IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific Discussion

Pregabalin 20 mg/ml oral solution
PREGABALIN
PA0688/064/001

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.

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I. INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the HPRA has granted a marketing authorisation on 17 July 2020 for Pregabalin 20mg/ml oral solution, from Chanelle Medical on for the treatment of
- peripheral and central neuropathic pain in adults
- as adjunctive therapy in adults with partial seizures with or without secondary generalisation
- Generalised Anxiety Disorder (GAD) in adults

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

Name of the product	Pregabalin 20 mg/ml oral solution
Name(s) of the active substance(s) (INN)	PREGABALIN
Pharmacotherapeutic classification (ATC Code)	N03AX16
Pharmaceutical form and strength(s)	20, mg/ml, Oral liquid
Marketing Authorisation Number(s) in Ireland (PA)	PA0688/064/001
Marketing Authorisation Holder	Chanelle Medical Dublin Road Loughrea Co. Galway Ireland
MRP/DCP No.	IE/H/0649/001/DC
Reference Member State	Ireland
Concerned Member State(s)	DE UK

II. QUALITY ASPECTS

II.1. Introduction

This application is for Pregabalin 20 mg/ml oral solution.

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

Pregabalin 20 mg/ml

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/*Ancillary Substances*)

All ingredients comply with Ph. Eur./BP 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 liquid preparations for oral use, 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 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 20 mg/ml oral solution.

III. NON-CLINICAL ASPECTS

This active substance is a generic formulation of Lyrica 20mg/ml oral solution (Pfizer), on the European market since 2004. No new preclinical data have been submitted.

The pharmacodynamic, pharmacokinetic and toxicological properties of pregabalin are well known. As pregabalin is a widely used, well-known active substance, and this is a generic application, the applicant has not provided additional nonclinical studies and further studies are not required. The overview provided based on literature review is thus appropriate.

III.2 Ecotoxicity/environmental risk assessment

Since Pregabalin Chanelle 20 mg/ml oral solution 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.3 Discussion on the non-clinical aspects

The pharmacodynamic, pharmacokinetic and toxicological properties of pregabalin are well known. As pregabalin is a widely used, well-known active substance, and this is a generic application, the applicant has not provided additional nonclinical studies and further studies are not required. The non-clinical overview on the pre-clinical pharmacology, pharmacokinetics and toxicology provided is adequate. Non-clinical findings are adequately represented 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.

The content of the SmPC approved during the decentralised procedure is in accordance with that accepted for the reference product Lyrica.

As the product is an aqueous solution for oral administration, a BCS biowaiver would be appropriate and so no bioequivalence studies would be required. This was accepted by the RMS.

Essential similarity with the reference product was demonstrated.

IV.2 Pharmacokinetics

Pharmacokinetics

Absorption: 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.

Linearity: The pharmacokinetics of pregabalin is linear over the recommended daily dose range.

Elimination: The terminal half-life is 6.3 hours. Pregabalin is eliminated primarily by renal excretion as unchanged drug.

BCS-based biowaivers are possible for highly soluble drug substances with known human absorption and considered not to have a narrow therapeutic index.

The applicant claimed in the Clinical overview that bioequivalence between the liquid formulation of pregabalin and the corresponding reference product Lyrica has been appropriately demonstrated by sufficient literature data and as such further clinical bioequivalence studies can therefore be waived.

From a pharmacokinetic point of view, a BCS-class I based biowaiver is acceptable for an immediate release drug product if the drug substance has proven to exhibit complete absorption and the excipients that might affect bioavailability are quantitatively and qualitatively the same.

Absorption

According to the bioequivalence guideline complete absorption is considered to be established where measured extent of absorption is >85%. Data from absolute bioavailability or mass-balance studies could be used to support this claim.

The applicant stated that pregabalin oral bioavailability is estimated to be ≥ 90% and is independent of dose. Thus, oral bioavailability of pregabalin averaged ≥ 90% across the therapeutic dose range.
Previous assessments of pregabalin from various national competent authorities have accepted that the pharmacology of pregabalin is such to support a BCS-based biowaiver.

Excipients

The applicant states that, with regard to the composition of the product, none of the excipients present in the formulation is suspected of having an impact on the bioavailability of the API.
Further information on this aspect can be found in the Quality Assessment Report, but it is accepted that the excipients are such as not to affect the absorption of the test product relative to that of the reference liquid formulation.

Therapeutic index

A BCS-based biowaiver is only possible for substances that are not considered to have a narrow therapeutic index.
According to previous application procedures pregabalin is not considered as a drug with a narrow therapeutic index in the sense that the acceptance criteria would need to be tightened in a bioequivalence study. The recommended dose range is wide (150 mg/day – 600 mg/day) and the risks associated with a potentially small increase in exposure above the highest recommended exposure of the originator seems negligible. As such, a BCS based biowaiver is possible in this aspect.

Overall, the justification for BCS-based biowaiver can be accepted.

IV.3 Pharmacodynamics

No new data have been submitted. No data are required for an abridged application provided bioequivalence has been satisfactorily demonstrated.

IV.4 Clinical Efficacy & Safety

The efficacy and safety of pregabalin has been established for the reference product and so can be inferred for the generic equivalent. No additional clinical data are needed for this type of application and so none have been provided. This is accepted by the RMS.
Absorbtion and bioavailabilty, distribution, metabolism, elimination, dose proportionality and time dependence, target/special populations, interactions, relationship between concentration and effect.

IV.6 Discussion on the clinical aspects

The clinical aspects of pregabalin are well-established, and the applicant has appropriately demonstrated that a BCS biowaiver is applicable for this particular product.

IV.7 Pharmacovigilance System

IV.8 Risk Management Plan (RMP)

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 20 mg/ml oral solution.
The submitted Risk Management Plan, version 0.2 signed 31/05/2018 is considered acceptable. Routine pharmacovigilance and routine risk minimisation are considered sufficient. The Applicant is requested to ensure it maintains the RMP in line with the latest SmPC updates and maintains regular reviews.

Summary table of safety concerns as approved in RMP

Important identified risks	Dizziness, Somnolence, Loss of Consciousness, Syncope, and Potential for Accidental Injury Discontinuation events Drug Interactions ((lorazepam, ethanol 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 lactation

IV.9 Periodic Safety Update Report (PSUR).
With regard to PSUR submission, the MAH should take the following into account:

- 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. Marketing authorisation holders shall continuously check the European medicines web-portal for the DLP and frequency of submission of the next PSUR.
- For medicinal products authorized under the legal basis of Article 10(1) or Article 10a of Directive 2001/83/EC, no routine PSURs need to be submitted, unless otherwise specified in the EURD list.
- In case the active substance will be removed in the future from the EURD list because the MAs have been withdrawn in all but one MS, the MAH shall contact that MS and propose DLP and frequency for further PSUR submissions together with a justification.

V. OVERALL CONCLUSIONS

Pregabalin 20 mg/ml oral solution is a generic form of Lyrica. Pregabalin is a well-known medicinal product with a proven chemical-pharmaceutical quality and an established favourable efficacy and safety profile.

Demonstration of bioequivalence was waived in compliance with the CHMP guidance on BCS biowaivers. 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 Chanelle demonstrated bioequivalence with the reference product as well as a satisfactory risk/benefit profile and therefore granted a marketing authorisation.

VI. REVISION DATE

21.05.2025