IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific Discussion

Pregabalin Wockhardt 20 mg/ml oral solution
Pregabalin
PA0281/249/001

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.

CONTENTS

I. INTRODUCTION

This product was initially authorised under procedure number UK/H/6702/1/DC with the UK as RMS. The responsibility of RMS was transferred to Ireland on 02/07/2018 under procedure number IE/H/0626/1/DC.
Please note the following detail for the product in IE:
Marketing Authorisation Number: PA0281/249/001
Marketing Authorisation Holder: Pinewood Laboratories Ltd

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

The UK public assessment report published at the time of the initial marketing authorisation is provided herein.

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Medicines and Healthcare products Regulatory Agency (MHRA) granted Wockhardt UK Limited, a marketing authorisation for the medicinal product Pregabalin Oral Solution (PL 29831/0673; UK/H/6702/001/DC). This product is a prescription-only medicine (POM).

Pregabalin Oral Solution is indicated for:

- Neuropathic pain: for the treatment of peripheral and central neuropathic pain in adults.
- Epilepsy: as adjunctive therapy in adults with partial seizures with or without secondary generalisation.
- Generalised Anxiety Disorder: for the treatment of Generalised Anxiety Disorder (GAD) in adults.

The application was submitted using the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS) and Germany (DE), Ireland (IE), Italy (IT), Spain (ES) and The Netherlands (NL) as a Concerned Member State (CMS). The application was submitted under Article 10(1) of Directive 2001/83/EC, as amended, as a generic application. The reference medicinal product for this application is Lyrica 20 mg/ml Oral Solution (EU/1/04/279/044) which was granted to Pfizer Limited on 06 July 2004 via the centralised procedure.

The active substance, pregabalin, belongs to the pharmacotherapeutic group antiepileptics/other antiepileptics with ATC code: N03AX16. Pregabalin is a gamma-aminobutyric acid analogue [(S)-3-(aminomethyl)-5- methylhexanoic acid]. Pregabalin binds to an auxiliary subunit (α2-δ protein) of voltage-gated calcium channels in the central nervous system.

No new non-clinical studies were submitted, which is acceptable given that the application was based on being a generic medicinal product of an originator product that has been in clinical use for over 10 years.

No new clinical data have been submitted and none are required for an application of this type. A bioequivalence study was not necessary to support this application as both test and reference product are oral solutions at the time of administration.

The RMS has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for this product type at all sites responsible for the manufacture, assembly and batch release of these products.

For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

The RMS considered that the application could be approved at the end of procedure on 24 February 2018. After a subsequent national phase, a licence was granted in the UK on 20 March 2018.

II. QUALITY ASPECTS

II QUALITY ASPECTS

II.1 Introduction

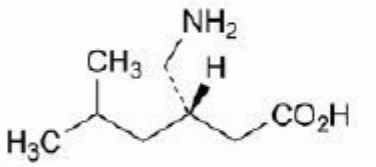
Each ml of solution contains 20 mg of pregabalin. The excipients present are methyl parahydroxybenzoate (E218), propyl parahydroxybenzoate (E216), sucralose, sodium dihydrogen phosphate dihydrate, disodium Phosphate anhydrous (E339), purified water and artificial strawberry flavour. The strawberry flavour consists of propylene glycol, flavourings and ascorbic acid.

The finished product is packed in a white high-density polyethylene (HDPE) bottle with polyethylene-lined tamper evident closure, containing 473 ml of oral solution, in a cardboard carton. The carton also contains a 5 ml graduated oral syringe and a Press-In Bottle adapter (PIBA).

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with the current European regulations concerning materials in contact with food.

II.2 Drug Substance

INN:	Pregabalin
Chemical name:	(3S)-3-(Aminomethyl)-5-methylhexanoic acid
Structure:	



Molecular formula:	$C_8H_{17}CO_2$
Molecular weight:	159.23 g/mol
Appearance	White or almost white powder
Solubility	Sparingly soluble in water, very slightly soluble in methanol, practically insoluble in heptane.

Pregabalin is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of the active substance, are covered by the European Directorate for the Quality of Medicines and Healthcare (EDQM) Certificate of Suitability.

II.3. Medicinal Product

Pharmaceutical Development

The objective of the development programme was to develop a safe, efficacious, oral solution containing 20 mg pregabalin per ml of oral solution that is comparable in performance to the reference product Lyrica 20 mg/ml Oral Solution (Pfizer Limited). The development of the product has been described, the choice of excipients is justified, and their functions explained.

All excipients used apart from the strawberry flavouring, comply with their respective European Pharmacopeia monographs. The strawberry flavouring adheres to its in house specifications.

Satisfactory specifications and Certificates of Analysis have been provided for the packaging components.

None of the excipients used in this product contain material of animal or human origin.

This product does not contain or consist of genetically modified organisms (GMO).

