were collected at pre-dose and at 1, 2, 3, 4, 5, 5.5, 6, 6.5, 7, 8, 9, 9.5 10, 10.5, 11, 12, 14, 18, 24, 36, 48 and 72 hours after administration of the products.

The design of the study is acceptable. The nutrient content of the breakfast is in accordance to the recommended high fat and high calorie meal. Subjects using drugs which can modify CYP1A2 and CYP2D6 enzymes were excluded. This is agreed as duloxetine is extensively metabolised by CYP1A2 and CYP2D6.

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 dropped out of the study due to vomiting after administration and another subject due to a personal reason. 42 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=42	AUC_{0-t} ng.h/ml	C_{max} ng/ml	t_{max} h
Test	442 ± 263	32.8 ±18	6.5 (1.0 - 9.0)
Reference	401 ± 268	29.7 ± 17	7.0 (3.0 - 11.0)
***Ratio (90% CI)**	1.12 (1.06 – 1.18)	1.12 (1.05 – 1.19)	--
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*

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

Both formulations were found to be safe and equally well-tolerated based on the two bioequivalence studies.

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 Onelar.

Summary table of safety concerns as approved in RMP:

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) • Upper gastrointestinal (UGIT), bleeding events with concomitant use of NSAIDs • Renal failure
Missing information	• Characterisation of the safety and tolerability of duloxetine in paediatric patients • Prospective data about potential risk of exposure during pregnancy • Safety of duloxetine in elderly patients ≥75 years of age with concomitant NSAIDs use

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 product Yentreve. No new clinical studies were conducted. The MAH demonstrated through a bioequivalence study 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

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 Yentreve and Cymbalta. The report showed that the proposed PL is identical to the centrally authorised leaflets. The layout was tested. Therefore, the bridging report submitted by the MAH has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Onelar 20 mg, 30 mg, 40 mg and 60 mg gastro-resistant capsules, hard, have a proven chemical-pharmaceutical quality and are generic forms of Yentreve 20 mg, 30 mg, 40 mg and 60 mg gastro-resistant capsules, hard. Yentreve 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 Onelar 20 mg, 30 mg, 40 mg and 60 mg with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 8 February 2016.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE – SUMMARY

Scope	Procedure number	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval/ non approval	Assessment report attached
To extend the shelf life of the finished product from 12 to 24 months for the PVC/PE/PVDC-Alu blisters and from 24 to 36 months for the PA/Al/PVC-Alu blisters in accordance with the currently available stability data	NL/H/3305/ 001-004/IB/001	IB	25-8-2016	24-9-2016	Approval	No