CBG MEB

Public Assessment Report

Scientific discussion

Pregabalin Warren 25 mg, 50 mg, 75 mg, 100 mg, 150 mg, 200 mg, 225 mg and 300 mg, hard capsules

(pregabalin)

NL/H/3590/001-008/DC

Date: 28 July 2017

This module reflects the scientific discussion for the approval of Pregabalin Warren hard capsules. The procedure was finalised on 12 December 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

AE	Adverse Event
ASMF	Active Substance Master File
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 Pregabalin Warren hard capsules, from Warren Generics s.r.o.

The product is indicated for:

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

- Generalised Anxiety Disorder
  Pregabalin Warren is indicated for the treatment of Generalised Anxiety Disorder (GAD) in adults.

- Neuropathic pain
  Pregabaline Warren is indicated for the treatment of peripheral and central neuropathic pain in adults. The MEB has been informed that the application of this active substance for this indication was being protected by a patent of a third party.

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 Ltd since 6 July 2004 via a centralised procedure (EU/1/04/279).

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

Pregabalin Warren is a hard gelatin capsule filled with white to off white powder. Each capsule contains 25 mg, 50 mg, 75 mg, 100 mg, 150 mg, 200 mg, 225 mg or 300 mg of pregabalin:

Pregabalin Warren 25 mg is a white capsule of size “4’’ with “I’’ printed on the cap and “33’’ on the body.

Pregabalin Warren 50 mg is a white capsule of size “3’’ with “I’’ printed on the cap and “34’’ on the body.

Pregabalin Warren 75 mg is a white and orange capsule of size “4’’ with “I’’ printed on the cap and “35’’ on the body.

Pregabalin Warren 100 mg is an orange capsule of size “3’’ with “I’’ printed on the cap and “36’’ on the body.

Pregabalin Warren 150 mg is a white capsule of size “2’’ with “I’’ printed on the cap and “37’’ on the body.

Pregabalin Warren 200 mg is an orange capsule of size “1’’ with “I’’ printed on the cap and “38’’ on the body.

Pregabalin Warren 225 mg is a white and orange capsule of size “1’’ with “I’’ printed on the cap and “39’’ on the body.

Pregabalin Warren 300 mg is a white and orange capsule of size “0’’ with “I’’ printed on the cap and “40’’ on the body.

The hard capsules are packed in transparent PVC/Aluminium blisters.

The excipients are:
Capsule content - lactose monohydrate, maize starch and talc
Capsule shell - gelatin, titanium dioxide (E171), sodium laurilsulphate and iron oxide red (E172) (75 mg, 100 mg, 200 mg, 225 mg, 300 mg strength)
Printing ink - shellac, propylene glycol, strong ammonia solution, black iron oxide (E172) and potassium hydroxide

The 300 mg, 225 mg, 200 mg, 150 mg, 100 mg, 75 mg strengths are dose proportional. The two lowest strengths (25 mg and 50 mg) are also dose proportional.

II.2 Drug Substance

The active substance is pregabalin, an established active substance described in the European Pharmacopoeia (Ph.Eur.). Pregabalin is a white to off white crystalline powder which is sparingly soluble in water. It contains one chiral centre in its structure and exist as S(+) and R(-) isomers. The drug substance manufacturer produces the S-isomer of pregabalin. Polymorph form I is manufactured.

The Active Substance Master File (ASMF) procedure is used for the active substance. The main objective of the ASMF procedure, commonly known as the European Drug Master File (EDMF) procedure, is to allow valuable confidential intellectual property or ‘know-how’ of the manufacturer of the active substance (ASM) to be protected, while at the same time allowing the applicant or marketing authorisation holder (MAH) to take full responsibility for the medicinal product, the quality and quality control of the active substance. Competent Authorities/EMA thus have access to the complete information that is necessary to evaluate the suitability of the use of the active substance in the medicinal product.

Manufacturing process
The manufacturing process of pregabalin consists of two parts. No class I solvents are used in the manufacture. Relevant specifications have been adopted.

Quality control of drug substance
The active substance specification is considered adequate to control the quality. Batch analytical data demonstrating compliance with this specification have been provided for 12 commercial batches.

Stability of drug substance
Stability data on the active substance have been provided for six commercial size batches stored at 25ºC/60% RH (up to 60 months) or 40ºC/75% RH (up to six months). The claimed retest period of 60 months is acceptable. No specific storage conditions are needed.

