IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific Discussion

Levetiracetam Thame 100 mg/ml oral solution
Levetiracetam
PA22697/012/001

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/5754/1/DC with the UK as RMS. The responsibility of RMS was transferred to Ireland on 03/10/2018 under procedure number IE/H/0784/1/DC.
Please note the following detail for the product in IE:
Marketing Authorisation Number: PA22697/012/001
Marketing Authorisation Holder: SYRI Limited, t/a Thame Laboratories

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 have granted a Marketing Authorisation (MA) for the medicinal product Levetiracetam 100mg/ml Oral Solution.

This product is a prescription-only medicine (legal status POM) indicated 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 is also indicated as adjunctive therapy:

- in the treatment of partial onset seizures with or without secondary generalisation in adults, adolescents, 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; and
- 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 Ireland as a Concerned Member State (CMS).

The application was made under Article 10(1) of Directive 2001/83/EC, as amended, as a generic medicinal product. The reference medicinal product which has been authorised in accordance with Community provisions in force for not less than 10 years in the European Economic Area is Keppra 100 mg/ml Oral Solution; this reference product was authorised to UCB Pharma SA, through the centralised procedure, on 20 September 2000 (EU/1/00/146/027, 031, 032).

Levetiracetam 100mg/ml Oral Solution contains the active ingredient levetiracetam. Levetiracetam is a pyrrolidone derivative (S-enantiomer of α-ethyl-2-oxo-1-pyrrolidine acetamide), chemically unrelated to existing antiepileptic active substances.

The mechanism of action of levetiracetam still remains to be fully elucidated but appears to be different from the mechanisms of current antiepileptic medicinal products. *In vitro* and *in vivo* experiments suggest that levetiracetam does not alter basic cell characteristics and normal neurotransmission. *In vitro* studies show that levetiracetam affects intraneuronal Ca^{2+} levels by partial inhibition of N type Ca^{2+} currents and by reducing the release of Ca^{2+} from intraneuronal stores. In addition, it partially reverses the reductions in GABA- and glycine-gated currents induced by zinc and β-carbolines. Furthermore, levetiracetam has been shown in *in vitro* studies to bind to a specific site in rodent brain tissue. This binding site is the synaptic vesicle protein 2A, believed to be involved in vesicle fusion and neurotransmitter exocytosis. Levetiracetam and related analogues show a rank order of affinity for binding to the synaptic vesicle protein 2A, which correlates with the potency of their anti-seizure protection in the mouse audiogenic model of epilepsy. This finding suggests that the interaction between levetiracetam and the synaptic vesicle protein 2A seems to contribute to the antiepileptic mechanism of action of the medicinal product.

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

Since Levetiracetam 100mg/ml Oral Solution is intended for generic substitution, this will not lead to an increased exposure to the environment. An Environmental Risk Assessment (ERA) is, therefore, not deemed necessary.

According to the CPMP *Guideline on the investigation of bioequivalence* (CPMP/EWP/QWP/1401/98 Rev. 1/Corr**) a bioequivalence study may be waived for oral aqueous solutions that contain an active substance in the same concentration as an approved oral solution. The applicant has not submitted a bioequivalence study on this basis, and this is acceptable.

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 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.

A Risk Management Plan (RMP) and a summary of the pharmacovigilance system have been provided with this application and are satisfactory.

The RMS and CMS considered that the application could be approved at the end of procedure (Day 210) on 21 July 2015. After a subsequent National phase, a licence was granted in the UK on 17 August 2015.

II. QUALITY ASPECTS

II Quality aspects

II.1 Introduction

This application is submitted according to Article 10(1) of Directive 2001/83/EC, as amended, with Keppra 100 mg/ml Oral Solution, Marketing Authorisation Holder UCB Pharma SA, as a reference product in the Community.

Levetiracetam 100mg/ml Oral Solution is formulated as a clear, colourless solution with grape flavour. Each ml of oral solution contains 100 mg levetiracetam. The excipients present in the formulation are: sodium citrate (E331) (for pH-adjustment), citric acid monohydrate (for pH-adjustment), methyl parahydroxybenzoate (E218), ammonium glycyrrhizate, glycerol (E422), liquid maltitol (E965), grape flavour (contains propylene glycol (E1520)) and purified water.

