CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Levetiracetam Sandoz 100 mg/ml, oral solution
Sandoz B.V., the Netherlands

levetiracetam (as hydrochloride)

This assessment report is published by the MEB pursuant Article 21 (3) and (4) of Directive 2001/83/EC. The report comments on the registration dossier that was submitted to the MEB and its fellow –organisations in all concerned EU member states.
It reflects the scientific conclusion reached by the MEB and all concerned member states at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation.
This report is intended for all those involved with the safe and proper use of the medicinal product, i.e. healthcare professionals, patients and their family and carers. Some knowledge of medicines and diseases is expected of the latter category as the language in this report may be difficult for laymen to understand.

This assessment report shall be updated by a following addendum whenever new information becomes available.

General information on the Public Assessment Reports can be found on the website of the MEB.

To the best of the MEB's knowledge, this report does not contain any information that should not have been made available to the public. The MAH has checked this report for the absence of any confidential information.

EU-procedure number: NL/H/2198/001/DC
Registration number in the Netherlands: RVG 108496

26 January 2012

Pharmacotherapeutic group:	other antiepileptics
ATC code:	N03AX14
Route of administration:	oral
Therapeutic indication:	as monotherapy in 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 partial onset seizures with or without secondary generalisation in patients > 1 month of age with epilepsy; as adjunctive therapy in myoclonic seizures in patients > 12 years with Juvenile Myoclonic Epilepsy; as adjunctive therapy in primary generalised tonic-clonic seizures in patients > 12 years with Idiopathic Generalised Epilepsy.
Prescription status:	prescription only
Date of authorisation in NL:	25 November 2011
Concerned Member States:	Decentralised procedure with BE, DE, ES, FR, LU
Application type/legal basis:	Directive 2001/83/EC, Article 10(1)

For product information for healthcare professionals and users, including information on pack sizes and presentations, see Summary of Product Characteristics (SPC), package leaflet and labelling.

I INTRODUCTION

Based on the review of the quality, safety and efficacy data, the member states have granted a marketing authorisation for Levetiracetam Sandoz 100 mg/ml, oral solution from Sandoz B.V. The date of authorisation was on 25 November 2011 in the Netherlands.

The product 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.

The product is indicated as adjunctive therapy:

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

A comprehensive description of the indications and posology is given in the SPC.

The active substance, levetiracetam, is a pyrrolidone derivative (S-enantiomer of α-ethyl-2-oxo-1-pyrrolidine acetamide), chemically unrelated to existing antiepileptic active substances.
The mechanism of action of levetiracetam still remains to be fully elucidated but appears to be different from the mechanisms of current antiepileptic medicinal products. *In vitro* and *in vivo* experiments suggest that levetiracetam does not alter basic cell characteristics and normal neurotransmission.

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Keppra. Keppra 250, 500, 750 and 1000 mg film-coated tablets have been registered in the EEA by UCB Pharma through centralised procedure EU/1/00/146/001-029 since 29 September 2000 (original product). For the 100 mg/ml oral solution, reference has been made to Keppra 100 mg/ml oral solution which has been registered in the EEA by UCB Pharma, Belgium through centralised procedure EU/1/00/146/027 since 3 March 2003.

The marketing authorisation is granted based on article 10(1) of Directive 2001/83/EC.

This type of application refers to information that is contained in the pharmacological-toxicological and clinical part of the dossier of the authorisation of the reference product. A reference product is a medicinal product authorised and marketed on the basis of a full dossier, i.e. including chemical, biological, pharmaceutical, pharmacological-toxicological and clinical data. This information is not fully available in the public domain. Authorisations for generic products are therefore linked to the 'original' authorised medicinal product, which is legally allowed once the data protection time of the dossier of the reference product has expired.
The MAH provided sufficient justification for not including a bioequivalence study, see section II.3 "Clinical Aspects". This generic product can be used instead of its reference product.

No new pre-clinical and clinical studies were conducted, which is acceptable for this abridged application.

No scientific advice has been given to the MAH with respect to these products and no paediatric development programme has been submitted, as this is not required for a generic application.

