IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific Discussion

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 quality, safety and efficacy data, the Member States have granted a marketing authorisation for Levetiracetam Wockhardt 100mg/ml Oral Solution (levetiracetam) from Wockhardt UK Ltd

The product is indicated*:*

as monotherapy
· in the treatment of partial onset seizures with or without secondary generalisation in patients from 16 years of age with newly diagnosed epilepsy

as adjunctive therapy
· in the treatment of partial onset seizures with or without secondary generalisation in adults, children and infants from 1 month of age with epilepsy.
· in the treatment of myoclonic seizures in adults and adolescents from 12 years of age with Juvenile Myoclonic Epilepsy.
· in the treatment of primary generalised tonic-clonic seizures in adults and adolescents from 12 years of age with Idiopathic Generalised Epilepsy.

A comprehensive description of the indications and posology is given in the SmPC.

II. QUALITY ASPECTS

II.1 Introduction

This application is for Levetiracetam Wockhardt 100mg/ml Oral Solution (levetiracetam)

II.2 2.2 Drug Substance

Levetiracetam is a well know active substance and it is monographed in the European Pharmacopoeia. The EDQM CEP procedure is used. The manufacturer of the drug substance levetiracetam has obtained a certificate of suitability and the CEP is presented in the documentation.

The active substance specification is considered adequate to control the quality and meets the requirements of the Ph.Eur monograph for Levetiracetam and additional requirements as stated on the CEP. Batch analytical data demonstrating compliance with this specification have been provided for three representative batches.

II.3 Medicinal Product

II.3.1 Composition

The Drug Product is presented as a clear to slightly yellow oral solution containing levetiracetam 100mg/ml as the active substance. It contains methyl parahydroxybenzoate and propyl parahydroxybenzoate as preservatives. The product is packaged in Type III amber glass bottles with child resistant closure. There are two authorised pack sizes 150ml and 300ml. A 10ml graduated oral syringe is provided with the 300ml bottle, and either a 3ml or a 1ml graduated oral syringe is provided with the 150ml bottles.

II.3.2 Pharmaceutical Development

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines. The purpose of the development was to develop a stable product essentially similar to the reference product Keppra 100mg/ml Oral Solution. Comparative analysis with the reference product on the EEA market demonstrated essential similarity. The qualitative composition of both the reference product and this product are also identical.

II.3.3 Manufacture of the product

The product is manufactured in accordance with the principles of good manufacturing practice (GMP). The product is manufactured using conventional manufacturing techniques. The manufacturing process has been validated using pilot scale batches and the validation protocol for the production scale batches (and a commitment to validate three batches) has been provided. The results show good production performance throughout production. All tests meet the requirements in the finished product specification and the data demonstrate reproducibility of the manufacturing process.

II.3.4 Control of Excipients

All excipients comply with their respective European Pharmacopoeia monographs where one exists for that excipient. Any non-pharmacopoeial excipients are controlled appropriately.
There are no excipients of human or animal origin used in the manufacture of the product. There are no novel excipients used in the manufacture of the product.

II.3.5 Control of Finished Product.

The finished product specification is adequate to control the relevant parameters for the dosage form. The release specifications for the drug product are based on the relevant European guidelines and the standard requirements associated with oral solutions. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. Satisfactory validation data for analytical methods have been provided. Batch analytical data from the proposed production site have been provided demonstrating compliance with the specification.

II.3.6 Packaging Material

The product is presented in Type III amber glass bottles containing 150ml or 300ml of drug product in an outer cardboard carton. A 10ml graduated oral syringe is provided with the 300ml bottle, and either a 3ml or a 1ml graduated oral syringe is provided with the 150ml bottles.
Bottle drawings and test certificates are provided. The packaging material complies with the relevant European guidelines.

II.3.7 Stability of the Finished Product

Stability data on the finished product in the proposed packaging have been provided in accordance with EU guidelines demonstrating the stability of the product. The approved shelf life of the product as packaged for sale and the storage conditions are stated in the Summary of Product Characteristics (SPC). Once open the product should be used within 30 days (see the SPC for further information).

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 Levetiracetam Wockhardt 100mg/ml Oral Solution.

