IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific Discussion

Pregabalin Pinewood 50 mg hard capsules
Pregabalin
PA0281/217/002

The Public Assessment Report reflects the scientific conclusion reached by the Health Products Regulatory Authority (HPRA) at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation for a specific medicinal product for human use. It is made available by the HPRA for information to the public, after deletion of commercially sensitive information. The legal basis for its creation and availability is contained in Article 21 of Directive 2001/83/EC, as amended. It is a concise document which highlights the main parts of the documentation submitted by the applicant and the scientific evaluation carried out by the HPRA leading to the approval of the medicinal product for marketing in Ireland.

CONTENTS

I. INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the HPRA has granted a marketing authorisation for Pregabalin Pinewood hard capsules, from Pinewood Laboratories Ltd on 21st October 2022 for:

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

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

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

This application for a marketing authorisation was submitted in accordance with Article 10.1 of Directive 2001/83/EC and is referred to as a 'generic' application. Pregabalin Pinewood hard capsules has the same qualitative and quantitative composition in terms of active substances and the same pharmaceutical form as the originator product, Lyrica hard capsules.

In Ireland, medicinal products containing pregabalin are designated products subject to prescription which may not be renewed (A). Supply is through pharmacies only and advertising is to healthcare professionals only.

No national scientific advice was requested by the applicant in advance of this application.

The Summary of Product Characteristics for (SmPC) for this medicinal product is available on the HPRA's website at www.hpra.ie.

Name of the product	Pregabalin Pinewood
Name(s) of the active substance(s) (INN)	PREGABALIN
Pharmacotherapeutic classification (ATC code)	N03AX16
Pharmaceutical form and strength(s)	25,50,75,100,150,200,300 mg capsule, hard
Marketing Authorisation Number(s) in Ireland (PA)	PA0281/217/001-007
Marketing Authorisation Holder	Pinewood Laboratories Ltd
Case No.	CRN009SN0

II. QUALITY ASPECTS

II.1. Introduction
This application is for Pregabalin Pinewood 25 mg, 50 mg, 75 mg, 100 mg, 150 mg, 200 mg, 300 mg Hard Capsules.

II.2 Drug substance
The active substance is Pregabalin, an established active substance described in the European Pharmacopoeia, and is manufactured in accordance with the principles of Good Manufacturing Practice (GMP)

The active substance specification is considered adequate to control the quality and meets current pharmacopoeial requirements. Batch analytical data demonstrating compliance with this specification has been provided.

II.3 Medicinal product
P.1 Composition

*Composition of the medicinal product (*25 mg, 50 mg, 75 mg, 100 mg, 150 mg, 200 mg, 300 mg*).*

The excipients in the medicinal product are listed in section 6.1 of the SmPC.
A visual description of the product is included in section 3 of the SmPC.

P.2 Pharmaceutical Development

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

P.3 Manufacture of the Product
The product is manufactured in accordance with the principles of good manufacturing practice (GMP) at suitably qualified manufacturing sites.

The manufacturing process has been validated according to relevant European/ICH guidelines and the process is considered to be sufficiently validated.

P.4 Control of Other Substances (Excipients)
All ingredients comply with Ph. Eur. or are adequately controlled by the manufacturer's specifications.

P.5 Control of Finished Product
The Finished Product Specification is based on the pharmacopoeial monograph for hard capsules, and the tests and control limits are considered appropriate for this type of product.

The analytical methods used are described in sufficient detail and are supported by validation data.

Batch analytical data for a number of batches from the proposed production site(s) have been provided, and demonstrate the ability of the manufacturer to produce batches of finished product of consistent quality.

P.6 Packaging material
The approved packaging for this product is described in section 6.5 of the SmPC.

Evidence has been provided that the packaging complies with Ph. Eur./EU legislation for use with foodstuffs requirements.

P.7 Stability of the Finished Product
Stability data on the finished product in the proposed packaging have been provided in accordance with EU guidelines and support the shelf-life and storage conditions listed in sections 6.3 and 6.4 of the SmPC.

II.4 Discussion on Chemical, Pharmaceutical and Biological Aspects
The important quality characteristics of the product are well-defined and controlled. Satisfactory chemical and pharmaceutical documentation has been provided, assuring consistent quality of Pregabalin Pinewood 25 mg, 50 mg, 75 mg, 100 mg, 150 mg, 200 mg, 300 mg Hard Capsules.

III. NON-CLINICAL ASPECTS

III.1 Introduction
This active substance is a generic formulation of Lyrica on the European market. No new preclinical data have been submitted. As such, no pre-clinical assessment has been made on the application. This is acceptable for this type of application.

III.2 Ecotoxicity/environmental risk assessment
An Environmental Risk Assessment has not been performed as this product is intended for generic substitution and therefore will not result in an increase of risk to the environment during use, storage and disposal.

III.3 Discussion on the non-clinical aspects
Pharmacodynamic, pharmacokinetic and toxicological properties of Pregabalin are well known. As Pregabalin is a widely used, well-known active substance, the applicant has not provided additional studies and further studies are not required. Overview based on literature review is, thus, appropriate. The non-clinical overview on the pre-clinical pharmacology, pharmacokinetics and toxicology is adequate. Non-clinical findings are adequately mentioned in the appropriate sections of the SmPC.

IV. CLINICAL ASPECTS

IV.1 Introduction
Pregabalin is a well known active substance with established efficacy and tolerability.

