COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Levetiracetam AMETAS 100 mg/ml, oral solution (levetiracetam)

NL/H/4950/001/DC

Date: 11 October 2021

This module reflects the scientific discussion for the approval of Levetiracetam AMETAS 100 mg/ml, oral solution. The procedure was finalised at 13 January 2021. 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 AMETAS 100 mg/ml, oral solution, from AMETAS medical GmbH.

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 AMETAS is indicated as adjunctive therapy:

- in the treatment of partial onset seizures with or without secondary generalisation in adults, adolescents, 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 Summary of Product Characteristics (SmPC).

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Keppra 100 mg/ml oral solution, which has been registered in the European Economic Area via a centralised procedure by UCB Pharma S.A. since 3 March 2003 (EMEA/H/C/000277).

The concerned member state (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 AMETAS is an oral solution and is a clear liquid. Each ml of the oral solution contains as active substance 100 mg levetiracetam.

The oral solution is packed in bottles of different sizes:

- a 300 ml amber glass bottle (type III) with a white child resistant closure (polypropylene) in a cardboard box also containing a 10 ml graduated oral syringe (polyethylene, polystyrene) and an adaptor for the syringe (polyethylene).

- a 150 ml amber glass bottle (type III) with a white child resistant closure (polypropylene) in a cardboard box also containing a 3 ml graduated oral syringe (polyethylene, polystyrene) and an adaptor for the syringe (polyethylene).
- a 150 ml amber glass bottle (type III) with a white child resistant closure (polypropylene) in a cardboard box also containing a 1 ml graduated oral syringe (polyethylene, polystyrene) and an adaptor for the syringe (polyethylene).

The excipients are: citric acid monohydrate (E330), sodium citrate (E331), saccharin sodium (E954), sodium chloride, sorbitol, liquid (non-crystallising) (E420), methyl parahydroxybenzoate (E218), propyl parahydroxybenzoate (E216), banana flavour (contains benzyl alcohol (E1519) and propylene glycol (E1520)) and purified water.

II.2 Drug Substance

The active substance is levetiracetam, an established active substance described in the European Pharmacopoeia (Ph. Eur.). Levetiracetam is a white to off-white crystalline powder, freely soluble in water, chloroform and methanol, soluble in ethanol, sparingly soluble in acetonitrile and practically insoluble in n-hexane. The active substance is manufactured by two suppliers. The drug substance has a chiral centre. Polymorphism is not relevant as the drug substance is in solution in the drug product.

The CEP procedure is used for the active substance. Certificates have been provided for both manufacturers of 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 Ph. Eur.

Manufacturing process
CEPs have been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance
The active substance specification is considered adequate to control the quality and meets the requirements of the monograph in the Ph. Eur. Batch analytical data demonstrating compliance with this specification have been provided for three batches from both manufacturers.

Stability of drug substance
The active substance from manufacturer I is stable for three years when stored in either a polyethylene bag in an aluminium film bag placed in a fibre drum, or a polypropylene bag

lined with polyethylene bags (outer black). Assessment thereof was part of granting the CEP and has been granted by the EDQM.
The active substance from manufacturer II is stable for five years when stored under nitrogen atmosphere in a double polyethylene bag placed in a polyethylene drum. 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 are explained. The pharmaceutical development is based on the similarity with the innovator product Keppra.

Three dosing pipettes were proposed with the sizes 1, 3, and 10 ml. The syringes are in line with the EMA Q&A on Graduation of measuring devices for liquid dosage forms. The graduation of the syringes is suitable for the proposed posology, and the accuracy of the syringes has been demonstrated by validating for each syringe size the accuracy of the delivered dose at the minimum and maximum dose that can be given with each syringe.

Since the product is also indicated for the paediatric population, it is agreed with the MAH that the current formulation is in line with the requirements of the EMA Guideline on pharmaceutical development of medicines for paediatric use. All excipients have been justified and their quantities are in general less than approved in other formulations for use in children. Furthermore, the newly proposed syringes are appropriate for the intended dosages for children.

Manufacturing process
The oral solution is manufactured by dissolving the excipients and drug substance in purified water. 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. The product is manufactured using conventional manufacturing techniques.

Control of excipients
The excipients (except for the banana flavour) comply with Ph. Eur. requirements. For the flavour, in-house criteria are used. There are no novel excipients included in the drug product. The specifications are acceptable and the control of excipients is appropriate.

