**IPAR**

**Public Assessment Report for a**
**Medicinal Product for Human Use**

Scientific Discussion

Levetiracetam Pinewood 100 mg/ml concentrate for solution for infusion
Levetiracetam
PA0281/238/001

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/5555/01/DC with the UK as RMS. The responsibility of RMS was transferred to Ireland on 20/06/2018 under procedure number IE/H/0616/1/DC.
Please note the following detail for the product in IE:
Marketing Authorisation Number: PA0281/238/001
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 Member States considered that the application for Levetiracetam Wockhardt 100mg/ml concentrate for solution for infusion could be approved. This prescription only medicine (POM) is used as monotherapy in the treatment of partial onset seizures with or without secondary generalisation in adults and adolescents from 16 years of age with newly diagnosed epilepsy. Levetiracetam Wockhardt 100mg/ml concentrate for solution for infusion is also indicated as adjunctive therapy

- in the treatment of partial onset seizures with or without secondary generalisation in adults adolescents, and children from 4 years 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.

This application was submitted using the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS) and Cyprus, France and Ireland as Concerned Member States (CMS). This application was made under Article 10(1) of Directive 2001/83/EC, as amended, as a so-called generic application. The reference medicinal product for this application is Keppra 100mg/ml concentrate for solution for infusion, which was first authorised to UCB Pharma S.A. on 29 September 2000 through Centralised procedure EU/1/00/146/030. The reference product has been authorised in the EEA for at least 10 years, therefore, the legal basis of this application is acceptable.

Levetiracetam, is a pyrrolidone derivative (S-enantiomer of α-ethyl-2-oxo-1-pyrrolidine acetamide), chemically unrelated to existing antiepileptic active substances.

No new non-clinical or clinical data were submitted, which is acceptable given that the application is for an intravenous product which is a generic medicinal product of an originator product that has been in clinical use for over 10 years.

The RMS has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for these product types at all sites responsible for the manufacture and assembly of this product. 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. For manufacturing sites outside the Community, the RMS has accepted copies of current GMP Certificates of satisfactory inspection summary reports, 'close-out letters' or 'exchange of information' issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.

The RMS considers that the pharmacovigilance system, as described by the MA holder, fulfils the requirements and provides adequate evidence that the MA holder has the services of a qualified person responsible for pharmacovigilance, and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country. The MA holder has provided a Risk

Management Plan (RMP).

The lack of an Environmental Risk Assessment (ERA) with this application for a generic product is acceptable.

The RMS and CMS considered that the application could be approved at Day 210 of the procedure on 5 October 2014. After a subsequent national phase, the Marketing Authorisation was granted in the UK on 3 November 2014.

## II. QUALITY ASPECTS

### II Quality aspects

### II.1 Introduction

The product is a clear, colourless concentrate for solution for infusion. Each ml of concentrate contains 100 mg of levetiracetam. The excipients are sodium chloride, sodium acetate trihydrate, acetic acid solution and water for injections.

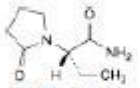
The concentrate is presented in 5ml, clear, neutral glass (Type I) vials. The vials are sealed with 13mm grey chlorobutyl PTFE (Teflon) faced rubber closures, secured with magenta aluminium flip-off caps. The vials are packed in a PVC tray and cardboard box in packs of five.

### II.2 Drug Substance

INN: Levetiracetam

Chemical name: (2*S*)-2-(2-Oxopyrrolidin-1-yl)butanamide

Structure:



Molecular formula: $C_8H_{14}N_2O_2$

Molecular weight: 170.2

All aspects of the manufacture and control of the active substance, levetiracetam, are covered by the European Directorate for the Quality of Medicines and Healthcare (EDQM) Certificate of Suitability and the levetiracetam complies with current Ph.Eur monograph requirements.

### II.3 Medicinal Product

**Pharmaceutical development**

The aim of the pharmaceutical development of Levetiracetam Wockhardt 100mg/ml concentrate for solution for infusion was to develop a generic version of the innovator product, Keppra 100mg/ml concentrate for solution for infusion.

Comparable impurity profiles were provided for the proposed and the reference products.

All excipients comply with their European Pharmacopoeia monographs, with the exception of acetic acid solution, which is controlled in line with a suitable in house specification. Satisfactory certificates of analysis have been provided for all excipients showing compliance with their proposed specifications.

None of the excipients contain materials of animal or human origin.

**Manufacture of the product**
A satisfactory batch formula has been provided for the manufacture of the finished product, together with an appropriate account of the manufacturing process. The manufacturing process has been validated with pilot scale batches and a validation protocol reflecting the full scale batch is provided and is satisfactory.

**Finished Product Specification**
The finished product specification is satisfactory. Test methods have been described and have been adequately validated, as appropriate. Batch data have been provided from pilot-scale batches and comply with the release specification. Certificates of analysis have been provided for any working standards used.

**Stability of the product**
Stability studies were performed in accordance with current guidelines on batches of the finished product, packed in the packaging proposed for marketing. The data from these studies support a shelf-life of 18 months for the product when the storage precaution 'Store below 25°C' is applied.

Chemical and physical in-use stability has been demonstrated for 7 days at 5-22°C when the concentrate is diluted with 0.9% sodium chloride, 5% dextrose or Hartmann's Solution to 2mg/ml. From a microbiological point of view, in-use storage time and conditions prior to use are the responsibility of the user.

**II.4 Discussion on chemical, pharmaceutical and biological aspects**
The grant of a marketing authorisation is recommended.

**II.5 SmPC, PIL and labelling**
In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPC) and Patient Information Leaflets (PIL) for products granted Marketing Authorisations at a national level are available on the MHRA website.