II SCIENTIFIC OVERVIEW AND DISCUSSION

II.1 Quality aspects

Compliance with Good Manufacturing Practice
The MEB has been assured that acceptable standards of GMP (see Directive 2003/94/EC) are in place for this product type at all sites responsible for the manufacturing of the active substance as well as for the manufacturing and assembly of this product prior to granting its national authorisation.

Active substance
The active substance is levetiracetam, an established active substance described in the European Pharmacopoeia (Ph.Eur.*). Levetiracetam is a white or almost white powder, which is very soluble in water, soluble in acetonitrile and practically insoluble in hexane. Levetiracetam has one chiral center and the S-enantiomer is produced. The drug substance has three polymorphic forms. Form I is consistently produced.

The Active Substance Master File (ASMF) procedure is used for the active substance. The main objective of the ASMF procedure, commonly known as the European Drug Master File (EDMF) procedure, is to allow valuable confidential intellectual property or 'know-how' of the manufacturer of the active substance (ASM) to be protected, while at the same time allowing the applicant or marketing authorisation holder (MAH) to take full responsibility for the medicinal product, the quality and quality control of the active substance. Competent Authorities/EMA thus have access to the complete information that is necessary to evaluate the suitability of the use of the active substance in the medicinal product.

Manufacturing process
A flow chart and a brief description of the manufacturing process, including all reagents and solvents have been presented. The information on the manufacturing process is deemed acceptable.

Quality control of drug substance
The drug substance specification is based on the requirements described in the Ph.Eur. monograph of Levetiracetam with additional in-house tests for residual solvents, polymorphism by XRD and particle size. The limits are in line with or more stringent than described in the monograph and therefore acceptable. The limits for residual solvents are in line with the ICH guidance and the microbial limits are in line with the Ph.Eur. Batch analytical data demonstrating compliance with the drug substance specification have been provided for four batches of production scale.

Stability of drug substance
Stability data on the active substance have been provided for three batches stored for 36 months and one batch stored for 24 months at 25°C/60% RH. The stability results show that, other than a slight increase in water content, no significant changes or trends were observed at either long-term or accelerated storage conditions. In view of the provided stability data, the proposed re-test period of 36 months is justified. The drug substance does not require specific storage conditions.

** Ph.Eur. is an official handbook (pharmacopoeia) in which methods of analysis with specifications for substances are laid down by the authorities of the EU.*

Medicinal Product

Composition
The drug product is formulated as a clear oral solution containing 100 mg levetiracetam per ml of solution.

The excipients are sodium citrate (for pH adjustment), citric acid monohydrate (for pH adjustment), methyl parahydroxybenzoate (E218), glycerol (E422), acesulfame potassium (E950), liquid maltitol (E965), raspberry liquid and purified water.

The drug product is packed in 150 ml or 300 ml amber glass bottles (type III) with a white child resistant closure (polypropylene). The bottles are packed in a cardboard box containing a 1 or 3 ml oral syringe

graduated respectively every 0.05 ml (corresponding to 5 mg) and every 0.1 ml (corresponding to 10 mg) (in the 150 ml pack), or a 10 ml oral syringe graduated every 0.25 ml (corresponding to 25 mg). (in the 300 ml pack) The oral syringes are made of polypropylene/polyethylene and an adaptor for the syringe (polyethylene) is included. The excipients and packaging are usual for this type of dosage form.

Pharmaceutical development

The development of the product has been described, the choice of excipients is justified and their functions explained. The product has been developed as a generic form similar to the originator's finished product, Keppra. The formulation was optimized on microbial preservation, taste, buffering capacity, liquid maltitol content, pH optimisation and amount of purified water in relation to final pH.
The final formulation contains excipients that are also present in the innovator product, with the same or similar quantitative amounts of maltitol and methyl paraben, with the exception of the flavouring agent (raspberry instead of grape).
The omission of a bioequivalence study is justified. The pharmaceutical development of the product has been adequately performed.

