Medicines & Healthcare products Regulatory Agency

MHRA Regulating Medicines and Medical Devices

Public Assessment Report

Decentralised Procedure

Levetiracetam 100 mg/ml concentrate for solution for infusion

(levetiracetam)

Procedure No: UK/H/6789/001/DC

UK Licence Number: PL 17509/0088

Intrapharm Laboratories Limited

LAY SUMMARY

Levetiracetam 100 mg/ml concentrate for solution for infusion
(levetiracetam)

This is a summary of the Public Assessment Report (PAR) for Levetiracetam 100 mg/ml concentrate for solution for infusion (PL 17509/0088; UK/H/6789/001/DC). It explains how Levetiracetam 100 mg/ml concentrate for solution for infusion 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 100 mg/ml concentrate for solution for infusion

For practical information about using Levetiracetam 100 mg/ml concentrate for solution for infusion, patients should read the package leaflet or contact their doctor or pharmacist.

What is Levetiracetam 100 mg/ml concentrate for solution for infusion and what is it used for?
Levetiracetam 100 mg/ml concentrate for solution for infusion is a 'generic medicine'. This means that Levetiracetam 100 mg/ml concentrate for solution for infusion is similar to a 'reference medicine' already authorised in the European Union (EU) called Keppra 1 mg/ml concentrate for solution for infusion (UCB Pharma SA).

Levetiracetam is used is an antiepileptic medicine (a medicine to treat seizures in epilepsy).

Levetiracetam 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 patients have 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 is given by your 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 and children from 4 years 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).

Levetiracetam concentrate for solution for infusion is an alternative for patients when administration of the antiepileptic oral Levetiracetam medicine is temporarily not feasible.

How does Levetiracetam 100 mg/ml concentrate for solution for infusion work?
This medicine contains the active ingredient levetiracetam. Levetiracetam film-coated tablets contain the active substance levetiracetam This is an antiepileptic medicine Epilepsy is caused by excessive electrical activity in the brain. The exact way that levetiracetam works is still unclear, but it seems to interfere with a protein called 'synaptic vesicle protein 2A', which is found in the spaces between nerves and is involved in the release of chemical messengers from nerve cells. This helps levetiracetam to stabilise electrical activity in the brain and prevent seizures.

How is Levetiracetam 100 mg/ml concentrate for solution for infusion used?
The pharmaceutical form of Levetiracetam 100 mg/ml concentrate for solution for infusion is a concentrate for solution for infusion and the route of administration of this medicine is intravenous (into a vein).

A doctor or a nurse will administer Levetiracetam 100 mg/ml concentrate for solution for infusion as an intravenous infusion. Levetiracetam 100 mg/ml concentrate for solution for infusion must be administered twice a day, once in the morning and once in the evening, at about the same time each day.

The intravenous formulation is an alternative to your oral administration. The patient can switch from the film-coated tablets or from the oral solution to the intravenous formulation or reverse directly without dose adaptation. The patient's total daily dose and frequency of administration remain identical.

Monotherapy

Dose in adults and adolescents (from 16 years of age):
General dose: between 1,000 mg and 3,000 mg each day. When you will first start taking Levetiracetam 100 mg/ml concentrate for solution for infusion, your doctor will prescribe you a **lower dose** during 2 weeks before giving you the lowest general dose.

Add-on therapy

Dose in adults and adolescents (12 to 17 years) weighing 50 kg or more:
General dose: between 1,000 mg and 3,000 mg each day.

Dose in children (4 to 11 years) and adolescents (12 to 17 years) weighing less than 50 kg:
General dose: between 20 mg per kg bodyweight and 60 mg per kg bodyweight each day.

Method and route of administration:
The recommended dose must be diluted in at least 100 ml of a compatible diluent and infused over 15-minutes. For doctors and nurses, more detailed direction for the proper use of Levetiracetam concentrate for solution for infusion is provided in section 6 of the package leaflet.

Duration of treatment:
There is no experience with administration of intravenous Levetiracetam 100 mg/ml concentrate for solution for infusion for a longer period than 4 days.

Stopping Levetiracetam concentrate for solution for infusion treatment:
If stopping treatment, as with other antiepileptic medicines, Levetiracetam 100 mg/ml concentrate for solution for infusion should be discontinued gradually to avoid an increase of seizures. If the doctor decides to stop their patient's Levetiracetam 100 mg/ml concentrate for solution for infusion treatment, he/she will provide instruction about the gradual withdrawal of Levetiracetam 100 mg/ml concentrate for solution for infusion. If the patient has any further questions on the use of this medicine, they should speak to their doctor or pharmacist.

