COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Levetiracetam Amarox 100 mg/ml, concentrate for solution for infusion

(levetiracetam)

NL/H/4828/001/DC

Date: 2 February 2021

This module reflects the scientific discussion for the approval of Levetiracetam Amarox 100 mg/ml, concentrate for solution for infusion. The procedure was finalised at 27 November 2020. 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 Amarox 100 mg/ml, concentrate for solution for infusion, from Amarox Pharma 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 were Germany and Spain.

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

II. QUALITY ASPECTS

II.1 Introduction

Levetiracetam Amarox is a clear, colourless, concentrate for solution for infusion. Each ml contains 100 mg of levetiracetam.

The concentrate is packed in a 5 ml clear lyo bottom tubular glass vial (type I) closed by a stopper 20 mm serum GBB west S-127 stopper grey westar rubber stopper and sealed with 20 mm Raymond blue flip-off seal.

The excipients are: sodium acetate trihydrate (E262), glacial acetic acid (E260) (for pH adjustment), sodium chloride and 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 a white or almost white crystalline powder and freely soluble in water. The drug substance has a single chiral centre. The required isomer is (2S)-2-(2-Oxopyrrolidin-1-yl)butanamide

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 residual solvents, polymorphism, bacterial endotoxins and microbial enumeration. 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 batches.

Stability of drug substance

The active substance is stable for 5 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 product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines. The choice of excipients is justified and their functions explained. The sterilisation process is justified. The MAH prepared an initial drug product batch. The tested parameters were within the specification.

The sterilisation method, pH of the product and nitrogen purging were varied. Furthermore, a risk assessment was performed to determine the critical quality attributes. The pharmaceutical development of the product has been adequately performed.

Manufacturing process

The concentrate for infusion is manufactured by dissolving the excipients and the levetiracetam in water for injection. After each addition the pH is monitored and adjusted in case needed. Subsequently, the drug product is filtered, filled into the vials and sterilised by steam. The manufacturing process been adequately validated according to relevant European guidelines. The product is manufactured using conventional manufacturing techniques.

Control of excipients

The excipients comply with Ph. Eur. requirements. These specifications are acceptable.

Quality control of drug product

The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for appearance, identification, colour and clarity, appearance of solution, uniformity of dosage units, osmolality, pH, extractable volume, assay, related substances, particulate contamination, bacterial endotoxins and sterility. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. Satisfactory validation data for the analytical methods have been provided. Batch analytical data from four batches from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product

Stability data on the product have been provided for four batches stored at 25°C/60% RH (12 months) and 40°C/75% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. The shelf-life of 2 years and storage conditions “This medicinal product does not require any special storage conditions” can be accepted, as no changes in drug product quality were observed during the formal stability and photostability studies. The in-use stability claim is acceptable.

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.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Levetiracetam Amarox 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 Amarox 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 Amarox 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 authorised reference medicinal product (NfG CPMP/EWP/QWP 1401/98). The quantitative composition of Levetiracetam Amarox 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 Amarox.

Table 1. Summary table of safety concerns as approved in RMP

Important identified risks	- Abnormal behaviour - Blood dyscrasias - Suicidal ideation and behaviour - Suicidality - Seizure Worsening
Important potential risks	None
Missing information	- Long term effects on learning, intelligence, growth, endocrine function, puberty and childbearing potential in children with epilepsy or in children exposed in utero - Deterioration of seizure control during pregnancy - Decreased bone mineral density after prolonged levetiracetam exposure

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. Risk management is adequately addressed. This generic medicinal product can be used instead of the reference product.

V. USER CONSULTATION

A user consultation with target patient groups on the package leaflet (PL) has been performed on the basis of a bridging report making reference to Keppra 100 mg/ml concentrate for solution for infusion (for content) and Levetiracetam Hetero 750 mg film-coated tablets (for design and layout). The bridging report submitted by the MAH has been found acceptable; bridging is justified for both content and layout of the leaflet.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Levetiracetam Amarox 100 mg/ml, concentrate for solution for infusion has a proven chemical-pharmaceutical quality and is a generic form of Keppra 100 mg/ml concentrate for solution for infusion. 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. A biowaiver has been granted.

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 Amarox with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 27 November 2020.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Procedure number	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse