CBG MEB

Public Assessment Report

Scientific discussion

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

(duloxetine hydrochloride)

NL/H/3288/001-002/DC

Date: 7 September 2016

This module reflects the scientific discussion for the approval of Duloxetine Accord 30 mg and 60 mg, gastro-resistant capsules, hard. The procedure was finalised on 9 September 2015. 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 Accord 30 mg and 60 mg, gastro-resistant capsules, hard, from Accord Healthcare Ltd.

The product is indicated for the treatment of:

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

The products are 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 30 mg and 60 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 Austria, Cyprus, Denmark, Estonia, Finland, France, Malta, Norway, Sweden and the UK.

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

II. QUALITY ASPECTS

II.1 Introduction

Duloxetine Accord 30 mg and 60 mg are hard gelatin gastro-resistant capsules filled with white to off white coloured pellets.

The 30 mg capsules have an opaque blue cap and opaque white body imprinted with ‘H’ on the cap and ‘191’ on the body. Each capsule contains 30 mg of duloxetine (as hydrochloride).

The 60 mg capsules have an opaque blue cap opaque green body imprinted with ‘H’ on the cap and ‘192’ on the body. Each capsule contains 60 mg duloxetine (as hydrochloride).

The capsules are packed in Aluminium/Aluminium blisters.

The excipients are:
Capsule content – sugar spheres (containing maize starch and sucrose), hypromellose 2910 (E464), crospovidone (type B), talc, sucrose, carboxy methyl ethyl cellulose, povidone, titanium dioxide (E171), macrogel (E1521), polysorbate 80 (E433).
Capsule shell 60 mg,– gelatin, titanium dioxide (E171), sodium laurilsulphate, iron oxide yellow (E172), indigo carmine (E433).
Capsule shell 30 mg – gelatin, titanium dioxide (E171), sodium laurilsulphate, indigo carmine (E433).
Edible ink 30 mg – shellac (E904), propylene glycol, yellow iron oxide (E172).
Edible ink 60 mg – shellac (E904), propylene glycol, titanium dioxide (E171).

The capsule fill of the two 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. The active substance is sparingly soluble in water and freely soluble in methanol and practically

insoluble in hexane. 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 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 a CEP has 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 CEP and meets the requirements of the monograph in the Ph. Eur. In addition, requirements are included for particle size and microbiological examination. Batch analytical data demonstrating compliance with this specification have been provided for two full scale batches.

Stability of drug substance
Stability data on the active substance have been provided for five full-scale batches stored at 25°C/60% RH (6-60 months) and 40°C/75% RH (6 months). All parameters tested remain relatively stable at both storage conditions. Based on the stability data provided the proposed re-test period of 60 months is considered acceptable. Although not necessary in view of the stability data, the MAH applies the storage restriction 'Preserve in tight, light resistant containers, store at 25ºC, excursions permitted between 15ºC and 30ºC'. This is acceptable

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. Bioequivalence studies were performed with the 60 mg product. For the 30 strength 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 F2 values are above 50. The pharmaceutical development of the product has been adequately performed.

Manufacturing process
The manufacturing process consist of drug loading of the sugar spheres, sub coating, enteric coating, film coating, filling in capsules and packaging. The process has been validated according to relevant European guidelines. It is considered non-standard. Process validation data on the product have been presented for three full scaled batches of each strength.

Control of excipients
All excipients comply with the requirements of their respective Ph. Eur. monographs. An in-house specification has been provided for carboxy methyl ethyl cellulose 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 relevant monograph in the Ph. Eur. and 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. Satisfactory validation data for the

analytical methods have been provided. Batch analytical data from three full scaled batches of each strengths 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 full scaled batches of each strength in accordance with applicable ICH guidelines stored for 12-36 months at 25°C/60% RH and for 6 months at 40°C/75% RH. The conditions used in the stability studies are according to the ICH stability guideline. There were no differences observed between the strengths. Some changes are noted in water content, however the results remain well within specification. The drug substance was tested in a photodegradation study. The results show that no significant changes were observed. Based on the stability data provided a shelf life of 36 months has been granted for the drug product. No special storage condition is required.

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 Duloxetine Accord 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 Accord 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 Accord 60 mg (Accord Healthcare Ltd, UK) 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

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

- The strengths are manufactured by the same manufacturing process
- The qualitative composition of the two strengths is the same
- The composition of the strengths is quantitatively proportional
- Satisfactory comparative dissolution between strengths were 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 F2 calculations showed similarity: the F2's are above 50. Comparison of the 30 mg with the 60 mg product (biobatch), show the same results; the F2 calculations support the findings that dissolution for both strengths is similar to the biobatch.

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 19-43 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 0.50, 1.0,1.50, 2.00, 2.50, 3.00, 3.50, 4.00, 4.33, 4.67, 5.00, 5.33, 5.67, 6.0, 6.33, 6.67, 7.0, 7.5, 8.0, 9.00, 10.0, 12.0, 24, 36, 48.00 and 72 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

One of the subjects withdrew from the study due to adverse events (nausea and vomiting), one subject did not provide a consent and one subject did not return to the facility for the second period. Therefore, 52 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=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	-	0.97	-

	(0.94 – 1.04)		(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
t_{max} time for maximum concentration
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 48 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 within 30 minutes after being served a standard non-vegetarian, high-calorie, high-fat breakfast (bread with butter, egg omelette with butter, french fries, milk with sugar and Chicken Tikka garnished with ginger, garlic and masala). There were 2 dosing periods, separated by a washout period of 7 days.

Blood samples were collected pre dose and at 1.0, 2.00, 3.00, 4.00, 5.00, 6.0,, 7.0, 7.5, 8.0, 9.00, 9.50, 10.0, 10.50, 11.0, 12.0, 12.0, 13, 14, 16, 18, 24, 36, 48.00 and 72 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

One of the subjects withdrew from the study due to adverse events (nausea and vomiting) and two subjects did not return to the facility for the second period. One subject was not included in the statistical description and analysis as that subject did not show positive plasma concentrations after intake of the reference product. Therefore, 45 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=45	**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
t_{max} time for maximum concentration
CV coefficient of variation

**ln-transformed values*

Conclusion on bioequivalence studies:

The 90% confidence intervals calculated (AUC_{0-t}, $AUC_{0-\infty}$ for fed conditions and $AUC_{0-\infty}$ and C_{max} for the fasted conditions) are within the bioequivalence acceptance range of 0.80 – 1.25 for both fasted and fed conditions. Based on the submitted bioequivalence studies Duloxetine Accord 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 Duloxetine Accord.

- Summary table of safety concerns as approved in RMP

Important identified risks	- Suicidality - 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	- Safety of duloxetine in elderly patients ≥ 75 years old - Prospective data about potential risks of exposure to duloxetine during pregnancy - Characterization of the safety and tolerability of duloxetine in pediatric patients - Long-term safety data in chronic pain patient

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 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

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

Duloxetine Accord 30 mg and 60 mg, gastro-resistant capsules, hard, have a proven chemical-pharmaceutical quality and are generic forms of Yentreve 30 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, both under fasting and fed conditions.

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 Accord 30 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 9 September 2015.

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
Addition of a batch size of common pellets, in addition to the approved batch size.	NL/H/3288/ II/001	II	03-03-2016	02-05-2016	Approval	No
Deletion of a non-significant specification parameter in the drug substance specification.	NL/H/3288/ IB/002	IB	30-05-2016	29-06-2016	Approval	No