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 talc concentration and lactose monohydrate: maize starch ratio was optimised for dissolution. The pharmaceutical development of the product has been adequately performed.

A bioequivalence study has been submitted for the 50 mg and 300 mg product strength against the same product strengths of the innovator. The bioequivalence study test batch was manufactured according to the finalised manufacturing process and composition. Biowaivers of strength are claimed for the other product strengths. Dissolution similarity between the 25 mg and 50 mg strengths and

between the 300 mg and 75 mg, 100 mg, 150 mg, 200 mg and 225 mg strengths is shown as dissolution in all strengths at the required pH 1.2, 4.5 and 6.8 is more than 85% within 15 minutes.

Manufacturing process
The manufacturing process consists of dispensing, sifting, blending and mixing, lubrication, capsule filling and packing. It is considered to be a standard process. The manufacturing process has been validated according to relevant European/ICH guidelines. Process validation data on the product have been presented for the lubricated blend and three consecutive exhibit scale batches of each strength. Process validation for full-scale batches will be performed post authorisation.

Control of excipients
All the excipients used are official in the Ph.Eur. and are in compliance with their respective monograph. The used colourants in the capsules are approved and ingredients comply with relevant Ph.Eur. monographs. 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, uniformity of dosage units, water, dissolution, assay, related substances and microbiological examination. The shelf-life requirements for water, total impurities and assay are wider than the release requirements which is acceptable. 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 pilot scale batches per strength from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product
Stability data on the product has been provided on three pilot scaled batches per strength and per packaging type stored at accelerated condition (40°C/75% RH, data available up to 6 months), intermediate condition (30°C/65% RH, data available up to 12 months) and at long-term condition (25°C/60% RH, data available up to 36 months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in the proposed packaging. Photo stability tests have been provided showing that the drug substance and drug product are photostable. Based on the currently available stability data a shelf life of 24 months can be claimed when stored below 30°C.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
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 Pregabalin Warren 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 Pregabalin Warren 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 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 two bioequivalence studies, which are discussed below.

IV.2 Pharmacokinetics

The MAH submitted one bioequivalence study with the 50 mg and one with the 300 mg formulation:

- A bioequivalence study in which the pharmacokinetic profile of the test product Pregabalin Warren 50 mg hard capsules (Warren Generics s.r.o., Czech Republic) is compared with the pharmacokinetic profile of the reference product Lyrica 50 mg hard capsules (Pfizer, UK).
- A bioequivalence study in which the test product Pregabalin Warren 300 mg, hard capsules (Warren Generics s.r.o., Czech Republic) is compared to reference product Lyrica 300 mg hard capsules (Pfizer, UK).

The choice of the reference product
The choice of the reference product in the bioequivalence study has been justified. The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Biowaiver
A biowaiver was requested and accepted for the 25 mg strength based on the study with the 50 mg capsules and for the 75 mg, 100 mg, 150 mg, 200 mg and 225 mg strength based on the study with the 300 mg capsules:

- The pharmaceutical products are manufactured by the same manufacturing process.
- The qualitative composition of the different strengths is the same.
- The compositions of the strengths are quantitatively proportional.
- Pregabalin exhibits linear pharmacokinetics in dose range of 25-300 mg.
- Dissolution similarity between the 25 mg and 50 mg strengths and between the 300 mg and 75 mg, 100 mg, 150 mg, 200 mg and 225 mg strengths is shown as dissolution in all strengths at pH 1.2, 4.5 and 6.8 is more than 85% within 15 minutes.

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.

Bioequivalence study I - 50 mg hard capsules
Design
A two-way cross over bioequivalence study was carried out under fasted conditions in 28 healthy male subjects, aged 21-44 years. Each subject received a single dose (50 mg) of one of the two pregabalin formulations. The tablet was orally administered with 240 ml water after an overnight fast of at least 8 hours. There were two dosing periods, separated by a washout period of seven days.

Blood samples were collected pre-dose and at 0.25, 0.5, 0.75, 1.0, 1.25, 1.5, 1.75, 2.0, 2.333, 2.667, 3.0, 3.5, 4.0, 5.0, 6.0, 8.0, 10.0, 12.0, 16.0, 24.0 and 36.0 hours after administration of the products.