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

For further information on how Levetiracetam 100 mg/ml concentrate for solution for infusion is used, refer to the package leaflet and Summary of Product Characteristics available on the Medicines and Healthcare products Regulatory Agency (MHRA) website.

This medicine can only be obtained with a prescription.

What benefits of Levetiracetam 100 mg/ml concentrate for solution for infusion have been shown in studies?
No additional studies were needed as Levetiracetam 100 mg/ml concentrate for solution for infusion is a generic medicine that is given intravenously and contains the same active ingredient as the reference medicine, Keppra 100 mg/mL concentrate for solution for infusion (UCB Pharma SA).

What are the possible side effects of Levetiracetam 100 mg/ml concentrate for solution for infusion?
Because Levetiracetam 100 mg/ml concentrate for solution for infusion is a generic medicine, its benefits and possible side effects are taken as being the same as the reference medicine Keppra 100 mg/mL concentrate for solution for infusion (UCB Pharma SA).

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

For the full list of all side effects reported with Levetiracetam 100 mg/ml concentrate for solution for infusion, see section 4 of the package leaflet available on the MHRA website.

Why was Levetiracetam 100 mg/ml concentrate for solution for infusion approved?
It was concluded that, in accordance with EU requirements, Levetiracetam 100 mg/ml concentrate for solution for infusion has been shown to have comparable quality and to be otherwise comparable to Keppra 100 mg/mL concentrate for solution for infusion (UCB Pharma SA).
Therefore, the MHRA decided that, as for Keppra 100 mg/mL concentrate for solution for infusion (UCB Pharma SA), the benefits are greater than its risk and recommended that it can be approved for use.

What measures are being taken to ensure the safe and effective use of Levetiracetam 100 mg/ml concentrate for solution for infusion?
A risk management plan (RMP) has been developed to ensure that Levetiracetam 100 mg/ml concentrate for solution for infusion is used as safely as possible. Based on this plan, safety information has been included in the Summary of Product Characteristics (SmPC) and the package leaflet for Levetiracetam 100 mg/ml concentrate for solution for infusion 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 100 mg/ml concentrate for solution for infusion
Ireland and the UK agreed to grant a Marketing Authorisation for Levetiracetam 100 mg/ml concentrate for solution for infusion on 17 August 2018. A Marketing Authorisation was granted in the UK on 13 September 2018.

The full PAR for Levetiracetam 100 mg/ml concentrate for solution for infusion follows this summary.

For more information about treatment with Levetiracetam 100 mg/ml concentrate for solution for infusion, read the package leaflet, or contact your doctor or pharmacist.

This summary was last updated in October 2018.

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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) granted Intrapharm Laboratories Limited, a marketing authorisation for the medicinal product Levetiracetam 100 mg/ml concentrate for solution for infusion (PL 17509/0088; UK/H/6789/001/DC). This product is a prescription-only medicine (POM) and 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.
- 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.

Levetiracetam concentrate for solution for infusion is an alternative for patients when oral administration is temporarily not feasible.

This application was submitted using the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS) and Ireland 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 EU reference product for this application is Keppra 100 mg/mL concentrate for solution for infusion by UCB Pharma SA registered in EU since September 2000.

The mechanism of action of levetiracetam remains to be fully elucidated but appears to be different from the mechanisms of current antiepileptic medicinal products. Findings suggest 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 submitted, which is acceptable given that the application was based on being a generic medicinal product of a reference product that has been in clinical use for over 10 years.

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

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.

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 17 August 2018. After a subsequent national phase, a licence was granted in the UK on 13 September 2018.

II QUALITY ASPECTS

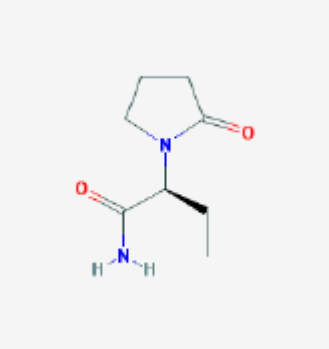
II.1 Introduction

Each 5 ml vial contains 500 mg levetiracetam, each ml contains 100 mg of levetiracetam.
Other ingredients consist of the pharmaceutical excipients sodium acetate trihydrate, glacial acetic acid, sodium chloride, and water for injections.

The finished product is presented in 5 ml glass vial (type I) closed by a grey bromobutyl rubber stopper and sealed with an aluminium blue flip off cap, each carton contains 10 vials.