For this generic application, the applicant has requested a BCS based biowaiver as opposed to submitting an *in vivo* bioequivalence study.

The content of the SmPC approved during the national procedure is in accordance with that accepted for the reference product, Lyrica hard capsules marketed by Upjohn EESV.

The choice of reference product in considered appropriate.

IV.2 Pharmacokinetics
No pharmacokinetic studies were submitted by the applicant.

For this generic application, the applicant has requested a BCS based biowaiver as opposed to submitting an *in vivo* bioequivalence study.

The proposed products meet the requirements set out in the guideline for BCS based biowaivers for an immediate release drug product in that:

- The drug substance is BCS class I
- It shows very rapid (>85% within 15 minutes) *in vitro* dissolution characteristics of the test and reference product (Lyrica capsules)
- The main excipients proposed (lactose monohydrate, maize starch, talc, gelatine, titanium dioxide) are qualitatively the same as the reference product.
- Pregabalin has an oral bioavailability of greater than or equal to 90%.

A BCS class biowaiver for pregabalin has been accepted for other pregabalin authorisation procedures in the EEA.

The pharmacokinetics of pregabalin is linear over the recommended daily dose range.
Pregabalin has an oral bioavailability of ≥90 % independent of dose. Following an oral dose of pregabalin maximal plasma concentrations occur within one hour. The rate of pregabalin absorption is decreased when given with food but the extent of absorption is not significantly affected by food, and therefore there are no restrictions with respect to food in the SmPC of the originator product.
The terminal half-life is 6.3 hours. Pregabalin is eliminated primarily by renal excretion as unchanged drug.
A BCS based biowaiver for all strengths is considered acceptable based on the known pharmacokinetics of the active substance, the composition of the product and regulatory guidelines/precedent.

IV.3 Pharmacodynamics
No pharmacodynamic studies were submitted by the applicant.

IV.4 Clinical Efficacy
No efficacy studies were submitted by the applicant.

IV.5 Clinical Safety
No safety studies were submitted by the applicant.

Pregabalin is not considered to have a narrow therapeutic index.

Risk Management Plan
A risk management plan was submitted, 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.

Summary of safety concerns:

Important identified risks	Dizziness, somnolence, loss of consciousness, syncope, and the potential for accidental injury Discontinuation events Drug interaction (ethanol, lorazepam and CNS depressants) Euphoria Congestive heart failure Vision-related events

	Abuse and drug dependence
Important potential risks	Suicidality Off-label use in paediatric patients
Missing information	Pregnancy and lactating women

Routine pharmacovigilance activities and routine risk minimisation measures are considered sufficient to identify, characterise, prevent or minimise risks relating to pregabalin.

Periodic safety update reports (PSURs) shall be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

IV.6 Discussion on the clinical aspects

This application for a marketing authorisation was submitted in accordance with Article 10.1 of Directive 2001/83/EC and is referred to as a 'generic' application. Generic applications avoid the need for repetitive tests on humans. Pregabalin Pinewood hard capsules has the same qualitative and quantitative composition in terms of active substances and the same pharmaceutical form as the originator product, Lyrica hard capsules. The chosen reference medicinal product is considered acceptable.

The applicant has requested a BCS based biowaiver as opposed to submitting an *in vivo* bioequivalence study for this marketing authorisation application.

The proposed products meet the requirements set out in the guideline for BCS based biowaivers for an immediate release drug product in that:

- The drug substance is BCS class I
- It shows very rapid (>85% within 15 minutes) *in vitro* dissolution characteristics of the test and reference product (Lyrica capsules)
- The main excipients proposed (lactose monohydrate, maize starch, talc, gelatine, titanium dioxide) are qualitatively the same as the reference product.
- Pregabalin has an oral bioavailability of greater than or equal to 90%.

Pregabalin is a well known active substance with established efficacy and tolerability. It is not considered to be a narrow therapeutic index medicine. The pharmacokinetics of pregabalin is linear over the recommended daily dose range.
A BCS based biowaiver for all strengths is considered acceptable based on the known pharmacokinetics of the active substance, the composition of the product and regulatory guidelines/precedent.
Routine pharmacovigilance activities and routine risk minimisation measures are considered sufficient to identify, characterise, prevent or minimise risks relating to pregabalin.
Periodic safety update reports (PSURs) shall be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

V. OVERALL CONCLUSIONS

Pregabalin Pinewood Hard Capsules is a generic form of Lyrica Hard Capsules. Lyrica Hard Capsules is a well-known medicinal product with a proven chemical-pharmaceutical quality and an established favourable efficacy and safety profile.

Bioequivalence studies are not required as a BCS based biowaiver for all strengths is considered acceptable. The SmPC is consistent with that of the reference product.

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The HPRA, on the basis of the data submitted considered that Pregabalin Pinewood Hard Capsules is pharmaceutically equivalent to the reference product and has a satisfactory risk/benefit profile and therefore granted a marketing authorisation.

VI. REVISION DATE

VII. UPDATES

This section reflects the significant changes following finalisation of the initial procedure.

SCOPE	PROCEDURE NUMBER	PRODUCT INFORMATION AFFECTED	DATE OF START OF PROCEDURE	DATE OF END OF PROCEDURE
New National	N/A	SmPC Sections 1 to 9	21st October 2022	20th October 2027