## III. NON-CLINICAL ASPECTS

**III Non-clinical aspects**

**III.1 Introduction**
No new non-clinical data have been submitted and none are required for an application of this type. The applicant's non-clinical overview has been written by an appropriately qualified person and is satisfactory.

**III.2 Pharmacology**
No new pharmacology data are required for this application and none have been submitted.

**III.3 Pharmacokinetics**
No new pharmacokinetic data are required for this application and none have been submitted.

**III.4 Toxicology**
No new toxicology data are required for this application and none have been submitted.

**III.5 Ecotoxicity/environmental risk assessment (ERA)**
Since the formulation of Levetiracetam Wockhardt 100mg/ml concentrate for solution for infusion is intended for generic substitution, it will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

**III.6 Discussion on the non-clinical aspects**
The grant of a marketing authorisation is recommended.

**IV. CLINICAL ASPECTS**

## IV Clinical aspects

### IV.1 Introduction

No new clinical data have been submitted and none are required for an application of this type. The applicant's clinical overview has been written by an appropriately qualified person and is considered acceptable.

### IV.2 Pharmacokinetics

In accordance with the guideline on the investigation of bioequivalence the applicant is not required to submit a therapeutic equivalence study if the product is to be administered as an aqueous intravenous solution containing the same active substance, in the same concentration as the reference product (CPMP/EWP/1401/98, subpoint 5.1.6, Parenteral solutions).

### IV.3 Pharmacodynamics

No new pharmacodynamic data are required for this application and none have been submitted.

### IV.4 Clinical efficacy

No new clinical efficacy data are required for this application and none have been submitted.

### IV.5 Clinical safety

No new clinical safety data are required for this application and none have been submitted.

### IV.6 Risk Management Plan

The applicant has submitted an RMP, 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 Levetiracetam Wockhardt 100mg/ml concentrate for solution for infusion. Routine pharmacovigilance activities and risk minimisation measures should be adequate for

this product, which contains a widely used active substance with a well-established safety profile.

A summary of safety concerns and planned risk minimisation activities, as approved in the RMP, is listed below:

| Safety concern | Routine risk minimisation measures | Additional risk minimisation measures |
|---|---|---|
| Abnormal behaviour and suicide | Routine risk minimisation.<br>The SmPC is up to date.<br>**Section 4.4, Special warnings and precautions for use state:** "Suicide, suicide attempt, suicidal ideation and behaviour have been reported in patients treated with anti-epileptic agents (including levetiracetam). A meta-analysis of randomized placebo-controlled trials of anti-epileptic medicinal products has shown a small increased risk of suicidal thoughts and behaviour. The mechanism of this risk is not known.<br>Therefore patients should be monitored for signs of depression and/or suicidal ideation and behaviours and appropriate treatment should be considered. Patients (and caregivers of patients) should be advised to seek medical advice should signs of depression and/or suicidal ideation or behaviour emerge."<br><br>Section 4.8, Undesirable effects state "Suicide attempt, suicidal ideation psychotic disorder, abnormal behaviour, hallucination, anger, confusional state, panic attack affect lability/mood swings, agitation" and "Completed suicide, personality disorder, thinking abnormal". | No additional risk minimisation activities are necessary for the safe and effective use of the medicinal product. |
| Safety and efficacy in infants with epilepsy aged less than 1 year. | Routine risk minimisation<br>The SmPC is up to date.<br>**Section 4.2, Posology and method of administration, states** "*Monotherapy* - The safety and efficacy of levetiracetam has not been thoroughly assessed in infants with epilepsy aged less than 1 year. Only 35 infants aged less than 1 year with partial onset seizures have been exposed in clinical studies of which only 13 were aged < 6 months."<br>*Add-on therapy for infants and children less than 4 years*<br>The safety and efficacy of Levetiracetam concentrate for Solution for infusion in infants and children less than 4 years have not yet been established.<br>Currently available data are described in section 4.8., 5.1 and 5.2 but no recommendation on a posology can be made. | No additional risk minimisation activities are necessary for the safe and effective use of the medicinal product. |

| Safety concern | Routine risk minimisation measures | Additional risk minimisation measures |
|---|---|---|
| | Section 4.4, Special warnings and precautions for use, state: "The safety and efficacy of levetiracetam has not been thoroughly assessed in infants with epilepsy aged less than 1 year. Only 35 infants aged less than 1 year with partial onset seizures have been exposed in clinical studies of which only 13 were aged < 6 months." | |
| Long term effects on learning, intelligence, growth, endocrine function, puberty and childbearing potential in children. | Routine risk minimisation<br>The SmPC is up to date.<br>**Section 4.4, Special warnings and precautions for use states:** "Available data in children did not suggest impact on growth and puberty. However, long term effects on learning, intelligence, growth, endocrine function, puberty and childbearing potential in children remain unknown."<br><br>Section 4.6, Fertility, pregnancy and lactation states "Infants born from mothers who have been taking morphine on a chronic basis may exhibit withdrawal symptoms." | No additional risk minimisation activities are necessary for the safe and effective use of the medicinal product. |

**IV.7 Discussion on the clinical aspects**

The grant of a Marketing Authorisation is recommended for this application.

**V User consultation**

The package leaflet has been evaluated via a user consultation study, in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The language used for the purpose of user testing the PIL was English.

The results show that the package leaflet meets the criteria for readability, as set out in the guideline on the readability of the label and package leaflet of medicinal products for human use.

## 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 levetiracetam is considered to have demonstrated the therapeutic value of the compound. The benefit/risk balance 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/5555/DC to IE/H/0616/1/DC | | | |
| MAH transfer | | | | 11/01/2022 |