Public Assessment Report

Decentralised Procedure

Levetiracetam Medsolutions 100mg/ml Oral solution

(Levetiracetam)

Procedure No: UK/H/6100/001/DC

UK Licence No: PL 44400/0001

Medsolutions (Europe) Limited.
This is a summary of the Public Assessment Report (PAR) for Levetiracetam Medsolutions 100mg/ml Oral solution (PL 44400/0001; UK/H/6100/001/DC). It explains how Levetiracetam Medsolutions 100mg/ml Oral solution was assessed and its authorisation recommended, as well as its conditions of use. It is not intended to provide practical advice on how to use Levetiracetam Medsolutions 100mg/ml Oral solution.

The product will be referred to as Levetiracetam Oral Solution throughout the remainder of this PAR.

For practical information about using Levetiracetam Oral Solution, patients should read the package leaflet or contact their doctor or pharmacist.

What is Levetiracetam Oral Solution and what is it used for?
Levetiracetam Oral Solution is a ‘generic medicine’. This means that Levetiracetam Oral Solution is similar to a ‘reference medicine’ already authorised in the European Union (EU) called Keppra 100 mg/ml oral solution (UCB Pharma SA, Belgium).

Levetiracetam Oral Solution is used:
- On its own in adults and adolescents from 16 years of age with newly diagnosed epilepsy, to treat a certain form of epilepsy. Epilepsy is a condition where the patient has repeated fits (seizures). Levetiracetam is used for the epilepsy form in which the fits initially affect only one side of the brain, but could thereafter extend to larger areas on both sides of the brain (partial onset seizure with or without secondary generalisation). Levetiracetam has been given to the patient by their doctor to reduce the number of fits.
- As an add-on to other antiepileptic medicines to treat:
  - Myoclonic seizures (short, shock-like jerks of a muscle or group of muscles) in adults and adolescents from 12 years of age with juvenile myoclonic epilepsy.
  - Primary generalised tonic-clonic seizures (major fits, including loss of consciousness) in adults and adolescents from 12 years of age with idiopathic generalised epilepsy (the type of epilepsy that is thought to have a genetic cause).
  - Partial onset seizures with or without generalisation in adults, adolescents, children and infants from one month of age.

How does Levetiracetam Oral Solution work?
Levetiracetam Oral Solution contains the active ingredient levetiracetam, which is an antiepileptic medicine used to treat seizures in epilepsy.

How is Levetiracetam Oral Solution used?
The pharmaceutical form of Levetiracetam Oral Solution is an oral solution and the route of administration is via the mouth (oral).

This medicine should be taken by mouth using the oral syringe provided to measure the correct dose. Levetiracetam Oral Solution may be diluted in a glass of water or baby’s bottle and may be taken with or without food.

The patient must take this medicine exactly as their doctor has told them. The patient should check with
their doctor or pharmacist if they are not sure.

This medicine must be taken twice a day, once in the morning and once in the evening, at about the same time each day.

Please read section 3 of the package leaflet for detailed information on dosing recommendations, the route of administration, and the duration of treatment.

Levetiracetam Oral Solution can only be obtained with a prescription.

**What benefits of Levetiracetam Oral Solution have been shown in studies?**
No additional studies were needed as Levetiracetam Oral Solution is a generic medicine that is taken orally, as a solution, and contains the same active substance, in the same concentration, as the reference medicine, Keppra 100 mg/ml oral solution (UCB Pharma SA, Belgium). For this reason Levetiracetam Oral Solution is expected to be bioequivalent with the reference medicine. Two medicines are bioequivalent when they produce the same levels of the active substance in the body.

**What are the possible side effects of Levetiracetam Oral Solution?**
Because Levetiracetam Oral Solution is a generic medicine, its benefits and possible side effects are taken as being the same as the reference medicine.

For the full list of restrictions, see the package leaflet.

For the full list of all side effects reported with Levetiracetam Oral Solution, see section 4 of the package leaflet available on the MHRA website.

**Why was Levetiracetam Oral Solution approved?**
It was concluded that, in accordance with EU requirements, Levetiracetam Oral Solution has been shown to have comparable quality and is considered bioequivalent to Keppra 100 mg/ml oral solution (UCB Pharma SA, Belgium). Therefore, the MHRA decided that as for Keppra 100 mg/ml oral solution (UCB Pharma SA, Belgium), the benefits are greater than their risk and recommended that it can be approved for use.

**What measures are being taken to ensure the safe and effective use of Levetiracetam Oral Solution?**
A risk management plan (RMP) has been developed to ensure that Levetiracetam Oral Solution is used as safely as possible. Based on this plan, safety information has been included in the Summary of Product Characteristics and the package leaflet for Levetiracetam Oral Solution including the appropriate precautions to be followed by healthcare professionals and patients.

Known side effects are continuously monitored. Furthermore new safety signals reported by patients/healthcare professionals will be monitored/reviewed continuously.
Other information about Levetiracetam Oral Solution
France, Netherlands, Sweden and the UK agreed to grant a Marketing Authorisation for Levetiracetam Oral Solution on 06 October 2016. A Marketing Authorisation was granted in the UK on 10 November 2016.

The full PAR for Levetiracetam Oral Solution follows this summary.

For more information about treatment with Levetiracetam Oral Solution read the package leaflet, or contact your doctor or pharmacist.

This summary was last updated in December 2016.
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I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Member States considered that the application for Levetiracetam Oral Solution (PL 44400/0001; UK/H/6100/001/DC) could be approved.

The product is a prescription-only medicine (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 Oral Solution 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 primary generalised tonic-clonic seizures in adults and adolescents from 12 years of age with Idiopathic Generalised Epilepsy.
- in the treatment of myoclonic seizures in adults and adolescents from 12 years of age with Juvenile Myoclonic Epilepsy.

The application was submitted using the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS) and France, Netherlands and Sweden as 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 Keppra 100 mg/ml oral solution which was first authorised to UCB Pharma SA, Belgium, on 29 September 2000 via the centralised procedure.

The active substance, levetiracetam, is a pyrrolidine 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. 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 was based on being a generic medicinal product of an originator product that has been licensed for over 10 years.

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

The RMS has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place 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.

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 and CMS considered that the application could be approved at the end of procedure on 06 October 2016. After a subsequent national phase, a licence was granted in the UK on 10 November 2016.
II QUALITY ASPECTS

II.1 Introduction
Each one ml of oral solution contains 100 mg levetiracetam. Other ingredients consist of the following pharmaceutical excipients sodium citrate, anhydrous citric acid, methyl parahydroxybenzoate (E218), propyl parahydroxybenzoate (E216), ammonium glycyrrhizate, acesulfame potassium (E950), glycerol (E422), liquid maltitol (E965), grape flavour, sucralose and purified water.

The finished product is packed into the following pack sizes and presentations:

- 300 ml amber glass bottles (type III) with a child resistant closure in a cardboard box also containing a 10 ml graduated oral syringe and an adaptor for the syringe.
- 150 ml amber glass bottles (type III) with a child resistant closure in a cardboard box also containing a 3 ml graduated oral syringe and an adaptor for the syringe.
- 150 ml amber glass bottles (type III) with a child resistant closure in a cardboard box also containing a 1 ml graduated oral syringe and an adaptor for the syringe.

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

II.2. Drug Substance
INN: Levetiracetam
Chemical name: \((2S)-2-(2-Oxopyrrolidin-1-yl)butanamide\)
Structural formula:

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\text{\begin{align*}
&\text{O} \\
&\text{H} \\
&\text{N} \\
&\text{H} \\
&\text{CH}_3 \\
\end{align*}}
\]

Molecular formula: \(\text{C}_8\text{H}_{14}\text{N}_2\text{O}_2\)
Molecular mass: 170.2 g/mol
Appearance: White or almost white powder.
Solubility: Very soluble in water, soluble in acetonitrile, practically insoluble in hexane

Levetiracetam is the subject of a European Pharmacopoeia monograph.

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.