Microbiological attributes
Microbiological testing is performed on the finished product in accordance with the Ph. Eur. Compliance is demonstrated in the scope of batch release. The MAH has sufficiently justified the level of the preservatives, and it has been shown that the used levels are adequate to ensure the stability of the drug product for the proposed shelf-life.

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 description, identification, pH, assay, related substances, preservatives content, microbial limits and efficacy of microbial preservation. The release and shelf-life limits are identical, except for the limit for total impurities. 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 has been provided for three batches of the 300 ml presentations, stored at 25°C/60% RH (36 months) and 40°C/75% RH (six months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in type III amber glass bottles. Stability studies on the 150 ml bottles have started and a commitment has been provided that these studies will be finished, however, the MAH has sufficiently justified that the stability data for the 300 ml bottles is representative for the 150 ml bottles as well. Photostability studies were performed in accordance with ICH recommendations and showed that the product is stable when exposed to light.

On basis of the data submitted, a shelf life was granted of three years. The labelled storage conditions are “do not freeze”.

Further, stability data have been provided demonstrating that the product remains stable for four months following first opening of the container.

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 AMETAS 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 AMETAS 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.

For this generic application, the MAH has submitted a bioequivalence study, which is discussed below.

IV.2 Pharmacokinetics

The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Levetiracetam AMETAS 100 mg/ml, oral solution (AMETAS medical GmbH, Germany) is compared with the pharmacokinetic profile of the reference product Keppra 100 mg/ml oral solution (UCB Pharma S.A., Belgium).

The choice of the reference product in the bioequivalence study has been justified by comparative studies between the proposed drug product and the reference product, which showed essential similarity with respect to the major physicochemical parameters. The formula and preparation of the bioequivalence batch are identical to the formula proposed for marketing.

Bioequivalence studies

Design

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 16 healthy subjects, aged 18 - 54 years. Each subject received either 10 ml of 100 mg/ml of one of the two levetiracetam formulations mixed with 100 ml of water after an overnight fast of at least eight hours. Thereafter another 100 ml water was administered. There were two dosing periods, separated by a washout period of 17 days. Blood samples were collected pre-dose and at 0.083, 0.167, 0.25, 0.33, 0.5, 0.67, 0.83, 1, 1.33, 1.67, 2, 2.50, 3, 4, 5, 7, 9, 12, 24, 36 and 48 hours after administration of the products. The design of the study is acceptable.

Analytical/statistical methods

The analytical method has been adequately validated and is considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Results

All 16 subjects were eligible for pharmacokinetic analysis.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of levetiracetam under fasted conditions.

Treatment N=16	**AUC_{0-t} (ng.h/ml)**	**$AUC_{0-\infty}$ (ng.h/ml)**	**C_{max} (ng/ml)**	**t_{max} (h)**
Test	280117 ± 37582	285038 ± 38017	31819 ± 4634	0.4 (0.25 - 0.83)
Reference	284421 ± 41040	288880 ± 42056	30714 ± 5858	0.6 (0.25 - 2.00)
***Ratio (90% CI)**	0.986 (0.95 - 1.023)	--	1.045 (0.973 - 1.122)	--

$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
C_{max} maximum plasma concentration
t_{max} time for maximum concentration

**ln-transformed values*

Conclusion on bioequivalence study

The 90% confidence intervals calculated for AUC_{0-t} and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence study Levetiracetam AMETAS is considered bioequivalent with Keppra.

The MEB has been assured that the bioequivalence study has been conducted in accordance with acceptable standards of Good Clinical Practice (GCP, see Directive 2005/28/EC) and Good Laboratory Practice (GLP, see Directives 2004/9/EC and 2004/10/EC).

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 AMETAS.

Table 2. Summary table of safety concerns as approved in RMP

Important identified risks	• Abnormal behaviour • Suicidality • Blood dyscrasias
Important potential risks	• Seizures worsening
Missing information	• Long term effects om 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. The MAH demonstrated through a bioequivalence study that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of this reference product. 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 the innovator product Keppra for content, and to Valsartif 80 and 160 mg, film-coated tablets for lay-out. 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 AMETAS 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. Bioequivalence has been shown to be in compliance with the requirements of European guidance documents.

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 AMETAS with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 13 January 2021.

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