The overall study design is acceptable. The wash-out and sampling period are long enough considering the half life of about 6 hours. The sampling scheme is adequate to estimate the pharmacokinetic variables. As the product can be taken regardless of food, a study under fasting conditions is appropriate.

Results
All 28 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 50 mg pregabalin under fasted conditions.

Treatment N=28	**AUC_{0-t}** µg.h/ml	**$AUC_{0-\infty}$** µg.h/ml	**C_{max}** µg/ml	**t_{max}** h
Test	8.20± 1.45	8.93 ± 1.53	1.21 ± 0.18	1.0 (0.5 - 2.0)
Reference	8.04 ± 1.44	8.75 ± 1.53	1.19 ± 0.18	1.0 (0.50 - 2.67)
***Ratio (90% CI)**	1.02 (1.00 - 1.04)	1.02 (1.00 - 1.04)	1.02 (0.97 - 1.07)	--
CV (%)	4.9	4.7	10.99	--

$AUC_{0-\infty}$	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*

Safety
No adverse events (AEs) were reported for the test product.

Bioequivalence study II – 300 mg hard capsules
Design
A two-way cross over bioequivalence study was carried out under fasted conditions in 24 healthy male subjects, aged 21-44 years. Each subject received a single dose (300 mg) of one of the two pregabalin formulations. The tablet was orally administered with 240 ml water after an overnight fast of at least 8 hours. There were two dosing periods, separated by a washout period of seven days.

Blood samples were collected pre-dose and at 0.167, 0.333, 0.5, 0.66, 0.83, 1.0, 1.25, 1.5, 2.0, 2.5, 3.0, 4.0, 5.0, 6.0, 8.0, 10.0, 12.0, 16.0 and 24.0 hours after administration of the products.

The design of the study is acceptable. The wash-out and sampling period are long enough considering the half life of about 6 hours. The sampling scheme is adequate to estimate the pharmacokinetic variables. As the product can be taken regardless of food, a study under fasting conditions is appropriate.

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 withdrew in the second period on its own accord. Therefore 23 subjects were eligible for pharmacokinetic analysis.

Table 2 Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of 300 mg pregabalin under fasted conditions.

Treatment N=23	AUC_{0-t} µg.h/ml	$AUC_{0-\infty}$ µg.h/ml	C_{max} µg/ml	t_{max} h
Test	58.46 ± 9.90	62.98 ± 11.58	7.19 ± 1.60	1.5 (0.67 - 6.0)
Reference	57.77 ± 8.68	62.08 ± 9.99	7.61 ± 1.67	1.5 (0.67 - 5.03)
***Ratio (90% CI)**	1.01 (0.99 - 1.03)	1.01 (0.99 - 1.03)	0.95 (0.88 - 1.02)	--
CV (%)	3.3	3.8	15.4	--

$AUC_{0-\infty}$ 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
CV coefficient of variation

**ln-transformed values*

Safety Results
In this study, a single dose of 300 mg pregabalin was well tolerated by all the subjects except for one (vomiting during period I). No serious adverse event was observed during the entire course of the study.

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 Pregabalin Warren hard capsules is considered bioequivalent with Lyrica hard capsules.

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).

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 Pregabalin Warren.

Summary table of safety concerns as approved in RMP:

Important identified risks	• Weight gain • Peripheral oedema and oedema-related events • Dizziness, somnolence, loss of consciousness, syncope and potential for accidental injury • Discontinuation events • Drug interactions • Euphoria • Hypersensitivity and allergic reactions • Congestive heart failure • Vision-related events • Abuse, misuse, and drug dependence
Important potential risks	• Suicidality • Haemangiosarcoma • Off-label use in paediatric patients
Missing information	• Pregnancy and lactation

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

The package leaflet (PL) has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The test consisted of: a pilot test with two participants, followed by two rounds with ten participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. The results show that the PL meets the criteria for readability as set out in the Guideline on the readability of the label and PL of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Pregabalin Warren 25 mg, 50 mg, 75 mg, 100 mg, 150 mg, 200 mg, 225 mg and 300 mg, hard capsules have a proven chemical-pharmaceutical quality and are generic forms of Lyrica 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 Pregabalin Warren with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 12 December 2016.

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

*Only procedure qualifier, chronological number and grouping qualifier (when applicable)