London, 20 October 2011
EMA/CHMP/657653/2011
Committee for Medicinal Products for Human Use (CHMP)

CHMP assessment report

Levetiracetam SUN

International non-proprietary name: **levetiracetam**

Procedure No.: **EMEA/H/C/002051**

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Product information

Marketing authorisation application

Name of the medicinal product:	Levetiracetam SUN
Applicant:	Sun Pharmaceutical Industries Europe B.V. Polarisavenue 87 NL-2132 JH Hoofddorp The Netherlands
Active substance:	Levetiracetam
International Nonproprietary Name:	Levetiracetam
Pharmaco-therapeutic group (ATC Code):	Other antiepileptics (N03AX14)
Therapeutic indication(s):	Levetiracetam SUN is indicated as monotherapy in the treatment of partial onset seizures with or without secondary generalisation in patients from 16 years of age with newly diagnosed epilepsy. Levetiracetam SUN is indicated as adjunctive therapy • in the treatment of partial onset seizures with or without secondary generalisation in adults 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 SUN is an alternative for patients when oral administration is temporarily not feasible.
Pharmaceutical form:	Concentrate for solution for infusion
Strength:	100 mg/ml
Route of administration:	Intravenous use
Packaging:	Colourless glass vial
Package size:	10 vials

Table of contents

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Sun Pharmaceutical Industries Europe B.V. submitted on 5 October 2010 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Levetiracetam SUN, through the centralised procedure under Article 3 (3) of Regulation (EC) No. 726/2004 – 'Generic of a Centrally authorised product'. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 29 September 2009.

The application concerns a generic medicinal product as defined in Article 10(2)(b) of Directive 2001/83/EC and refers to a reference product for which a Marketing Authorisation is or has been granted in the Community on the basis of a complete dossier in accordance with Article 8(3) of Directive 2001/83/EC.

The applicant applied for the following indication: Levetiracetam SUN is indicated as monotherapy in the treatment of partial onset seizures with or without secondary generalisation in patients from 16 years of age with newly diagnosed epilepsy.

Levetiracetam SUN is indicated as adjunctive therapy:

- in the treatment of partial onset seizures with or without secondary generalisation in adults 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 SUN is an alternative for patients when oral administration is temporarily not feasible.

The legal basis for this application refers to Article 10(1) of Directive 2001/83/EC.

The application submitted is composed of administrative information and complete quality data.

Information on paediatric requirements

Not applicable

Information relating to orphan market exclusivity

Not applicable.

Similarity

Not applicable

The chosen reference product is:

■ Medicinal product which is or has been authorised in accordance with Community provisions in accordance with Community provisions in force for not less than 6/10 years in the EEA:

- Product name, strength, pharmaceutical form: **Keppra 250, 500, 750, 1000 mg Film-coated tablets**
- Marketing authorisation holder: **UCB Pharma S.A.**
- Date of authorisation: **29/09/2000**
- Marketing authorisation granted by: **Community**
- Community Marketing authorisation number: **EU/1/00/146/001-026**

■ Medicinal product authorised in the Community/Members State where the application is made or European reference medicinal product:

- Product name, strength, pharmaceutical form: **Keppra 100 mg/ml Concentrate for solution for infusion.**
- Marketing authorisation holder: **UCB Pharma S.A., Belgium**
- Date of authorisation: **29/03/2006**
- Marketing authorisation granted by: **Community**
  - Community Marketing authorisation number: **EU/1/00/146/030**

■ Medicinal product which is or has been authorised in accordance with Community provisions in force and to which bioequivalence has been demonstrated by appropriate bioavailability studies:

- **Not applicable**

Scientific advice

The applicant did not seek scientific advice at the CHMP.

Licensing status

The product was not licensed in any country at the time of submission of the application.

1.2. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP was:

Rapporteur: **George Aislaitner**

- The application was received by the EMA on 5 October 2010.
- The procedure started on 20 October 2010.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 11 January 2011
- During the meeting on 14-17 February 2011, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 18 February 2011.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 16 June 2011.
- The Rapporteur circulated the Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 13 September 2011.
- During the CHMP meeting on 19-22 September 2011, the CHMP agreed on a list of outstanding issues to be addressed in writing and by the applicant.
- The applicant submitted the responses to the CHMP consolidated List of Outstanding Issues on 27 September 2011.
- The Rapporteur circulated the Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 13 October 2011.
- During the meeting on 17-20 October 2011, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Levetiracetam SUN on 20 October 2011.

