Medicines & Healthcare products
Regulatory Agency

Public Assessment Report

National Procedure

Levetiracetam Rudipharm 250mg Film-coated Tablets
Levetiracetam Rudipharm 500mg Film-coated Tablets
Levetiracetam Rudipharm 750mg Film-coated Tablets
Levetiracetam Rudipharm 1000mg Film-coated Tablets

levetiracetam

PL 49565/0133-0136

Rudipharm Limited

LAY SUMMARY

Levetiracetam Rudipharm 250, 500, 750 & 1000mg Film-coated Tablets
levetiracetam

This is a summary of the Public Assessment Report (PAR) for Levetiracetam Rudipharm 250, 500, 750 & 1000mg Film-coated Tablets. It explains how these products were assessed and their authorisation recommended, as well as their conditions of use. It is not intended to provide practical advice on how to use these products.

These products will be referred to as Levetiracetam Tablets in this lay summary for ease of reading.

For practical information about using Levetiracetam Tablets, patients should read the Patient Information Leaflet (PIL) or contact their doctor or pharmacist.

What are Levetiracetam Tablets and what are they used for?
These products are generic medicines. This means that these medicines are the same as, and considered interchangeable with, reference medicines already authorised, called Keppra 250, 500, 750 & 1000 mg Film-coated Tablets.

Levetiracetam Tablets are used:

- on their 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 patients have repeated fits (seizures). Levetiracetam Tablets are 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 Tablets have been given to the patient by their doctor to reduce the number of fits.
- as an add-on to other antiepileptic medicines to treat:
  - partial onset seizures with or without generalisation in adults, adolescents, children and infants from one month of age.
  - 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).

How do Levetiracetam Tablets work?
Levetiracetam is an antiepileptic medicine (a medicine used to treat seizures in epilepsy).

How are Levetiracetam Tablets used?
The pharmaceutical form of these medicines is a film-coated tablet and the route of administration is oral (by mouth).

The patient should take the number of tablets following their doctor’s instructions.

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

Adjunctive Therapy and Monotherapy (from 16 years of age)
Adults (≥18 years) and adolescents (12 to 17 years) weighing 50 kg or more:
Recommended dose: between 1,000 mg and 3,000 mg each day.

When the patient will first start taking Levetiracetam Tablets, their doctor will prescribe them a lower dose during 2 weeks before giving them the lowest daily dose.

Example: if the patient's daily dose is intended to be 1,000 mg, their reduced starting dose is 1 tablet of 250 mg in the morning and 1 tablet of 250 mg in the evening, and the dose will be gradually incremented to reach 1,000 mg daily after 2 weeks.

Adolescents (12 to 17 years) weighing 50 kg or less:
The patient's doctor will prescribe the most appropriate pharmaceutical form of Levetiracetam according to weight and dose.

Dose in infants (1 month to 23 months) and children (2 to 11 years) weighing less than 50 kg:
The patient's doctor will prescribe the most appropriate pharmaceutical form of Levetiracetam according to the age, weight and dose.

Levetiracetam 100 mg/ml oral solution is a formulation more appropriate to infants and children under the age of 6 years and to children and adolescents (from 6 to 17 years) weighing less than 50kg and when tablets don't allow accurate dosage.

Method of administration:
The patient should swallow Levetiracetam Tablets with a sufficient quantity of liquid (e.g. a glass of water). The patient may take Levetiracetam with or without food. After oral administration the bitter taste of levetiracetam may be experienced.

Duration of treatment:
• Levetiracetam is used as a chronic treatment. The patient should continue Levetiracetam treatment for as long as their doctor has told them.
• The patient should not stop their treatment without their doctor's advice as this could increase their seizures.

For further information on how Levetiracetam Tablets are used, refer to the PIL and Summaries of Product Characteristics (SmPCs) available on the Medicines and Healthcare products Regulatory Agency (MHRA) website.
These medicines can only be obtained with a prescription.

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

What benefits of Levetiracetam Tablets have been shown in studies?
Because Levetiracetam Tablets are generic medicines, studies in healthy volunteers have been limited to tests to determine that it is bioequivalent to 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 Tablets?
For the full list of all side effects reported with these medicines, see Section 4 of the PIL or the SmPCs available on the MHRA website.

If a patient gets any side effects, they should talk to their doctor, pharmacist or nurse. This includes any possible side effects not listed in the product information or the PIL that comes with the medicine. Patients can also report suspected side effects themselves, or a report can be made on their behalf by someone else who cares for them, directly via the Yellow Card scheme at https://yellowcard.mhra.gov.uk or search for 'MHRA Yellow Card' online. By reporting side effects, patients can help provide more information on the safety of this medicine.

Because Levetiracetam Tablets are generic medicines and are bioequivalent to the reference medicines, their benefits and possible side effects are considered to be the same as the reference medicines.