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

II.2 Drug Substance

INN:	Levetiracetam
Chemical name:	(S)-2-(2-0xopyrrolidin-1-yl) butanamide (S)-(-)-α- ethyl-2-oxo-1-pyrrolidine acetamide (Oxo-2-pyrrolidinyl-1)-2-butyramide-(S) (S)-(-)- α-ethyl-pyrrolidone acetamide
Structure:	
Molecular formula:	$C_8H_{14}N_2O_2$
Molecular weight:	170.21
Description:	White or almost white powder
Solubility:	Levetiracetam is a highly soluble drug substance.

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) Certificates of Suitability.

II.3. Medicinal Product

Pharmaceutical Development

The objective of the development programme was to formulate a safe, efficacious, concentrate for solution for infusion containing 500 mg levetiracetam, that was comparable to the reference product Keppra 100 mg/mL concentrate for solution for infusion (UCB Pharma SA). A satisfactory account of the pharmaceutical development has been provided.

All excipients comply with their respective European Pharmacopeia monographs. Satisfactory Certificates of Analysis have been provided for each excipient. Suitable batch analysis data have been provided for each excipient.

None of the excipients used contain material of animal or human origin.

This product does not contain or consist of genetically modified organisms (GMO).

Manufacture of the product
A satisfactory batch formula has been provided for the manufacture of the product, together with an appropriate account of the manufacturing process. Process validation data on three pilot scale batches have been provided. The results are satisfactory.

Finished Product Specification
The finished product specification proposed is acceptable. Test methods have been described that have been adequately validated. Batch data complying with the release specification have been provided. 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 the finished product in the packaging proposed for marketing. The data from these studies support a shelf-life of 3 years for the unopened product with no special storage conditions.

From a microbiological point of view, the product should be used immediately after dilution. If not used immediately, in-use storage time and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8°C, unless dilution has taken place in controlled and validated aseptic conditions.

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

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
Impurity limits applied by the drug product manufacturer for the drug product are in line with Ph.Eur. A risk assessment of elemental impurities has been provided and is acceptable.

III.5 Ecotoxicity/environmental risk assessment (ERA)

Since Levetiracetam 100 mg/ml concentrate for solution for infusion is intended for generic substitution, this will not lead to an increase of the environmental exposure. 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 pharmacodynamic, pharmacokinetic, clinical efficacy and safety properties of levetiracetam are well known. A comprehensive review of the published literature has been provided by the MAH. The clinical overview has been written by an appropriately qualified person and is considered acceptable.

IV.2 Pharmacokinetics

The proposed product, Levetiracetam 100 mg/ml concentrate for solution for infusion (Intrapharm Laboratories Limited) is an aqueous intravenous solution that contains the same qualitative and quantitative composition in terms of active substance, levetiracetam and the same pharmaceutical form as the reference product; Keppra 100 mg/mL concentrate for solution for infusion (UCB Pharma SA). According to CPMP guidelines (CPMP/EWP/QWP/1401/98/rev1/corr**2010, sub-point 5.1.6, Parental solutions), the MAH is not required to submit a bioequivalence study if the product is to be administered as an aqueous intravenous solution containing the same active substance in the same concentration as the currently authorised product.

IV.3 Pharmacodynamics

No new pharmacodynamic data were submitted and none were required for applications of this type.

IV.4 Clinical efficacy

No new efficacy data were submitted and none were required for applications of this type.

IV.5 Clinical safety

No new safety data were submitted and none are required.

IV.6 Risk Management Plan (RMP) and Pharmacovigilance System

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 100 mg/ml concentrate for solution for infusion.

Levetiracetam was first approved in 2000, and there is now more than 15 years post authorisation experience with the active substance.

The safety profile of levetiracetam can be considered to be well established and no product specific pharmacovigilance issues were identified pre- or post-authorization which are not adequately covered by the current SmPC. Additional risk minimization activities have not been identified for the reference medicinal product.

The MAH has a pharmacovigilance system at their disposal, which is based on the current European legislation. Routine pharmacovigilance activities are considered as sufficient to identify any risks with the generic product.

A summary of safety concerns, as approved in the RMP, are listed below:

Important identified risks	• Anaphylaxis and hypersensitivity • Haemotological abnormalities • Suicide and behaviour disorders • Renal impairment • Hepatic impairment
Important potential risks	• Fertility, Pregnancy and Lactation • Interaction with other medicinal products • Medication error
Missing information	• Long term effects on children > 4 years • Use in children <4 years

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 viewpoint.

