COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Pregabaline Laurus 25 mg, 50 mg, 75 mg, 100 mg, 150 mg, 200 mg, 225 mg, 300 mg film-coated tablets

(pregabalin)

NL/H/4330/001-008/DC

Date: 20 February 2020

This module reflects the scientific discussion for the approval of Pregabaline Laurus 25 mg, 50 mg, 75 mg, 100 mg, 150 mg, 200 mg, 225 mg, 300 mg film-coated tablets. The procedure was finalised at 6 March 2019. 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
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 Laurus 25 mg, 50 mg, 75 mg, 100 mg, 150 mg, 200 mg, 225 mg, 300 mg film-coated tablets from Laurus Generics GmbH.

The product is indicated for:

Neuropathic pain
Pregabalin is indicated for the treatment of peripheral and central neuropathic pain in adults.

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

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

The concerned member states (CMS) involved in this procedure were Germany, Denmark, Spain, France, 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 Laurus is a hard capsule filled with white to off-white granular powder. Each capsule contains 25 mg, 50 mg, 75 mg, 100 mg, 150 mg, 200 mg, 225 mg or 300 mg of pregabalin:

- Pregabaline Laurus 25 mg is a white opaque/white opaque hard capsule imprinted with “LA” on cap and “41” on body with black ink.

- Pregabaline Laurus 50 mg is a white opaque/white opaque hard capsule imprinted with "LA" on cap and "42" on body with black ink.
- Pregabaline Laurus 75 mg is a red opaque/white opaque hard capsule imprinted with "LA" on cap and "43" on body with black ink.
- Pregabaline Laurus 100 mg is a red opaque/white opaque hard capsule imprinted with "LA" on cap and "44" on body with black ink.
- Pregabaline Laurus 150 mg is a white opaque/white opaque hard capsule imprinted with "LA" on cap and "45" on body with black ink.
- Pregabaline Laurus 200 mg is an orange opaque/orange opaque hard capsule imprinted with "LA" on cap and "46" on body with black ink.
- Pregabaline Laurus 225 mg is an orange opaque/orange opaque hard capsule imprinted with "LA" on cap and "47" on body with black ink.
- Pregabaline Laurus 300 mg is a red opaque/white opaque hard capsule imprinted with "LA" on cap and "48" on body with black ink.

The hard capsules are packed in PVC/PVdC-Al and PVC/PE/Aclar-Al blisters and HDPE Bottles.

The excipients are:
Pregabaline Laurus 25 mg, 50 mg, 150 mg capsules, hard
Capsules content - pregelatinised maize starch, talc
Capsules shell - titanium dioxide (E171), gelatin, sodium lauryl sulfate, purified water
Printing ink – shellac, propylene glycol, iron oxide black (E172), potassium hydroxide

Pregabaline Laurus 75 mg, 100 mg, 200 mg, 225 mg, 300 mg capsules, hard
Capsules content - pregelatinised maize starch, talc
Capsules shell - titanium dioxide (E171), gelatin, sodium lauryl sulfate, purified water, iron oxide red (E172)
Printing ink – shellac, propylene glycol, iron oxide black (E172), 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.). The drug substance is sparingly soluble in water and exhibits pH dependent solubility (very soluble between pH 1-4, soluble at higher pH values). Pregabalin exhibits polymorphism. Form I is manufactured. The drug substance shows isomerism and corresponds to the S-enantiomer.

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 has been described in sufficient detail. No class-I solvents or heavy metal catalysts are used in the synthesis. Pregabalin has been adequately characterized and acceptable specifications for solvents and reagents used in the manufacturing process have been adopted. The discussion on the genotoxic impurities is acceptable.

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. It includes an additional requirement for particle size. Absence of a test for microbial purity is justified. Batch analytical data demonstrating compliance with this specification have been provided for 14 batches.

Stability of drug substance

Stability data on the active substance have been provided for ten batches stored at 25°C/60% RH (up to 24 months) and 40°C/75% RH (6 months). Storage under long-term and accelerated conditions did not show any out of specification results or trends indicating that the batches remain stable throughout the tested period. Based on the data submitted, a retest period could be granted of 36 months without specific storage restrictions.

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 level of excipients and particle size of the drug substance.