Manufacture of the product
Satisfactory batch formulae have been provided for the manufacture of the product, together with an appropriate account of the manufacturing process. Process validation data on commercial scale batches have been provided. The results are satisfactory.

Finished Product Specification
The finished product specification proposed is acceptable. Test methods have been described that have been adequately validated. Batch data complying with the release specification have been provided. Certificates of Analysis have been provided for all working standards used.

Stability of the Product
Finished product stability studies were performed in accordance with current guidelines on batches of the finished product in the packaging proposed for marketing. The data from these studies support a shelf-life of 18 months for the unopened bottle and an in-use shelf-life of 3 months with the storage conditions 'Do not store above 25°C'.

Suitable post approval stability commitments to continue stability testing on batches of finished product have been provided.

II.4 Discussion on chemical, pharmaceutical and biological aspects
There are no objections to the approval of this application from a pharmaceutical viewpoint.

III. NON-CLINICAL ASPECTS

III NON-CLINICAL ASPECTS

III.1 Introduction
As the pharmacodynamic, pharmacokinetic and toxicological properties of pregabalin are well-known, no new non-clinical studies are required and none have been provided. An overview based on the literature review is, thus, appropriate.

The applicant's non-clinical expert report has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the relevant non-clinical pharmacology, pharmacokinetics and toxicology.

III.2 Pharmacology
Not applicable for this product type. Refer to section 'III.1; Introduction' detailed above.

III.3 Pharmacokinetics
Not applicable for this product type. Refer to section 'III.1; Introduction' detailed above.

III.4 Toxicology
Not applicable for this product type. Refer to section 'III.1; Introduction' detailed above.

III.5 Ecotoxicity/environmental risk assessment (ERA)
Since Pregabalin Oral Solution is intended for generic substitution, this will not lead to an increased exposure of the environment to pregabalin. An environmental risk assessment is therefore not deemed necessary.

III.6 Discussion on the non-clinical aspects
There are no objections to the approval of this application from a non-clinical viewpoint.

IV. CLINICAL ASPECTS

IV CLINICAL ASPECTS

IV.1 Introduction

The pharmacodynamic, pharmacokinetic, clinical efficacy and safety properties of pregabalin are well known. A comprehensive review of the published literature has been provided by the applicant. The applicant's clinical overview has been written by an appropriately qualified person and is considered acceptable.

IV.2 Pharmacokinetics

In accordance with the guidance on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1) "A waiver of the need to provide equivalence data may be acceptable in the case of solutions, e.g. eye drops, nasal sprays or cutaneous solutions, if the test product is of the same type of solution (aqueous or oily), and contains the same concentration of the same active substance as the medicinal product currently approved', therefore no bioequivalence study was submitted, and this is acceptable for this aqueous solution of equal strength (20 mg/ml), containing the same active substance (Lyrica 20 mg/ml Oral Solution) as the reference product except for the propylene glycol in the strawberry flavour. It is agreed that this is of insufficient quantity to affect the bioavailability. Therefore, the criteria for biowaiver are fulfilled. No biostudy is required to compare the bioequivalence of the two products.

IV.3 Pharmacodynamics

No new pharmacodynamic data were submitted and none were required for an application of this type.

IV.4 Clinical efficacy

No new efficacy data were submitted, and none were required for an application of this type.

IV.5 Clinical safety

No new safety data were submitted and none are required.

IV.6 Risk Management Plan (RMP) and Pharmacovigilance System

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended.

There are no differences from the reference product in terms of proposed uses, maximum pack size / strength or pharmaceutical form / formulation that would have any implications for safety.
In line with the reference product, the applicant proposes only routine pharmacovigilance and routine risk minimisation measures for all safety concerns (labelling in the SmPC and the PIL). This is agreed.
The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.
An updated RMP should be submitted:

- At the request of the RMS;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a Periodic Safety Update Report and the update of a RMP coincide, they can be submitted at the same time, but via different procedures.

IV.7 Discussion on the clinical aspects

The grant of a marketing authorisation is recommended for this application from a clinical viewpoint.

V User consultation

A user consultation with target patient groups on the package information leaflet (PIL) has been performed on the basis of a bridging report making reference to Morphine Sulfate 10 mg/5 ml oral solution (PL 29831/0563). The PIL has been harmonised with the PIL for the reference product Lyrica 20 mg/ml Oral Solution (EU/1/04/279/044; Pfizer Limited). The bridging report submitted by the applicant is acceptable.

V. OVERALL CONCLUSIONS

VI Overall conclusion, benefit/risk assessment and recommendation

The quality of the product is acceptable, and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with pregabalin is considered to have demonstrated the therapeutic value of the compound. The benefit-risk is, therefore, considered to be positive.

VI. REVISION DATE

02/03/2022

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
RMS transfer	From UK/H/6702/1/DC to IE/H/0626/1/DC			
MAH Transfer				29/01/2021