2. Scientific discussion

2.1. Introduction

The Marketing Authorization Application of Levetiracetam SUN 100mg/ml concentrate for solution for infusion is a generic of the Centrally authorised product Keppra which exists as film-coated tablets of 250 mg, 500 mg, 750 mg and 1000 mg as oral solution (100 mg/ml) and as concentrate for solution for infusion (100 mg/ml).

The precise mechanism of action by which levetiracetam confers seizure protection is unknown, but it appears to be unrelated to the mechanisms identified for current antiepileptic drugs.

Levetiracetam is indicated for the treatment of Epilepsy.

The efficacy and safety of levetiracetam has been demonstrated in several well-controlled studies. A summary of these studies can be found in the EPAR of the reference product Keppra.

A summary of the literature with regard to clinical data of Levetiracetam SUN was provided and was accepted by the CHMP. This is in accordance with the relevant guideline and additional clinical studies were not considered necessary.

Bioequivalence testing with the reference product was not required under the provisions of the Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev.1: "Bioequivalence studies are generally not required if the test product is to be administered as an aqueous intravenous solution containing the same active substance as the currently approved product."

The therapeutic indication of Levetiracetam SUN is:

as monotherapy in the treatment of partial onset seizures with or without secondary generalisation in patients 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 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 SUN concentrate is an alternative for patients when oral administration is temporarily not feasible.

2.2. Quality aspects

2.2.1. Introduction

Levetiracetam SUN is available as a 100 mg/ml concentrate for solution for infusion contained in a colourless good alkali tubular glass vial (500 mg/5ml) with 20 mm grey bromobutyl rubber stopper sealed with white flip off aluminium seal.

The full list of ingredients is defined in section 6.1 of the SmPC.

2.2.2. Active substance

Levetiracetam is a white to off-white crystalline powder soluble in methanol and water. It presents one single asymmetric centre being the S-enantiomer the active one.

According to the synthetic process described in this application the active substance is consistently obtained as the S-enantiomer and is routinely controlled by a chiral purity test.

Levetiracetam produced by the proposed active substance supplier is of crystalline form. The consistency of the form has been established by melting point, Differential Scanning Calorimeter (DSC) and Fourier Transform Infra-Red (FTIR) analysis.

A monograph for Levetiracetam is included in the European Pharmacopoeia that came into force since 1 January 2011.

Manufacture

The information on the active substance levetiracetam is presented in the form of an Active Substance Master File.

The manufacture of Levetiracetam is a single stage process. The synthesis is described in sufficient detail. Critical steps and intermediates are presented in a satisfactory manner. Information regarding process validation has also been presented and considered acceptable.

Specification

Levetiracetam is described in the last edition of the European Pharmacopoeia (Ph. Eur.). Although the Ph. Eur. monograph was not valid at the time of submission, the specification of levetiracetam has been reviewed accordingly by the active and finished product manufacturers where applicable, unless fully justified.

The specification include tests for description, solubility, identification by Infrared (IR), by chiral High Performance Liquid Chromatography (HPLC) and by specific optical rotation, appearance of solution, enatiomeric purity, water content, sulphated ash, heavy metals, related substances, assay (HPLC), residual solvents by Gas Chromatography (GC), bacterial endotoxins and bioburden.

The in-house analytical procedures have been described and validated.

Impurities have been evaluated and found to be acceptable from the point of view of safety.

Batch analysis results from five different batches were provided. Results confirm batch to batch consistency and uniformity of the quality of the substance and indicate that the process is under control.

Stability

Satisfactory stability data of three batches of levetiracetam, stored in their proposed commercial packaging for over 12/18 months according to ICH conditions at 25° ± 2°C/ 60 % ± 5 % RH and 6 months at 40° ± 2°C/ 75 % ± 5 % RH, have been provided. The parameters tested were description, identification by IR and HPLC, water content, limit of Levetiracetam related compound-B, Limit of

Levetiracetam R-enantiomer, related compounds (by HPLC) and Assay by HPLC. As non routine tests bacterial endotoxins and bioburden tests are included in the stability testing plan.

Forced degradation studies have also been performed demonstrating that degradation in alkali and acid conditions occurs.

The stability data provided support the recommended retest period at the proposed packaging and storage conditions.

2.2.3. Finished medicinal product

Pharmaceutical development

Levetiracetam SUN has been developed in accordance with the reference medicinal product as to have the same qualitative composition. This generic medicinal product was developed as a sterile, aqueous solution of Levetiracetam concentrate for solution for infusion in a vial for intravenous infusion, same as the reference medicinal product.