II.5 Discussion on chemical, pharmaceutical and biological aspects

III. NON-CLINICAL ASPECTS

III.1 Discussion on non-clinical aspects

The pharmacodynamic, pharmacokinetic and toxicological properties of levetiracetam are well known. As levetiracetam is a widely used, well-known anti-epileptic drug the applicant has not provided additional studies and further studies are not required. An overview based on a literature review is considered appropriate.
The company's report has been compiled by an expert professional whose respective qualifications and experience are considered appropriate to perform the review as set out in Article 12 and in accordance with Annex I, Part I 1.4 of the Directive 2001/83/EC. The non-clinical overview contains summaries of a sufficient number of references, both non-clinical and clinical, to provide an extensive overview of current knowledge of levetiracetam with respect to treatment of epilepsy.

III.2 Ecotoxicity/environmental risk assessment (ERA)

Since Levetiracetam Wockhardt 100mg/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.

IV. CLINICAL ASPECTS

IV.1 Introduction

The application is for one strength of levetiracetam oral solution (100 mg/mL), under the name "Levetiracetam Wockhardt 100 mg/mL Oral Solution". The application is through the Mutual Recognition Procedure for a known active substance as a so called 'generic application' with the Ireland as the Reference Member State. The sole Concerned Member State is the UK. Levetiracetam has been registered for more than 10 years in the EU and the chosen reference medicinal product is Keppra oral solution (UCB Pharma SA) date of first marketing authorisation was 29th September 2000.

Levetiracetam is an established anti-epileptic medication in widespread clinical use throughout the EU. It is presented as an oral solution, suitable for paediatric use; or use by patients who have difficulty swallowing.

IV.2 Pharmacokinetics

Biowaiver

The product is a simple oral solution which contains the same active substance in the same concentration as the reference product and is therefore exempt from the requirement to show bioequivalence with the innovator product (CPMP/EWP/QWP/1401/98 "Note for Guidance on the Investigation of Bioavailability and Bioequivalence"). The applicant claims that as per the guideline, the proposed product does not contain any excipients that affect gastrointestinal transit, absorption or in vivo stability of the active substance.

IV.3 Clinical Pharmacology

The product is a generic formulation of a well known active substance. The applicant did not conduct any additional clinical pharmacology studies and this was considered appropriate.

IV.4 Clinical efficacy

The efficacy is considered to be demonstrated on the basis of studies conducted with the innovator product and the similarity between the generic and innovator products.

IV.5 Clinical safety

The Marketing Authorisation Holder submitted a set of documents describing the Pharmacovigilance System, including information on the availability of an EU Qualified Person for Pharmacovigilance (EU-QPPV) and the means for notification of adverse reaction reports in the EU or from a Third Country.

IV.6 Discussion on the clinical aspects

The clinical safety and efficacy of Levetiracetam Wockhardt100 mg/mL Oral Solution is based on its similarity to the innovator (original) product and the general principle of not requiring fresh animal and clinical tests to be conducted for every new brand of medicine developed.

V. OVERALL CONCLUSIONS

Levetiracetam Wockhardt 100mg/ml Oral Solution is a generic version of the clinically well established anti-epileptic drug levetiracetam and takes as reference the innovator product Keppra. No pre-clinical or clinical studies have been conducted in support of the application because under the relevant legislation and regulatory guidance they are not deemed necessary.

The product information has been recently updated to be consistent with that of Keppra. The risk benefit balance is considered to be positive.

VI. REVISION DATE

December 2020

VII. UPDATES

Procedure number	Product Information affected	Date of start of procedure	Date of end of procedure	Approval/non approval
IE/H/248/001/1B/010/G CRN 2133676 Scope: Change in the name of the medicinal product from 'Mevluxa' to 'Levetiracetam Wockhardt'.	SPC section 1, 4.4, 4.8	30/01/2017	21/06/2017	Approved
MA Transfer CRN009Z4T	SmPC section 7, 8, 10 Package Leaflet New MA Holder: Pinewood Laboratories Limited New PA number: PA0281/247/001	N/A	31/12/2020	Approved 31/12/2020