II.3. Medicinal Product
Pharmaceutical Development
The objective of the development programme was to formulate a safe, efficacious, oral solution containing 100 mg levetiracetam per ml of oral solution that is comparable in performance to the originator product Keppra 100 mg/ml oral solution (UCB Pharma SA, Belgium). A satisfactory account of the pharmaceutical development has been provided.
All excipients comply with their respective European Pharmacopoeia monographs with the exception of the grape flavour which is controlled to a suitable in-house specification. Satisfactory Certificates of Analysis have been provided for all excipients. Suitable batch analysis data have been provided for each excipient.

None of the excipients contain materials of 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 the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated at the commercial-scale batch size and shown satisfactory results. The process validation protocol to be followed for the full scale production batch size has been submitted and is satisfactory.

**Finished Product Specification**
The finished product specification proposed is acceptable. Test methods have been described that have been adequately validated. Batch data have been provided that comply with the release specifications. 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 finished product in the packaging proposed for marketing. The data from these studies support a shelf-life of 18 months for the unopened bottle with the storage condition ‘Store in the original container in order to protect from light.’ The in-use shelf life of the product is 7 months after first opening.

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

**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.1 Introduction
As the pharmacodynamic, pharmacokinetic and toxicological properties of levetiracetam 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 MAH’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 Levetiracetam 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.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.1 Introduction
The absence of a bioequivalence study has been adequately justified in line with the CPMP guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/Corr**). Since the test product is to be administered as an aqueous oral solution containing the same active substance concentration as the approved reference medicinal product, no bioequivalence data have been submitted with this application and none are required. The guideline also state that in case the excipients may affect gastrointestinal transit (e.g. sorbitol, mannitol), a bioequivalence study should be conducted, unless the differences in the amounts of these excipients can be adequately justified by reference to other data. The applicant included an identical amount of liquid maltitol in the formulation to that reported for Keppra 100 mg/ml oral solution. Apart from the addition of sucralose, the qualitative composition of the applicant’s Levetiracetam oral solution can be considered as similar to that of Keppra 100mg/ml oral solution. However the addition of sucralose is not expected to affect the bioavailability of levetiracetam, which is a highly soluble and permeable drug. Therefore the waiver for a bioequivalence study for Levetiracetam is acceptable.

No new efficacy or safety studies have been performed and none are required for this type of application. A comprehensive review of the published literature has been provided by the applicant, citing the well-established clinical pharmacology, efficacy and safety of levetiracetam.

Based on the data provided, Levetiracetam Oral Solution can be considered bioequivalent to the reference product Keppra 100 mg/ml oral solution (UCB Pharma SA, Belgium).
IV.2 Pharmacokinetics
In line with the CPMP guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/Corr**), no bioequivalence data have been submitted with this application and none are required for this product.

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 were required for this application.

IV.6 Risk Management Plan (RMP)
The marketing authorisation holder (MAH) has submitted a risk management plan (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 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:

| Important identified risks | • Hypersensitivity including serious skin reactions (drug reaction with eosinophilia and systemic symptoms [DRESS], toxic epidermal necrolysis, Stevens-Johnson Syndrome and erythema multiforme) |
|                           | • Use in patients with renal insufficiency |
|                           | • Abnormal behaviour and suicide |
|                           | • Blood dyscrasias |
| Important potential risks | • Use in pregnancy and lactation |

| Missing information | • Long-term effects on learning, intelligence, growth, endocrine function, puberty and childbearing potential in children |
|                    | • Safety and efficacy of Levetiracetam in children and adolescents below 16 years as monotherapy treatment |
|                    | • Effect on human fertility |

Routine pharmacovigilance and routine risk minimisation are proposed for all safety concerns.

IV.7 Discussion on the clinical aspects
The grant of a marketing authorisation is recommended for this application from a clinical point of view.

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.

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 and the product can be regarded as bioequivalent to the authorised reference product. The benefit-risk is, therefore, considered to be positive.
Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labels
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.

The approved labelling for this medicine is presented below:
Annex 1 - Table of content of the PAR update for MRP and DCP

**Steps Taken After The Initial Procedure With An Influence On The Public Assessment Report**
(Type II variations, PSURs, commitments)

<table>
<thead>
<tr>
<th>Scope</th>
<th>Procedure number</th>
<th>Product Information affected</th>
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<th>Date of end of procedure</th>
<th>Approval/ non approval</th>
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