The excipients used in the manufacturing of Levetiracetam SUN are commonly found in this type of pharmaceutical medicinal products and especially in solutions for infusion. All excipients are described in the European Pharmacopoeia and its specifications and analytical procedures are also in accordance with the European Pharmacopoeia standards.

The selection of the container closure system was based on the evaluation for individual characteristics and mutual integrity. The choice of the primary packaging materials is based on the reference medicinal product's primary packaging; the selection of the rubber is based on compatibility studies (adsorption study and compatibility study with the active substance); and a photostability study. Standard packaging materials are chosen.

Compatibility studies between the active substance and the different excipients were also performed. No change in description, assay, related substances, pH, and transmittance after 1 month at 40°C/75%RH as compared to initial results were encountered, demonstrating the compatibility of the excipients chosen with the active substance.

Compatibility studies of the medicinal product with different reconstitution diluents were also carried out on two batches of the finished product. Samples stored for 24 h were analyzed for description, assay of active substance, related substances, pH, absorbance, transmittance, osmolality and particulate matter and produced comparable results with the results for the initial samples and no time-dependent deterioration was found.

Adventitious agents

Declarations from the manufacturers of all components of Levetiracetam SUN confirm that they are all manufactured from raw materials that contain no animal parts, products or by-products and they have not come in contact with them. Therefore, all materials are Bovine Spongiform Encephalopathy (BSE)/ Transmissible Spongiform Encephalopathies (TSE) free.

Manufacture of the product

The manufacturing process consists in preparation of the bulk solution followed by sterile filtration, filling, vial sealing and standard terminal steam sterilization.

The manufacturing formula, flow chart and description of the manufacturing process are presented.

Process qualification by extensive sampling on three batches of Levetiracetam SUN demonstrated that the manufacturing process as described above is suitable to produce Levetiracetam SUN 100mg/ml Concentrate for solution for infusion in a constant quality complying with the selected in-process controls and the fixed specifications. Each study design, testing protocol/results and study conclusions are clearly described and documented.

The manufacturing process has been satisfactorily validated.

Product specification

Adequate release and shelf-life specifications have been presented for the finished product and include: description, identification by HPLC and by Ultra Violet (UV), pH, Absorbance at 420nm, %transmittance at 650nm, extractable volume, volume variation, particle matters, sterility, bacterial endotoxins, related substances (HPLC), sodium chloride content and assay (HPLC).

The proposed test procedures and acceptance criteria comply with the requirements of the Ph.Eur. and current guidelines. Analytical procedures are described and validated.

The batch analysis results of three commercial batches confirm consistency and uniformity of the product indicating that the process is under control.

Stability of the product

The conditions used in the stability studies are in accordance with the ICH stability guideline (40º ± 2ºC & 75% ± 5% RH and 25º ± 2ºC & 60% ± 5% RH).

The results of the following tests were submitted: description, identification of Levetiracetam by HPLC, pH, absorbance at 420nm, %transmittance at 650nm, particulate matter, sterility, related substances by HPLC and assay by HPLC.

Analysis of the stability samples has been performed by applying the validated and stability indicating test methods.

Photostability results demonstrated that the product is not sensitive to light.

Based on the stability results provided, the proposed shelf-life and storage conditions as defined in the Summary of Product Characteristics (SmPC) are acceptable.

2.2.4. Discussion on chemical, and pharmaceutical aspects

Information on development, manufacture and control of the active substance and finished medicinal product has been presented in a satisfactory manner. The results of tests carried out indicate satisfactory consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical

performance of the product have been investigated and are controlled in a satisfactory way. Data has been presented to give reassurance on TSE safety.

2.3. Non-clinical aspects

2.3.1. Introduction

A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. The non-clinical aspects of the SmPC are in line with the SmPC of the reference product. The impurity profile has been discussed and was considered acceptable.

Therefore, the CHMP agreed that no further non-clinical studies are required.

2.3.2. Ecotoxicity/environmental risk assessment

No Environmental Risk Assessment (ERA) was submitted. This was justified by the applicant as the introduction of Levetiracetam SUN manufactured by Sun Pharmaceutical Industries Europe B.V. is considered unlikely to result in any significant increase in the combined sales volumes for all levetiracetam containing products and the exposure of the environment to the active substance. Thus, the ERA is expected to be similar and not increased.

2.3.3. Conclusion on the non-clinical aspects

A summary of the literature with regard to non-clinical data of Levetiracetam SUN was provided and was accepted by the CHMP. This is in accordance with the relevant guideline and additional non clinical studies were not considered necessary.

