CBG MEB

Public Assessment Report

Scientific discussion

Levetiracetam ADOH 100 mg/ml concentrate for solution for infusion

(levetiracetam)

NL/3659/001/DC

Date: 16 March 2017

This module reflects the scientific discussion for the approval of Levetiracetam ADOH 100 mg/ml concentrate for solution for infusion. The procedure was finalised on 29 September 2016. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

ASMF	Active Substance Master File
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
ERA	Environmental Risk Assessment
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Levetiracetam ADOH 100 mg/ml concentrate for solution for infusion, from ADOH B.V.

The product 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 ADOH is indicated 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 ADOH concentrate is an alternative for patients when oral administration is temporarily not feasible.

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

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Keppra, which was first registered in the EEA on 29 September 2000 by UCB Pharma through centralised procedure EU/1/00/146/001-029. This first authorisation concerned film-coated tablets. Keppra 100 mg/ml concentrate for solution for infusion was approved in the EEA on 29 March 2006.

The concerned member states (CMS) involved in this procedure was Germany.

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC.

II. QUALITY ASPECTS

II.1 Introduction

Levetiracetam ADOH is a clear, colourless, liquid with pH 5.0~6.0. Each ml contains 100 mg of levetiracetam. The concentrate is packed in a 10 ml glass vial (type I) containing 5 ml of concentrate closed by a Teflon-coated grey chlorobutyl rubber stopper and sealed with an aluminium/ polypropylene flip-off cap.

The excipients are: sodium acetate, glacial acetic acid, sodium chloride, water for injections.

II.2 Drug Substance

The active substance is levetiracetam, an established active substance described in the European Pharmacopoeia (Ph.Eur.). The active substance is very soluble in water. The substance contains a stereogenic centre and the S-enantiomer is the active substance. The R-enantiomer is limited as specified impurity. Levetiracetam shows polymorphism; the supplier provides crystal form I. The substance is non-hygroscopic.

The CEP procedure is used for the active substance. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the general

monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the European Pharmacopoeia.

Manufacturing process
A CEP has been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance
The drug substance specification is in line with the Ph.Eur. and CEP, with additional requirements for pH, residual solvents, bacterial endotoxins and microbial limits. The specification is acceptable in view of the route of synthesis and the various European guidelines. Batch analytical data demonstrating compliance with the drug substance specification have been provided for three full-scale batches.

Stability of drug substance
The active substance is stable for 3 years when stored under the stated conditions. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

II.3 Medicinal Product

Pharmaceutical development
The development of the product has been described, the choice of excipients is justified and their functions explained. The MAH has performed risk analysis and used Quality by Design to develop the generic product. Formulation development was based on the reference product Keppra 100 mg/ml concentrate for solution for infusion. The Quality Target Product Profile was established and Critical Quality Attributes identified. The manufacturing process has been established based on the critical process parameters. A control strategy has been indicated. No clinical or bioequivalence studies were performed. These are indeed not considered necessary as the product is an aqueous-based parenteral product. Suitability of the container closure system has been demonstrated. Compatibility of the manufacturing process equipment with the drug product has been shown. In accordance with decision tree for sterilization method as specified in ICH, since the active substance is stable in high temperature, thus terminal steam sterilisation process is employed.
The pharmaceutical development of the product has been adequately performed.

Manufacturing process
The manufacturing process consists of the following steps: preparation of inner packaging materials, compounding, filtration, filling, capping, sterilization, visual inspection and packaging. The product is terminally sterilized using Ph.Eur. conditions. The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product has been presented for three full scaled batches. In addition, all relevant validation results of non-product specific operating processes are provided.

Control of excipients
The excipients comply with Ph.Eur. requirements and additional in-house tests. These specifications are acceptable.

Quality control of drug product
The product specification includes tests for appearance, identification, appearance of solution, pH, filling volume, visible particles, sub-visible particles, bacterial endotoxins, sterility, related substances and assay. A test for R-enantiomer is not included in the specification but has been tested during stability studies. The release and shelf-life requirements are identical and acceptable.
The analytical methods have been adequately described and validated.
Batch analytical data from the proposed production site have been provided on four full scaled batches, demonstrating compliance with the release specification.

Stability of drug product
Stability data on the product has been provided on three full scaled batches stored at 25°C/60% RH (up to 24 months), 30°C/65% RH (up to 24 months) and 40°C/75% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in the commercial packaging consisting of clear colourless borosilicate glass (Type I) vials with Teflon-coated chlorobutyl rubber stopper and aluminium-plastic overseal. Results show compliance with the

specification. Hence a shelf-life period of 36 months without any specific storage restrictions can be granted. Photostability results show that the product is not sensitive to light degradation.

In-use stability studies of the diluted product have been performed. The product can be diluted with 0.9% sodium chloride injection, 5% glucose injection, and sodium lactate Ringer's solution. The product remains stable for 24 hours following dilution, when stored at controlled room temperature.

Specific measures for 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.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Levetiracetam ADOH 100 mg/ml has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.
No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Levetiracetam ADOH is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.2 Discussion on the non-clinical aspects

This product is a generic formulation of Keppra, which is available on the European market. Reference is made to the preclinical data obtained with the innovator product. 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. Therefore, the member states agreed that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

Levetiracetam is a well-known active substance with established efficacy and tolerability.
A clinical overview has been provided, which is based on scientific literature. The overview justifies why there is no need to generate additional clinical data. Therefore, the member states agreed that no further clinical studies are required.

IV.2 Pharmacokinetics

Levetiracetam ADOH 100 mg/ml concentrate for solution for infusion is a parenteral formulation and therefore fulfils the exemption mentioned in the Note for Guidance on bioequivalence "5.1.6 parenteral solutions", which states that a bioequivalence study is not required if the product is administered as an aqueous intravenous solution containing the same active substance in the same concentration as the currently authorized reference medicinal product (NfG CPMP/EWP/QWP 1401/98). The qualitative quantitative composition of Levetiracetam ADOH 100 mg/ml is entirely the same as the originator. Therefore, it may be considered as therapeutic equivalent, with the same efficacy/safety profile as known for the active substance of the reference medicinal product. The current product can be used instead of its reference product.

IV.3 Risk Management Plan

The MAH has submitted a risk management plan, 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 ADOH.

- Summary table of safety concerns as approved in RMP

Important identified risks	• Abnormal behavior and suicide • Blood dyscrasias
Important potential risks	• Seizure worsening
Missing information	• Long-term effects on learning, intelligence, growth, endocrine function, puberty and childbearing potential in children • Safety and efficacy in infants and children less than 4 years old

The member states agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Keppra. No new clinical studies were conducted. The MAH demonstrated similarity to the reference product based on chemical-pharmaceutical characteristics. Risk management is adequately addressed. This generic medicinal product can be used instead of the reference product.

V. USER CONSULTATION

The package leaflet (PL) 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 test consisted of two rounds with 10 participants each. All questions were open questions and covered general impressions of the PL, finding specific information in the PL and understanding that information, and design and layout of the PL.
The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

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

Since both the reference and current product are intended for parenteral use, no bioequivalence study is deemed necessary.

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 ADOH 100 mg/ml with the reference product, and

have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 29 September 2016.

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