Microbiological attributes

Non-routine microbial testing is performed, which is acceptable for preserved oral solutions. The MAH demonstrated the efficacy of the anti-microbial preservative in line with Ph. Eur. 5.1.3 and adequately justified the concentration of the preservative.

Manufacturing process

The manufacturing process consists of the dissolution of the ingredients in purified water and filling of the solution in bottles.
The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product has been presented for three pilot scale batches in accordance with the relevant European guidelines. The MAH committed to validate three commercial-scale batches of Levetiracetam Sandoz 100 mg/ml, oral solution.

Control of Excipients

Except for the raspberry flavour, all excipients comply with the Ph.Eur. These specifications are acceptable. For raspberry flavour, composition and safety of components has been demonstrated.

Quality control of drug product

The drug product specification is acceptable. The release and shelf-life specification differ in total impurities and in the limits of the methyl parahydroxybenzoate assay. The specification includes tests for description, color of solution, identification of levetiracetam and enantiomer and preservative, related substances, assay (levetiracetam and methyl para-hydroxybenzoate), chiral impurity, pH, deliverable volume and microbial contamination.
The specification is acceptable. The analytical methods have been adequately described and validated.
Batch analytical data from the proposed production site have been provided on three pilot scaled batches, demonstrating compliance with the release specification.

Stability of drug product

Stability data on the product has been provided for three pilot scaled batches stored in amber glass type III bottles with polypropylene child-resistant closure at 25°C/60% RH (12 months) and 30°C/75% RH (12 months) and 40°C/75% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline.
Under accelerated storage conditions and similar but slower under intermediate and long-term storage conditions, the product demonstrates an increase in impurities and a decrease in assay. However, the results remain within limits. No changes in any of the other parameters were observed.
A photostability study has been performed in accordance with the NfG on photostability testing, ICH Q1B. The final drug product was demonstrated to be photostable when packed in the amber glass bottles.
The proposed shelf life of 18 months was granted for the product, when packed in an amber glass bottle (type III) with a white child resistant closure (polypropylene) and a polypropylene/polyethylene oral syringe with the storage condition "Store in the original packaging in order to protect from light". In-use stability data demonstrate stability for 4 months after first opening. The in-use stability study has been redesigned

to simulate daily practice and to cover 7 months in line with the in-use shelf-life of the innovator product. The MAH committed to perform the redesigned in-use stability study post-approval with a batch at the end of shelf-life.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded. Magnesium stearate is of vegetable origin.

II.2 Non clinical aspects

This product is a generic formulation of Keppra, which is available on the European market. No new preclinical data have been submitted, and therefore the application has not undergone preclinical assessment. This is acceptable for this type of application.

Environmental risk assessment
The product is intended as a substitute for other identical products on the market. The approval of this product will not result in an increase in the total quantity of levetiracetam released into the environment. It does not contain any component, which results in an additional hazard to the environment during storage, distribution, use and disposal.

II.3 Clinical aspects

Levetiracetam is a well-known active substance with established efficacy and tolerability.

The absence of a bioequivalence study has been adequately justified in accordance with Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98. The qualitative composition of the generic levetiracetam 100 mg/ml oral solution is similar to that of the innovator/reference product Keppra 100 mg/ml oral solution. Levetiracetam Sandoz 100 mg/ml, oral solution is an aqueous oral solution and contains the same concentration of active substance as the Keppra 100 mg/ml oral solution. Moreover, the amount of excipient maltitol used in the generic levetiracetam oral solution is identical as in Keppra oral solution, *i.e.* 300 mg/ml. Liquid maltitol is, as per the Ph. Eur., an aqueous solution of a hydrogenated, partly hydrolysed starch, composed of a mixture of mainly 4-O-α-d-glucopyranosyl-d-glucitol (d-maltitol) with d-glucitol (d-sorbitol) and hydrogenated oligo- and polysaccharides. Since the guideline CPMP/EWP/QWP/1401/98 Rev. 1 depicts 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 MAH included the identical amount of liquid maltitol in the formulation to that reported in the SPC of Keppra.