2.4. Clinical aspects

2.4.1. Introduction

This is an application for concentrate for solution for infusion containing levetiracetam.

The applicant provided a clinical overview outlining the pharmacokinetics and pharmacodynamics as well as efficacy and safety of levetiracetam based on published literature. The SmPC is in line with the SmPC of the reference product.

No formal scientific advice by the CHMP was given for this medicinal product. For the clinical assessment *Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev.1* in its current version is of particular relevance.

GCP

Not applicable. No clinical studies have been submitted in support of this application.

Exemption

Similarly to the reference product Levetiracetam SUN is an aqueous intravenous solution. Both products have the same concentration at the time of administration and the excipients are qualitatively identical. Therefore, bioequivalence testing with the reference product is not required under the provisions of the *Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev.1*: "Bioequivalence studies are generally not required if the test product is to be administered as an aqueous intravenous solution containing the same active substance as the currently approved product."

2.4.2. Pharmacodynamics

No new pharmacodynamic studies were presented and no such studies are required for this application.

2.4.3. Post marketing experience

No post-marketing data are available. The medicinal product has not been marketed in any country.

2.4.4. Conclusions on clinical aspects

A summary of the literature with regard to clinical data of Levetiracetam SUN was provided and was accepted by the CHMP. This is in accordance with the relevant guideline and additional clinical studies were not considered necessary.

Bioequivalence testing with the reference product is not required under the provisions of the Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev.1: "Bioequivalence studies are generally not required if the test product is to be administered as an aqueous intravenous solution containing the same active substance as the currently approved product."

2.5. Pharmacovigilance

Detailed description of the pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

Risk management plan

The CHMP did not require the applicant to submit a risk management plan because the application is based on a reference medicinal product for which no safety concerns requiring additional risk minimisation activities have been identified.

The CHMP, having considered the data submitted, was of the opinion that routine pharmacovigilance was adequate to monitor the safety of the product.

No additional risk minimisation activities were required beyond those included in the product information.

PSUR submission

The Periodic Safety Update Report (PSUR) submission schedule should follow the PSUR schedule for the reference product which currently is on a yearly cycle. The next data lock point for the reference medicinal product is 30 November 2011.

User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant 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.*

3. Benefit-risk balance

This application concerns a generic version of levetiracetam concentrate for solution for infusion. The reference product Keppra 100 mg/ml concentrate for solution for infusion is indicated as monotherapy in the treatment of partial onset seizures with or without secondary generalisation in patients from 16 years of age with newly diagnosed epilepsy.

Keppra 100 mg/ml concentrate for solution for infusion is indicated as adjunctive therapy:

• in the treatment of partial onset seizures with or without secondary generalisation in adults 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.

Keppra concentrate is an alternative for patients when oral administration is temporarily not feasible.

No nonclinical studies have been provided for this application but an adequate summary of the available nonclinical information for the active substance was presented and considered sufficient.

From a clinical perspective, this application does not contain new data on the pharmacokinetics and pharmacodynamics as well as the efficacy and safety of the active substance; the applicant's clinical overview on these clinical aspects based on information from published literature was considered sufficient.

Bioequivalence testing with the reference product is not required under the provisions of the Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev.1: "Bioequivalence studies are generally not required if the test product is to be administered as an aqueous intravenous solution containing the same active substance as the currently approved product."

The overall benefit-risk assessment is considered to be positive, since no new indication or population is claimed and reference is made to the innovator product for the benefits and risks of levetiracetam. Levetiracetam is considered a safe and effective antiepileptic drug with well established use for the treatment of various forms of epilepsy, this being supported by experience with marketed levetiracetam in a large number of patients. Thus, the CHMP considered there is sufficient support for concluding on a benefit/risk ratio comparable to the reference product.

The CHMP, having considered the data submitted in the application and available on the chosen reference medicinal product, is of the opinion that no additional risk minimisation activities are required beyond those included in the product information.

4. Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Levetiracetam SUN in the treatment of partial onset seizures with or without secondary generalisation in patients 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 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 is favourable and therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

Conditions and requirements of the Marketing Authorisation

Pharmacovigilance System

The MAH must ensure that the system of pharmacovigilance, presented in Module 1.8.1 of the marketing authorisation, is in place and functioning before and whilst the product is on the market.

Risk management system

Not applicable

PSUR cycle

The PSUR cycle for the product will follow PSURs submission schedule for the reference medicinal product.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Not applicable

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the member states.

Not applicable.