Why were Levetiracetam Tablets approved?
It was concluded that, Levetiracetam Tablets has been shown to be bioequivalent to the reference medicine. Therefore, the MHRA decided that, as for the reference medicine, the benefits are greater than the risks and recommended that it can be approved for use.

What measures are being taken to ensure the safe and effective use of Levetiracetam Tablets?
As for all newly-authorised medicines, a Risk Management Plan (RMP) has been developed for Levetiracetam Tablets. The RMP details the important risks of Levetiracetam Tablets, how these risks can be minimised, any uncertainties about Levetiracetam Tablets (missing information), and how more information will be obtained about the important risks and uncertainties.

The following safety concerns have been recognised for Levetiracetam Tablets:

Summary of safety concerns	
Important identified risks	• Suicidality in patients • Abnormal behaviour • Blood dyscrasias
Important potential risks	• Seizure worsening • Encephalopathy • Decreased levetiracetam efficacy when oral levetiracetam is concomitantly administered with macrogol
Missing information	• Long-term effects in children on learning, intelligence, growth, endocrine function, puberty, and childbearing potential

The information included in the SmPC and the PIL is compiled based on the available quality, non-clinical and clinical data, and includes appropriate precautions to be followed by healthcare professionals and patients. Side effects of Levetiracetam Tablets are continuously monitored and reviewed including all reports of suspected side-effects from patients, their carers, and healthcare professionals.

An RMP and a summary of the pharmacovigilance system have been provided with these applications and are satisfactory.

Other information about Levetiracetam Tablets

Marketing Authorisations for Levetiracetam Tablets were granted in the United Kingdom (UK) on 9 August 2024.

The full PAR for Levetiracetam Tablets follows this summary.

This summary was last updated in September 2024.

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I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Medicines and Healthcare products Regulatory Agency (MHRA) considered that the applications for Levetiracetam Rudipharm 250, 500, 750 & 1000mg Film-coated Tablets (PL 49565/0133-0136) could be approved.

The products are approved for the following indications:

Levetiracetam is 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 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.
- in the treatment of primary generalised tonic-clonic seizures in adults and adolescents from 12 years of age with Idiopathic Generalised Epilepsy.

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 Ca2+ levels by partial inhibition of N-type $Ca2^{+}$ currents and by reducing the release of $Ca2^{+}$ 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 analogs 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.

These applications were approved under Regulation 51B of The Human Medicines Regulation 2012, as amended (previously Article 10(1) of Directive 2001/83/EC, as amended), as generic medicines of suitable originator medicinal products, Keppra 250, 500, 750 & 1000 mg Film-coated Tablets that has been licensed for suitable time, in line with the legal requirements.

No new non-clinical studies were conducted, which is acceptable given that the applications are for generic medicinal products of suitable reference products.

With the exception of the bioequivalence study, no new clinical studies were conducted, which is acceptable given that the applications are for generic medicinal products of suitable reference products. The bioequivalence study was conducted in-line with current Good Clinical Practice (GCP).

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

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

Marketing Authorisations for Levetiracetam Tablets were granted in the United Kingdom (UK) on 9 August 2024.

II QUALITY ASPECTS

II.1 Introduction

The active substance is called levetiracetam.
Each Levetiracetam Rudipharm tablet contains 250, 500, 750 or 1000 mg of levetiracetam.

The core ingredients are: maize starch, croscarmellose sodium, povidone, colloidal anhydrous silica, talc and magnesium stearate.

The coating ingredients are: polyvinyl alcohol-part hydrolyzed, titanium dioxide, macrogol and talc.
The 250 mg tablets additionally include indigo carmine.
The 500 and 750 mg tablets additionally include iron oxide yellow.
The 750 mg tablets additionally include iron oxide red.

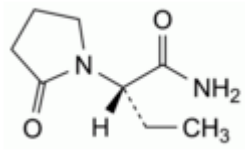
The finished products are packaged in Alu-PVC blister packs of 20, 30, 50, 60, 100 film-coated tablets.

Not all pack sizes may be marketed.

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

II.2 ACTIVE SUBSTANCE

rINN: levetiracetam
Chemical Name: (2*S*)-2-(2-Oxopyrrolidin-1-yl)butanamide.
Molecular Formula: $C_8H_{14}N_2O_2$



Chemical Structure:
Molecular Weight: 170.2
Appearance: White or almost white powder.
Solubility: Very soluble in water, soluble in acetonitrile, practically insoluble in heptane.

Levetiracetam is the subject of a European Pharmacopoeia monograph.

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

II.3 DRUG PRODUCTS

Pharmaceutical development
A satisfactory account of the pharmaceutical development was provided.

Comparative *in vitro* dissolution and impurity profiles were provided for the proposed and reference products.

All excipients comply with either their respective European/national monographs, or suitable in-house specification. Satisfactory Certificates of Analysis were provided for all excipients.

No excipients of animal or human origin are used in the final products.

Confirmation has been given that the magnesium stearate used in the tablets is of vegetable origin.

These products do not contain or consist of genetically modified organisms (GMO).