Biopharmaceutics Classification System (BCS) based biowaivers are proposed for all eight strengths. Dissolution profiles of the test products versus the European reference products are provided in 0.1N HCl, acetate buffer pH 4.5 and phosphate buffer pH 6.8. All profiles show dissolution of more than 85% after 15 minutes. 0.06N HCl is used as medium for routine dissolution testing with an acceptance criterion of NLT 80% (Q) in 15 minutes.

Manufacturing process

The manufacturing process is described in sufficient detail. It consists of sieving, dry blending, lubrication and filling of the empty gelatin capsules. The process 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 three exhibit/small scale batches in accordance with the relevant European guidelines.

Control of excipients
Excipients are tested according to the Ph.Eur. or in-house. 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, water, uniformity of dosage units, dissolution, related substances, assay and microbial contamination. 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 batches off all strengths from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product
Stability data on the product was provided for three production batches of the all strengths for 25°C/60% RH (up to 24 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 the proposed packaging. A photostability study has been performed. The photostability data demonstrate that the drug product is not sensitive to light. In-use stability studies have been performed at 30 days and up to 90 days. No trend was observed, hence no in-use period is proposed by the MAH.
Based on the provided formal stability study, a shelf life was granted of 36 months, with no specific storage restrictions.

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 Pregabaline Laurus 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 Laurus 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 Pharmacokinetics

Biowaiver

A BCS based biowaiver has been requested for all strengths. The BCS is a scientific framework to classify drugs on the basis of their aqueous solubility, permeability and dissolution. Drug substances can be classified in three classes according to the BCS:

- Class 1: High Solubility – High Permeability
- Class 2: Low Solubility – High Permeability
- Class 3: High Solubility – Low Permeability

The BCS based biowaiver is applicable to Class 1 highly soluble drugs with known human absorption formulated as oral, immediate release formulations with the same pharmaceutical form as an innovator product. To fulfil the requirements for such a biowaiver, the MAH provided comprehensive documentation on solubility, permeability and dissolution of the product. The MAH was also required to show that the composition of the generic and innovator product is similar. In addition, a supportive discussion was provided about the therapeutic index of the product. Hence a BCS based biowaiver is applicable only for drugs which are not considered to have a narrow therapeutic index.

Solubility

Solubility data at pH 1.2, 3.2, 4.5, 5.2, 6.8 and 7.5 showed that pregabalin can be considered a drug with high solubility, i.e. more than 300 mg (highest therapeutic dose i.e. 600 mg/day divided over 2 or 3 doses) dissolves in 250 ml media.

Permeability/absorption
Pregabalin is rapidly absorbed when administered in the fasted state, with peak plasma concentrations occurring within one hour following both single and multiple dose administration. Pregabalin oral bioavailability is estimated to be ≥90% and is independent of dose (SmPC Lyrica capsules).

In vitro dissolution
Very rapid (>85% within 15 minutes) *in vitro* dissolution characteristics of the test and reference product for all strengths have been demonstrated.

Qualitative and quantitative composition
The active substance in test and reference product is identical. Excipients that might affect bioavailability are qualitatively the same and quantitatively similar.

Therapeutic index
Pregabalin is not considered a narrow therapeutic index drug.

Conclusion
Based on the available data pregabalin is considered to be BCS Class 1 (high solubility and high permeability). The justification for BCS-based biowaiver is accepted.

IV.2 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 Laurus.

Table 1. 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, confusion, syncope and potential for accidental injury • Discontinuation events • Drug interactions (lorazepam, ethanol and CNS depressants) • Euphoria • Hypersensitivity and allergic reactions • Congestive heart failure • Vision-related effects • 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.3 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 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 Lyrica. 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 Laurus 25 mg, 50 mg, 75 mg, 100 mg, 150 mg, 200 mg, 225 mg, 300 mg film-coated tablets has a proven chemical-pharmaceutical quality and is a generic form of Lyrica 25 mg, 50 mg, 75 mg, 100 mg, 150 mg, 200 mg, 225 mg, 300 mg film-coated tablets. Lyrica is a well-known medicinal product with an established favourable efficacy and safety profile.

For this generic application, the MAH submitted an argumentation for not performing a bioequivalence study. The MAH applied for a BCS (Class I) based biowaiver, based on criteria according to the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98). The BCS-based biowaiver is fully justified and accepted.

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 Laurus with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 6 March 2019.

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
NL/H/4330/001-008/IA/001	B.III.1a.1 - Type IAIN Submission of a new Ph. Eur. certificate of suitability for an active substance by an already approved manufacturer	no	17-02-2020	Approval	