COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Pregabaline McCrowley and Hughes 25 mg, 50 mg, 75 mg, 100 mg, 150 mg, 200 mg, 225 mg and 300 mg tablets

(pregabalin)

NL/H/4196/001-008/DC

Date: 4 April 2019

This module reflects the scientific discussion for the approval of Pregabaline McCrowley and Hughes 25 mg, 50 mg, 75 mg, 100 mg, 150 mg, 200 mg, 225 mg and 300 mg tablets. The procedure was finalised at 12 December 2018. 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 Pregabaline McCrowley and Hughes 25 mg, 50 mg, 75 mg, 100 mg, 150 mg, 200 mg, 225 mg and 300 mg tablets, from McCrowley & Hughes SL.

The product is indicated for:

- Neuropathic pain
  This product is indicated for the treatment of peripheral and central and central neuropathic pain in adults.

- Epilepsy
  This product is indicated as adjunctive therapy in adults with partial seizures with or without secondary generalisation.

- Generalised Anxiety Disorder
  This product is indicated for the treatment of Generalised Anxiety Disorder (GAD) in 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 Lyrica 25 mg, 50 mg, 75 mg, 100 mg, 150 mg, 200 mg, 225 mg and 300 mg hard capsules, which has been registered in the EEA by Pfizer Europe MA EEIG since 6 July 2004 via a centralised procedure (EU/1/04/279).

The concerned member states (CMS) involved in this procedure were Italy, France, Poland, Portugal and the united kingdom.

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

II. QUALITY ASPECTS

II.1 Introduction

Pregabaline McCrowley and Hughes is a white, round biconvex scored tablet.
Pregabaline McCrowley and Hughes 25 mg: debossed with “I“ debossed on one side and contains 25 mg of pregabalin.
Pregabaline McCrowley and Hughes 50 mg: debossed with “M1”debossed on one side and contains 50 mg of pregabalin.

Pregabaline McCrowley and Hughes 75 mg: debossed with “I1”debossed on one side and contains 75 mg of pregabalin.
Pregabaline McCrowley and Hughes 100 mg: debossed with “M2”debossed on one side and contains 100 mg of pregabalin.
Pregabaline McCrowley and Hughes 150 mg: debossed with “I2”debossed on one side and contains 150 mg of pregabalin.
Pregabaline McCrowley and Hughes 200 mg: debossed with “M3” on one side and contains 200 mg of pregabalin.
Pregabaline McCrowley and Hughes 225 mg: debossed with “M7” on one side and contains 225 mg of pregabalin.
Pregabaline McCrowley and Hughes 300 mg: debossed with “I3” on one side and contains 300 mg of pregabalin.

The tablets can be divided into equal doses and are dose proportional.

The tablets packed in Polyamide/Aluminium /Polyvinylchloride-Aluminium blisters.

The excipients are: cellulose, microcrystalline and magnesium stearate.

II.2 Drug Substance

The active substance is pregabalin, an established active substance described in the European Pharmacopoeia (Ph.Eur.). It is a white to off-white crystalline powder. The active substance is sparingly soluble in water and exhibits pH dependent solubility (very soluble at pH values between 1-4 and soluble at pH values above). The drug product exhibits polymorphism. It possesses one chiral centre, which has the S-configuration and is consistently produced as polymorphic Form I. A test for the R-isomer is included in the drug substance specification.

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 specifications of the CEP with

additional requirements for microbiological purity and particle size. In-house methods have been adequately described and validated. Batch analytical data demonstrating compliance with this specification have been provided for four batches.

Stability of drug substance

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 development focussed on the optimisation of the choice of excipients, processability and particle size of the drug substance.

A bioequivalence study has been performed using the 300 mg strength versus the 300 mg Lyrica capsules as reference product. Biowaivers of strengths are proposed for the lower seven strengths. Dissolution profiles of the test product, reference product and lower strengths are provided in 0.1 N HCl, acetate buffer pH 4.5 and phosphate buffer pH 6.8. All profiles show dissolution of more than 85% after 15 minutes.

The tablets contain break marks or score-lines. The division of the tables into equal doses has been established.

Manufacturing process

The manufacturing process consists of sieving, dry blending, lubrication and compression and is considered to be a standard process. The process has been validated according to relevant European guidelines. A protocol and results for validation of the commercial manufacturing process was provided. This is acceptable, based on the proposed tests and results of the pilot scaled batches.

Control of excipients

Excipients are tested according to the Ph.Eur. with some additional functionality-related characteristics tested. 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, colour, dimension, average mass, uniformity of dosage units, water content, identification of the active, dissolution, related compounds, assay and microbial contamination. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. The release and shelf-life specifications are identical except for total impurities. This is acceptable. Satisfactory validation data for the analytical methods have been provided. Batch analytical data from two 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 four batches of the 25 mg strength and five batches of the 300 mg strength. A bracketing approach is proposed, which is acceptable as the extremes of the range are included and all strengths are derived from a common blend. Results are provided for 25°C/60% RH (two batches up to 24 months, other batches up to 6 months) and 40°C/75% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. Tablets were stored in polyamide/Aluminium/PVC-aluminium blisters. A photostability study has been performed. The photostability data demonstrate that the drug product is not sensitive to light. Based on the provided data, a shelf-life period of 36 months with no specific storage restrictions, can be granted.