Manufacture of the products
A description and flow-chart of the manufacturing method has been provided.

Satisfactory batch formulation data have been provided for the manufacture of the products, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results.

Finished Product Specifications
The finished product specifications at release and shelf-life are satisfactory. The test methods have been described and adequately validated. Batch data have been provided that comply with the release specifications. Certificates of Analysis have been provided for any working standards used.

Stability
Finished product stability studies have been conducted in accordance with current guidelines, using batches of the finished product stored in the packaging proposed for marketing. Based on the results, a shelf-life of 3 years, with no special storage conditions, is acceptable.

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
The grant of marketing authorisations was recommended.

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.

III.2 Pharmacology
No new pharmacology data were provided, and none were required for these applications.

III.3 Pharmacokinetics
No new pharmacokinetic data were provided, and none were required for these applications.

III.4 Toxicology
No new toxicology data were provided, and none were required for these applications.

III.5 Ecotoxicity/Environmental Risk Assessment

Suitable justification was provided for non-submission of an Environmental Risk Assessment. As the applications are for generic versions of already authorised products, an increase in environmental exposure is not anticipated following approval of the marketing authorisations for the proposed products.

III.6 Discussion on the non-clinical aspects

The grant of marketing authorisations was recommended.

IV CLINICAL ASPECTS

IV.1 Introduction

The clinical pharmacology, efficacy and safety of levetiracetam are well-known. With the exception of data from a single bioequivalence study undertaken (08-VIN-236), no new clinical data are provided or are required for this type of application. An overview based on a literature review and a review of these study is, thus, satisfactory.

IV. 2 Pharmacokinetics

In support of the application, the applicant submitted the following:

Study 1: 08-VIN-236

This study was a randomised, open label, two treatment, two period, two sequence, single dose, crossover, bioequivalence study comparing Levetiracetam 1000mg tablets (test product) with Keppra® (containing Levetiracetam 1000rng) tablets (reference product) in healthy, human, adult subjects under fasting conditions.

A single dose of either the test or reference product was administered after an overnight fast of at least 10 hours, in each study period. Blood samples were taken pre-dose and up to 36 hours post dose, with a washout period of 7 days between the treatment periods.

A summary of the pharmacokinetic results is presented below:

Parameters (Units)	ln-transformed Geometric LSM			90% Confidence Interval (ln-transformed)
	R	T	(T/R)%	
C_{max} (ng/mL)	24910.244	23804.494	95.56	90.81% - 1 00.56%
AUC_{0-t} (ng.h/ml)	245142.877	244345.221	99.67	96.72% - 102.70%
$AUC_{0-\infty}$ (ng.h/ml)	256008.684	255313.749	99.73	97.10% - 102.43%

In accordance with the regulatory requirements, the Test/Reference ratios and their 90% confidence intervals were within the specified limits to show bioequivalence between the test product and the reference product.

As the additional (250, 500 & 750mg) strengths of the product meet the biowaiver criteria specified in the current bioequivalence guideline, the results and conclusions from the bioequivalence study on the product strength can be extrapolated to the other strengths.

IV.3 Pharmacodynamics

No new pharmacodynamic data were submitted for these applications and none were required.

IV.4 Clinical efficacy
No new efficacy data were submitted with these applications and none were required.

IV.5 Clinical safety
With the exception of the safety data submitted with the bioequivalence study, no new safety data were submitted with these applications.

The safety data from the bioequivalence study showed that the test and reference products were equally well tolerated. No new or unexpected safety issues were raised from the bioequivalence study.

IV.6 Risk Management Plan (RMP)
The applicant has submitted an RMP, in accordance with the requirements of Regulation 182 of The Human Medicines Regulation 2012, as amended. The applicant proposes only routine pharmacovigilance and routine risk minimisation measures for all safety concerns. This is acceptable.

IV.7 Discussion on the clinical aspects
The grant of marketing authorisations was recommended for these applications.

V USER CONSULTATION

A full colour mock-up of the Patient Information Leaflet (PIL) was provided with the application in accordance with legal requirements, including user consultation.

VI OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality of the products 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 is, therefore, considered to be positive.

The Summaries of Product Characteristics (SmPCs), Patient Information Leaflet (PIL) and labelling are satisfactory, in line with current guidelines and consistent with the reference products.

In accordance with legal requirements, the current approved UK versions of the SmPCs and PIL for these products are available on the MHRA website.

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Steps taken after the initial procedure with an influence on the Public Assessment Report (non-safety variations of clinical significance).

Please note that only non-safety variations of clinical significance are recorded below and in the annexes to this PAR. The assessment of safety variations where significant changes are made are recorded on the MHRA website or European Medicines Agency (EMA) website. Minor changes to the marketing authorisation are recorded in the current SmPC and/or PIL available on the MHRA website.

Application type	**Scope**	**Product information affected**	**Date of grant**	**Outcome**	**Assessment report attached Y/N**