The oral solution is presented in 150 ml and 300 ml volume European Pharmacopoeia (Ph. Eur) Type III amber glass bottles, closed with tamper evident, child resistant white plastic caps consisting of a polypropylene inner, polyethylene outer and expanded polyethylene (EPE) liner.

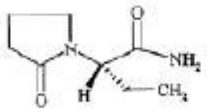
The 150 ml glass bottle is filled with 150 ml Levetiracetam 100mg/ml Oral Solution and is packed in a cardboard box containing a 1 ml oral syringe, with 0.05 ml graduation markings, or a 3 ml oral syringe, with 0.1 ml graduation markings. The cardboard box also includes an adaptor for the syringe.

The 300 ml glass bottle is filled with 300 ml Levetiracetam 100mg/ml Oral Solution and is packed in a cardboard box containing a 10ml oral syringe, with 0.25 ml graduation markings, and an adaptor for the syringe.

II.2 Drug Substance

Levetiracetam

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
Appearance:	White or almost white powder
Solubility:	Very soluble in water, soluble in acetonitrile and practically insoluble in hexane

Levetiracetam is the subject of a Ph. Eur monograph.

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

II.3 Medicinal Product

Pharmaceutical development

The pharmaceutical development of Levetiracetam 100mg/ml Oral Solution has been described and is satisfactory.

The applicant has justified the absence of a bioequivalence study based on the CPMP *Guideline on the investigation of bioequivalence* (CPMP/EWP/QWP/1401/98 Rev.1/Corr**). This is discussed in Section IV.2.

Comparative dissolution studies have been provided for the proposed product versus the reference product under differing pH conditions, and in all cases drug release was > 85 % within 10 minutes.

All of the excipients used in the manufacture of Levetiracetam 100mg/ml Oral Solution, with the exception of the grape flavour, meet the requirements of the current European Pharmacopoeia. The grape flavour is controlled by a satisfactory in-house specification.

Satisfactory Certificates of Analysis have been provided for all excipients showing compliance with their proposed specifications.

None of the excipients are sourced from animal or human origin.

No genetically modified organisms (GMO) have been used in the preparation of this product.

Manufacture of the product

A satisfactory batch formula has been provided for the manufacture of this finished product, together with an appropriate account of the manufacturing process. A validation report for commercial scale batches has been provided. The process validation data provided is satisfactory.

Product Specifications

The finished product specification is satisfactory. Satisfactory batch analysis was performed on three production scale batches of the finished product. Certificates of Analysis have been provided for all 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 for the unopened bottle of 12 months, and an in-use shelf life of 7 months. There are no special storage conditions for this product.

Suitable post approval stability commitments have been provided.

II.4 Discussion on chemical, pharmaceutical and biological aspects

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

III. NON-CLINICAL ASPECTS

III Non-clinical aspects

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

The applicant's non-clinical overview has been written by an appropriately qualified person. The non-clinical overview on the pharmacology, pharmacokinetics and toxicology is adequate. The non-clinical sections of the SmPC are in line with the reference product.

Since the formulation of Levetiracetam 100mg/ml Oral Solution 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.

There are no major objections to the approval of this application from a non-clinical point of view.

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

No bioequivalence study to compare the test and the reference product has been provided. The applicant has justified the absence of a bioequivalence study based on the CPMP *Guideline on the investigation of bioequivalence* (CPMP/EWP/QWP/1401/98 Rev.1/Corr**), which states that 'if the test product is an aqueous oral solution at the time of administration and contains an active substance in the same concentration as an oral solution, bioequivalence studies may be waived'.

The excipients are very similar between the two products with the exception of acesulfame potassium, a sweetener, that is absent in the proposed oral solution and would not impact on gastro-intestinal (GI) motility. Furthermore, dissolution data have been presented between the test and the reference products and these are comparable (please see Section II.3). Since Levetiracetam 100mg/ml Oral Solution is completely soluble in water and the formulation contains the active substance at the same concentration and has the same excipients as the reference product, with the exception of the sweetener listed above, the waiver for bioequivalence studies is accepted.

