CBG MEB

Public Assessment Report

Scientific discussion

Duloxetine Sandoz 20 mg and 40 mg, gastro-resistant capsules, hard

(duloxetine hydrochloride)

NL/H/3322/001-002/DC

Date: 4 January 2017

This module reflects the scientific discussion for the approval of Duloxetine Sandoz 20 mg and 40 mg, gastro-resistant capsules, hard. The procedure was finalised on 15 January 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

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Duloxetine Sandoz 20 mg and 40 mg, gastro-resistant capsules, hard, from Sandoz B.V.

The product is indicated for women for the treatment of moderate to severe Stress Urinary Incontinence (SUI). The product is indicated for adults.

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 20 mg and 40 mg gastro-resistant capsules, hard (EU/1/04/280) which has been registered in Europe by a centralised procedure by Eli Lilly Nederland BV since 11 August 2004.

The concerned member state (CMS) involved in this procedure was Germany.

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

II. QUALITY ASPECTS

II.1 Introduction

Duloxetine Sandoz 20 mg and 40 mg are hard gelatin gastro-resistant capsules filled with white to off-white coloured pellets.

- Duloxetine Sandoz 20 mg is a hard gelatine capsule with an opaque blue cap and opaque blue body. The capsule is imprinted with '163' on the cap and 'A' on the body with black ink and contains 20 mg of duloxetine (as hydrochloride).
- Duloxetine Sandoz 40 mg is a hard gelatine capsule with an opaque blue cap and opaque orange body. The capsule is imprinted with '162' on the cap and 'A' on the body with black ink and contains 40 mg of duloxetine (as hydrochloride).

The 20 mg capsules are packed in Aluminium-Aluminium blisters and the 40 mg strength in transparent PVC/Aclar blisters sealed with aluminium foil.

The excipients are:
Capsule content – sugar spheres (containing maize starch and sucrose), hypromellose 2910 (E464), talc (E553b), sucrose, hypromellose phthalate (E464) and triethyl citrate (E1505).
Capsule shell – gelatin (E441), titanium dioxide (E171), sodium lauryl sulfate (E487) and indigo carmine (E131). The 40 mg strength also contains red and yellow iron oxide (E172).
Black ink – shellac (E904), propylene glycol, black iron oxide (E172) and potassium hydroxide.

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 is a white or almost white powder. The active substance is sparingly soluble in water and freely soluble in methanol and practically insoluble in hexane. The solubility is not pH dependant. Duloxetine hydrochloride exhibits polymorphism and Form A is manufactured. 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
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 is in line with the CEP, with additional requirements for residual solvents, particle size and microbial quality. The specification is acceptable in view of the route of synthesis and the various European guidelines. Batch analytical data demonstrating compliance with this specification have been provided for two full scaled batches of each supplier.

Stability of drug substance
manufacturer I
Stability data on the active substance have been provided for three pilot scaled batches stored at 25°C/60% RH (48 months) and 40°C/75% RH (6 months). All parameters tested remain relatively stable at both storage conditions. Based on the data submitted, a retest period could be granted of 48 months when stored protected from light.
manufacturer II
The active substance is stable for 60 months 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.
Two bioequivalence studies were performed with a 60 mg drug product. The batch used in the study contains the same bulk pellets and is manufactured in the same way as the commercial batches. The bioequivalence study is of sufficient size in relation to the intended commercial batch size. For the 20 mg and 40 mg strength a biowaiver was requested based on *in vitro* dissolution studies.
The 20 mg and 40 mg capsules are filled with the same pellets as the 60 mg capsules tested in the bioequivalence study and are therefore considered fully dose proportional. Dissolution testing according to EU requirements was carried out between the additional strengths and a representative 60 mg batch. The dissolution profiles of the batches were found to be similar.

Manufacturing process
The manufacturing process has been validated according to relevant European guidelines and consists of active coating, sub coating, enteric coating, blending, filling in capsules and packaging. The process is considered non-standard. Process validation data on the product have been presented for three production scaled batches in accordance with the relevant European guidelines.

Control of excipients
All excipients used comply with the requirements of their respective Ph. Eur. monographs. An in-house specification has been provided for 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 includes tests for appearance, identification, average filled content, assay, dissolution, related substances, content uniformity, residual solvents and microbial limits. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. The release and shelf life limits are identical except for related substances. Satisfactory validation data for the analytical methods have been provided. Batch analytical data 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 have been provided for three pilot scaled batches stored at 25°C/60% RH (36 months), 30°C/65% RH (12 months) and 40°C/75% RH (6 months) in accordance with applicable ICH stability guidelines. The same trends were observed in both capsule strengths at all conditions. Dissolution in the buffer stage increased after the initial time point and was stable from the second time point onwards. All other parameters tested remained relatively stable throughout the test periods at all test conditions and within specification limits. The results of stability studies showed no observed degradation and are therefore found acceptable. In addition, the product is not sensitive to light.
On basis of the data submitted, a shelf life was granted of 24 months in the proposed packaging. The labelled storage conditions are: 'Store in the original package in order to protect from moisture' and 'Do not store above 30°C'.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
The excipient gelatin is of animal origin. 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 Sandoz 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 Sandoz 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 Duloxetine Sandoz 60 mg (Sandoz B.V., NL) is compared with the pharmacokinetic profile of the reference product Cymbalta 60 mg hard gastro-resistant capsules (Eli Lilly Nederland B.V., 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. 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

This application concerns 2 strengths, i.e. 20 and 40 mg capsules filled with the same gastro-resistant pellets. The bioequivalence study was carried out with a 60 mg batch, which is filled with the same pellets. Dissolution testing according to EU requirements was carried out between the additional strengths and a representative 60 mg batch. The dissolution profiles of the batches were found to be similar. The dissolution data showed that the 20 and 40 mg formulations have comparable dissolution at 2h pH 1 followed by pH 6.8 and at 2h pH 4.5 followed by pH 6.8. No surfactants were used.
The requirements for the biowaiver for additional strengths have been fulfilled.