V User consultation

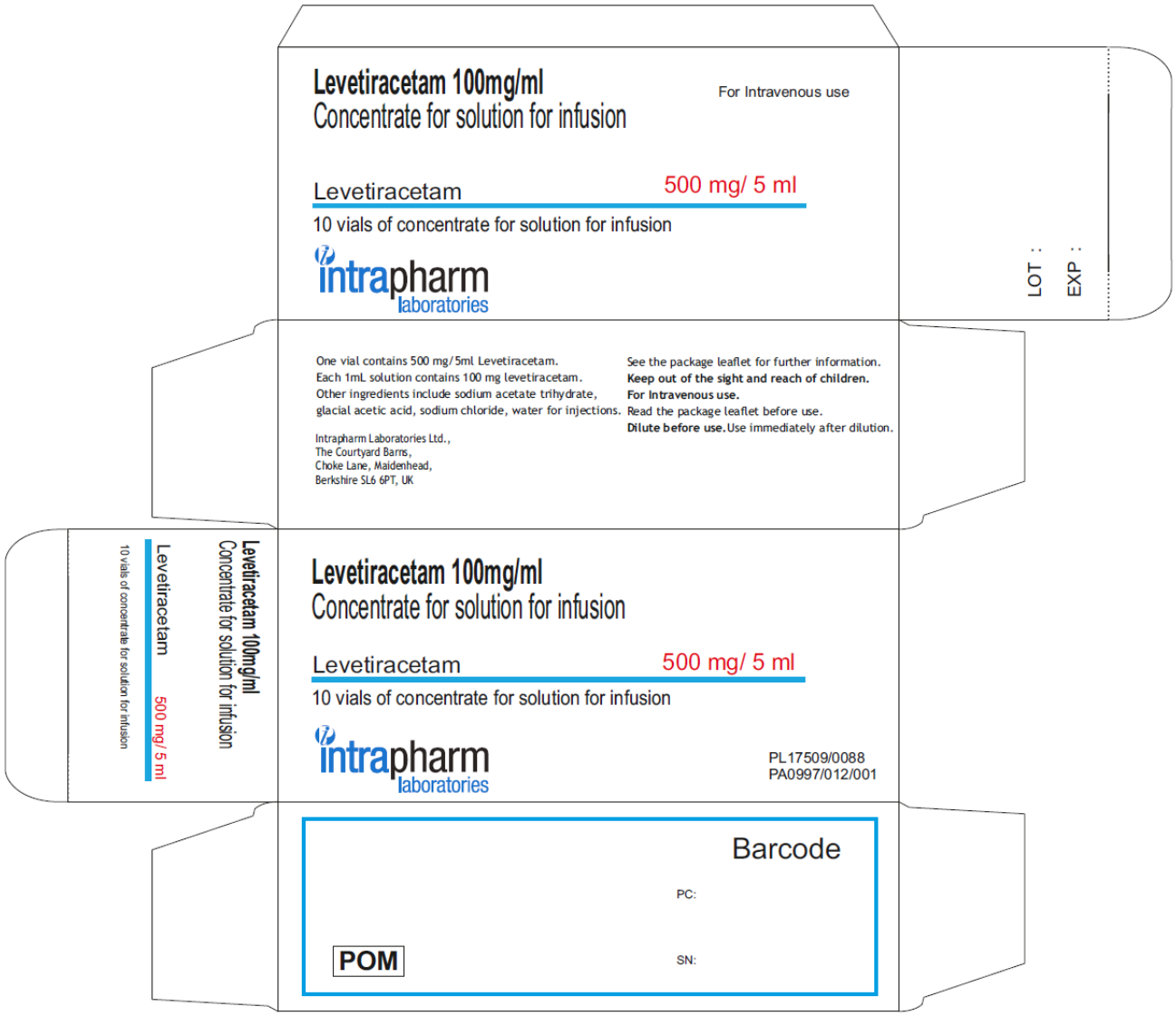
The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The language used for the purpose of user testing the PIL was English.

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 levetiracetum is considered to have demonstrated the therapeutic value of the compound. 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 Levetiracetam 100 mg/ml concentrate for solution for infusion is presented below:



Annex 1

Table of content of the PAR update

Steps taken after the initial procedure with an influence on the Public Assessment Report (Type II variations, PSURs, commitments)

Scope	Procedure number	Product information affected	Date of start of the procedure	Date of end of procedure	Approval/ non approval	Assessment report attached Y/N (version)