IV.3 Pharmacodynamics

No new pharmacodynamics 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 (RMP)

The Marketing Authorisation holder 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 100mg/ml Oral Solution.

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

Summary table of safety concerns

1.1.1 Summary of safety concerns	
Important identified risks	• Use in patients with hypersensitivity to levetiracetam or other excipients and severe skin reactions • Use in patients with renal and hepatic impairment (especially elderly) • Abrupt discontinuation of the medicinal product • Effects on performing skilled tasks • Use in patients with fructose intolerance • Decreased levetiracetam efficacy with concomitant use of osmotic laxative macrogol
Important potential risks	• Suicidal ideation and behaviour • Use in pregnancy and lactation • Risk of hypernatremia (consideration in patients on controlled sodium diet)
Missing information	• Use in children and adolescents below 16 years as monotherapy treatment

Planned risk minimisation activities

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Important identified risks		
Use in patients with hypersensitivity to levetiracetam or other excipients and severe skin reactions	The risks of use in patients with hypersensitivity to levetiracetam or other excipients and severe skin reactions associated with the use of the drug product are described in the SPC Sections 4.3, 4.4 and 4.8, and appropriate advice is provided to the prescriber to minimise these risks.	None
Use in patients with renal and hepatic impairment (especially in elderly)	The risks associated with the use of the drug product in patients with renal and hepatic impairment (especially elderly) associated with the use of the drug product, and (2) of hepatic impairment associated with the use of the drug product are described in the SPC Sections 4.2, 4.4, 4.8, and 5.2, and appropriate advice is provided to the prescriber to minimise these risks	None
Abrupt discontinuation of the medicinal product	The risks associated with abrupt discontinuation of the drug product are described in the SPC Sections 4.4 and 4.6, and appropriate advice is provided to the prescriber to minimise these risks.	None
Effects on performing skilled tasks	The risks of effects on performing skilled tasks associated with the use of the drug product are described in the SPC Sections 4.7, 4.8 and 4.9, and appropriate advice is provided to the prescriber to minimise these risks.	None
Use in patients with fructose intolerance	The risks associated with the use of the drug product in patients with fructose intolerance are described in the SPC Section 4.4, and appropriate advice is provided to the prescriber to minimise these risks.	None

Decreased levetiracetam efficacy with concomitant use of osmotic laxative macrogol	The risk of decreased levetiracetam efficacy on concomitant use of the drug product with osmotic laxative macrogol is described in the SPC Section 4.5, and appropriate advice is provided to the prescriber to minimise this risk.	None
Important potential risk		
Suicidal ideation and behaviour	The risk of suicide-related events associated with the use of the drug product is described in the SPC Sections 4.4 and 4.8, and appropriate advice is provided to the prescriber to minimise this risk.	None
Use in pregnancy and lactation	The risks associated with the use of the drug product in pregnancy and lactation, are described in the SPC Sections 4.6 and 5.3, and appropriate advice is provided to the prescriber to minimise these risks.	None
Risk of hypernatremia (consideration in patients on controlled sodium diet)	The risk of hypernatremia (consideration in patients on controlled sodium diet) associated with the use of the drug product is described in the SPC Section 4.4, and appropriate advice is provided to the prescriber to minimise these risks.	None
Missing information		
Use in children and adolescents below 16 years as monotherapy treatment	The SPC Sections 4.2 and 4.4 states that the safety and efficacy of levetiracetam in children and adolescents below 16 years as monotherapy treatment have not been established. There are no data available.	Not applicable

V.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 package leaflet 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 Levetiracetam 100mg/ml Oral Solution is acceptable and no new non-clinical or clinical safety concerns have been identified. The applicant gives an adequate justification for waiving a bioequivalence study. The overall benefit/risk assessment is, therefore, considered to be positive.

The Summary of Product Characteristics (SmPC), package leaflet and labelling are satisfactory, in line with current guidelines and consistent with the reference product. In accordance with Directive 2012/84/EU, the current approved UK versions of the SmPC and package leaflet for this product are available on the Medicines and Healthcare products Regulatory Agency website.

VI. REVISION DATE

23/02/2022

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/5754/1/DC to IE/H/0784/1/DC			