Bioequivalence studies

Bioequivalence study I: fasted conditions

Design

An open-label, balanced, single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 56 healthy male subjects, aged 20 - 43 years. Each subject received a single dose (60 mg) of one of the 2 duloxetine formulations. The tablet was orally administered with 240 ml water after an overnight fast. There were 2 dosing periods, separated by a washout period of 7 days.

Blood samples were collected pre-dose and at 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 4.0, 5.0, 6.0, 7.0, 7.5, 8.0, 8.5, 9.0, 9.5, 10.0, 10.5, 11.0, 12.0, 16.0, 24.0, 36.0, 48.0 and 72.0 hours after administration of the products.

The design of the study is acceptable. The sampling time and the washout period are adequate.

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

Two subjects were replaced by stand-by subjects prior to period one. Four subjects were withdrawn from the study due to vomiting. Overall, 49 subjects completed the study and 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=52	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	886 ± 615	952 ± 692	44 ± 25	6.9 ± 1.2	13.5 ± 4.0
Reference	863 ± 587	928 ± 669	43 ± 23	6.8 ± 1.2	13.3 ± 4.4
***Ratio (90% CI)**	1.01 (0.97 – 1.07)	1.02 (0.97 – 1.07)	1.01 (0.96 – 1.06)	--	--

CV (%)	15.3	13.6	15.1	--	--

$AUC_{0-\infty}$ 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
t_{max} time for maximum concentration
$t_{1/2}$ half-life
CV coefficient of variation
**ln-transformed values*

Bioequivalence study II: fed conditions

Design

An open-label, balanced, single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fed conditions in 56 healthy male subjects, aged 19 - 44 years. Each subject received a single dose (60 mg) of one of the 2 duloxetine formulations. The tablet was orally administered with 240 ml water 30 minutes after the start of intake of a high fat high caloric breakfast (including: toasted bread with butter, fried egg, hash brown potatoes, milk with 1 teaspoon sugar and fried chicken). There were 2 dosing periods, separated by a washout period of 7 days.

Blood samples were collected pre-dose and at 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 4.0, 5.0, 6.0, 7.0, 7.5, 8.0, 8.5, 9.0, 9.5, 10.0, 10.5, 11.0, 12.0, 16.0, 24.0, 36.0, 48.0 and 72.0 hours after administration of the products.

The design of the study is acceptable. The sampling time and the washout period are adequate.

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

Eight subjects were withdrawn from the study due to adverse events and two subject withdrew on their own accord. Therefore, 47 subjects completed the study and 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=49	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	1166 ± 507	1229 ± 544	57 ± 19	8.9 ± 3.0	13.2 ± 3.0
Reference	1009 ± 411	1068 ± 430	54 ± 17	7.3 ± 1.3	13.0 ± 2.8
***Ratio (90% CI)**	1.14 (1.08 – 1.20)	--	1.04 (1.00 – 1.09)	--	--
CV (%)	14.2	--	13.4	--	--

$AUC_{0-\infty}$ 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
t_{max} time for maximum concentration
$t_{1/2}$ half-life
CV coefficient of variation
**ln-transformed values*

Conclusion on 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 Sandoz is considered bioequivalent with Cymbalta under fasted and fed conditions.

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 Duloxetine Sandoz.

- Summary table of safety concerns as approved in RMP

Important identified risks	- Hepatic risks - Suicidality - Hyperglycemia - 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 tract (UGIT) bleeding events with concomitant use of NSAIDs - Renal failure
Missing information	- Use in elderly - Use in pregnant and breast-feeding women - Use in paediatric population

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

The MAH justifies the absence for not submitting a readability test to comply with Articles 59(3), 61(1), and 63(2) of Directive 2001/83/EC as amended by Directive 2004/27/EC as follows:

The absence of a new user test for the patient leaflet (PL) for Duloxetine Sandoz 20 mg and 40 mg hard gastro-resistant capsule is justified due to the following reasons:

- The content as well as the wording of the proposed and submitted PL is identical to the PL of Yentreve, which has been registered in the EU via the central procedure (EMEA/H/C/000545) in August 2004. This complies with the demands of regulatory authorities with the purpose of harmonised product information for originator product and generic product in all European countries.

- The PL is well understandable for patients due to chosen patient friendly wording and clear structure (e.g. use of bullet points).
- The medicine is a hard gastro-resistant capsule for easy and safe oral use and does not require special instructions for handling (as they are necessary e.g. for inhalers or parenteralia intended for self-administration). Furthermore, it is identical to the pharmaceutical form of Yentreve.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Duloxetine Sandoz 20 mg and 40 mg, gastro-resistant capsules, hard have a proven chemical-pharmaceutical quality and are generic forms of Yentreve 20 mg and 40 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 Duloxetine Sandoz with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 15 January 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