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

There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Pregabaline McCrowley and Hughes 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 Pregabaline McCrowley and Hughes 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 Lyrica 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

Pregabalin 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 one bioequivalence study, which is discussed below.

IV.2 Pharmacokinetics

The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Pregabaline McCrowley and Hughes 300 mg tablets (McCrowley & Hughes SL, Spain) is compared with the pharmacokinetic profile of the reference product Lyrica 300 mg hard capsules (Pfizer Europe MA EEIG, Belgium).

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

Biowaiver

The MAH applied a biowaiver for the strengths 25, 75, 100, 150, 200 and 225 mg with the following justification:

As pregabalin is a product with a linear absorption kinetics and the 300 mg formulation is proportional to the other strengths (25 mg, 50 mg, 75 mg, 100 mg, 150 mg, 200 mg, 225 mg), the bioequivalence study performed with the 300 mg strength can be extrapolated to the rest of strengths.

In accordance with the '*Guideline on the investigation of bioequivalence*' (CPMP/EWP/QWP/1401/98 Rev.1) the following criteria were met:

a) The pharmaceutical products concerned are manufactured by the same manufacturing process.
b) The qualitative composition of the tablets is the same (see table below).
c) The composition of the tablets of the different strengths is quantitatively proportional (see table below).
d) Appropriate in vitro dissolution data confirm the adequacy of waiving additional in vivo bioequivalence testing (see Quality part of assessment report and below under “Additional data”).

Bioequivalence study

Design

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 24 healthy male and female subjects, aged 20-40 years. Each subject received a single dose (300 mg) of one of the 2 pregabalin formulations. The tablet was orally administered with water after an overnight fast of at least 10 hours. There were 2 dosing periods, separated by a washout period of 7 days.

Blood samples were collected at pre-dose and at 0.25, 0.50, 0.75, 1.00, 1.25, 1.50, 1.75, 2.00, 2.50, 3.00, 4.00, 5.00, 6.00, 8.00, 12.00, 16.00, 24.00, 36.00 and 48.00 after administration of the products.

The design of the study is acceptable. The procedures followed for a fasting study are according to the bioequivalence guideline. A washout period of 7 days is appropriate considering the pregabalin mean t1/2 of 6.3 hours. The sampling time points are sufficient to cover the absorption and elimination phases. The handling and processing of the plasma samples are according to standard procedures.

Pregabalin may be taken without reference to food intake. From the literature it is known that food does not interact with the absorption of pregabalin. Therefore, a food interaction study is not deemed necessary. 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

All 24 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 pregabalin under fasted conditions.

Treatment N=24	**AUC_{0-t}** (ng.h/ml)	**$AUC_{0-\infty}$** (ng.h/ml)	**C_{max}** (ng/ml)	**t_{max}** (h)
Test	59655 ± 13262	60622 ± 13248	9448 ± 1750	0.75 (0.50 - 2.50)
Reference	58188 ± 12231	59133 ± 12173	8799 ± 1805	1.37 (0.75 - 3.00)
***Ratio (90% CI)**	1.02 (1.00 – 1.05)	--	1.08 (1.01 – 1.15)	--
CV (%)	4.4	--	12.3	--

$AUC_{0-\infty}$	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 study

The 90% confidence intervals calculated for AUC_{0-t} and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence study for Pregabaline McCrowley and Hughes is considered bioequivalent with Lyrica.

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 Pregabaline McCrowley and Hughes.

Table 2. Summary table of safety concerns as approved in RMP

Important identified risks	- Weight gain - Swelling (oedema) of the body, including in the extremities - Dizziness, sleepiness, loss of consciousness, fainting and potential for accidental injury - Events after pregabalin discontinuation - Interactions with other medicines - Euphoria - Hypersensitivity rations, including allergic reactions - Congestive heart failure - Vision-related events - Abuse, misuse and drug dependence
Important potential risks	- Cancer of the blood vessels - Thoughts of self-harming or suicide - Off-label use in children
Missing information	- Pregnancy and breastfeeding

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 Lyrica. 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 Pregabalin Lesvi 300 mg tablets. The bridging report submitted by the MAH has been found acceptable; bridging is justified for both content and layout of the leaflet.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Pregabaline McCrowley and Hughes 25 mg, 50 mg, 75 mg, 100 mg, 150 mg, 200 mg, 225 mg and 300 mg tablets have a proven chemical-pharmaceutical quality and are generic forms of Lyrica 25 mg, 50 mg, 75 mg, 100 mg, 150 mg, 200 mg, 225 mg and 300 mg hard capsules. Lyrica 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 Pregabaline McCrowley and Hughes with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 12 December 2018.

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