The only differences between Levetiracetam Sandoz 100 mg/ml and the innovator product are:

- taste masking agents *i.e.* grape flavour and ammonium glycyrrhizate used in the innovator's solution were replaced with raspberry flavour in the generic solution.
- antimicrobial preservative *i.e.* the MAH decided not to use propyl parehydroxybenzoate which is present in the innovator's formulation based on the request of EMA regarding removal of propyl parehydroxybenzoate from a different anti-epileptic oral solution containing lacosamide (see EPAR of Vimpat for argumentation).

The above mentioned differences in the qualitative composition are not expected to affect bioavailability of levetiracetam, which is a highly soluble and permeable drug. Therefore, it is acceptable to waive a bioequivalence study for Levetiracetam Sandoz 100 mg/ml, oral solution.

Risk management plan
Levetiracetam was first approved in 2000, and there is now more than 10 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 authorisation which are not adequately covered by the current SPC. Additional risk minimisation 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 sufficient to identify actual or potential risks and a detailed European Risk Management Plan is not necessary for this product.

Pharmacovigilance

The innovator product Keppra currently has a one-year PSUR cycle. Therefore, the MAH agreed to follow a one-year PSUR cycle upon approval for levetiracetam. The MAH also committed to submitting 6-monthly specific safety reports for children < 4 years old in between yearly PSURs, which is in correspondence with the agreed PSUR cycle of the innovator product.

Product information

SPC

The content of the SPC approved during the decentralised procedure is in line with the SPC for the innovator product.

Readability test

The package leaflet was demonstrated to be in line with the successfully user-tested PIL of the originator (Keppra), which was accepted. Therefore no separate user test is required.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Levetiracetam Sandoz 100 mg/ml, oral solution has a proven chemical-pharmaceutical quality and is a generic form of Keppra 100 mg/ml oral solution. Keppra is a well-known medicinal product with an established favourable efficacy and safety profile.

The absence of a bioequivalence study has been adequately justified and was accepted. In conclusion, the qualitative composition is considered similar to that of Keppra oral solution. The differences in taste masking agents and antimicrobial preservative are not expected to affect bioavailability of levetiracetam, which is a highly soluble and permeable drug.

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The SPC is consistent with that of the reference product. The SPC, package leaflet and labelling are in the agreed templates.

The Board followed the advice of the assessors.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Levetiracetam Sandoz 100 mg/ml, oral solution with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 30 August 2011. Levetiracetam Sandoz 100 mg/ml, oral solution was authorised in the Netherlands on 25 November 2011.

The date for the first renewal will be: 30 August 2016.

The following post-approval commitments have been made during the procedure:

Quality - medicinal product

- The MAH committed to provide process validation data for three commercial-scale batches of Levetiracetam Sandoz 100 mg/ml, oral solution.
- The MAH committed to perform the redesigned in-use stability study post-approval with a batch at the end of shelf-life to cover 7 months in line with the in-use shelf-life of the innovator product..

Pharmacovigilance

- The MAH committed to follow the one-year PSUR cycle for Levetiracetam Keppra. The MAH also committed to submitting 6-monthly specific safety reports for children < 4 years old in between yearly PSURs, which is in correspondence with the agreed PSUR cycle of the innovator product.

List of abbreviations

ASMF	Active Substance Master File
ATC	Anatomical Therapeutic Chemical classification
AUC	Area Under the Curve
BP	British Pharmacopoeia
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
C_{max}	Maximum plasma concentration
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CV	Coefficient of Variation
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EU	European Union
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
MEB	Medicines Evaluation Board in the Netherlands
OTC	Over The Counter (to be supplied without prescription)
PAR	Public Assessment Report
Ph.Eur.	European Pharmacopoeia
PIL	Package Leaflet
PSUR	Periodic Safety Update Report
SD	Standard Deviation
SPC	Summary of Product Characteristics
$t_{½}$	Half-life
t_{max}	Time for maximum concentration
TSE	Transmissible Spongiform Encephalopathy
USP	Pharmacopoeia in the United States

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Scope	Procedure number	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval/ non approval	Assessment report attached