COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Levetiracetam AMETAS 250 mg, 500 mg, 750 mg and 1000 mg, film-coated tablets (levetiracetam)

NL/H/4951/001-004/DC

Date: 5 October 2021

This module reflects the scientific discussion for the approval of Levetiracetam AMETAS 250 mg, 500 mg, 750 mg and 1000 mg, film-coated tablets. The procedure was finalised at 10 June 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
AUC	Area under the plasma concentration-time curve
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
C_{max}	Maximum plasma concentration
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
t_{max}	Time for maximum plasma concentration
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 250 mg, 500 mg, 750 mg and 1000 mg, film-coated tablets, 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 products Keppra 250 mg, 500 mg, 750 mg and 1000 mg, film-coated tablets, which have been registered in the European Economic Area via a centralised procedure by UCB Pharma S.A. since 29 September 2000 (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 are film-coated tablets, capsule shaped with a deep notch on one side. The tablets can be divided into equal halves. The different tablets strengths can be distinguished by colour and size:

- 250 mg film-coated tablets: blue coloured.
- 500 mg film-coated tablets: yellow coloured.
- 750 mg film-coated tablets: orange coloured.
- 1000 mg film-coated tablets: white coloured.

The film-coated tablets contain as active substance 250 mg, 500 mg, 750 mg or 1000 mg of levetiracetam, respectively.

The film-coated tablets are packed in aluminium/PVC blisters, aluminium/PVC/PVdC blisters or high-density polyethylene (HDPE) bottles. The HDPE bottles are closed with a child resistant and tamper evident polypropylene screw cap with a mounted desiccant.

The excipients for all strengths are:
Tablet core - maize starch, povidone K30, magnesium stearate and colloidal anhydrous silica.

Film-coating - polyvinyl alcohol partially hydrolysed, titanium dioxide (E171), macrogol 3350, talc (E553b), and either indigo carmine aluminium lake (E132) (250 mg product) or iron oxide yellow (E172) (500 mg product) or iron oxide red (E172) (750 mg product).

The tablet strengths are dose proportional over the dosing range of 250 mg to 1000 mg.

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 MAH has discussed the polymorphic form of the drug substance, from which can be concluded that the polymorphic form manufactured by both suppliers is constant (form I).

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.

<u>Manufacturing process</u>
CEPs have been submitted; therefore no details on the manufacturing process have been included.

<u>Quality control of drug substance</u>
The active substance specification is considered adequate to control the quality and meets the requirements of the monograph in the Ph. Eur. In addition, several parameters are tested that comply with in-house specifications, including residual solvents, impurities and

particle size. Since the active substance levetiracetam is a Biopharmaceutics Classification System (BCS) Class 1 drug, with a high solubility and high permeability, the particle size will not affect the drug product performance. The provided justification for not including a test for microbiological quality of the drug substance is acceptable; a test for microbiological quality is included in the drug product specification.

Batch analytical data demonstrating compliance with the specifications have been provided for both drug substance manufacturers, which showed compliance to the required limits.

Stability of drug substance

The active substance produced by the first manufacturer is stable for 36 months 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. The active substance produced by the second manufacturer is stable for five years when stored in a double polyethylene bag placed in a polyethylene drum. Assessment of the re-test periods was part of granting the CEPs and has been granted by the EDQM.

II.3 Medicinal Products

Pharmaceutical development

The products are established pharmaceutical forms and their development is adequately described in accordance with the relevant European guidelines. The pharmaceutical development is based on the similarity with reference products Keppra. The main pharmaceutical development studies concerned the characterisation of the reference products, optimisation of the formulation and of the manufacturing process, and dissolution method development. The MAH has adequately addressed, as per “Reflection paper on Dissolution specification for generic oral immediate release products”, the choice of dissolution method (volume, medium, rotation speed and apparatus). Complementary to the dissolution study, a bioequivalence study with the highest product strength was conducted, which will be discussed in section IV.

Since the products are also indicated for the paediatric population, the MAH has discussed and justified the choice of excipients as being qualitatively the same as the excipients in the reference products, and has compared the quantity of the excipients to those of other products which are on the market for the paediatric population.

Manufacturing process

The manufacturing process is considered standard and has been described with sufficient details. The manufacturing process has been validated according to relevant European/ICH guidelines.

Process validation data on the products have been presented for pilot scale batches for all strengths. For the 500 mg, 750 mg and 1000 mg strengths, process validation data of the largest batch size have also been submitted. The MAH has committed to perform process validation on the first three production scale batches of the finished products, in line with the process validation protocol. Further, the MAH has declared that three production scale

batches for each strength will be validated if the higher batch sizes are manufactured for each strength, depending on market demand, which is acceptable. The MAH has provided an adequate discussion and data showing that the homogeneity of the blend is unaffected by an increase in batch size. The minimum and maximum batch ranges possible for each strength have demonstrated a state of control for the process validation batches.

Control of excipients

For all excipients, except for the colourants, reference is made to the Ph. Eur. For the colourants, 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.

Quality control of drug products

The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for description, identification, water content, uniformity of dosage units, assay, dissolution, related substances, breakability and microbiological quality. The release and shelf life acceptance criteria are equal for all parameters. 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 on three batches per strength for the 250 mg, 500 mg and 1000 mg products and on two batches for the 750 mg product from the proposed drug production site have been provided, demonstrating compliance with the specification. For each strength, two batches were manufactured with levetiracetam from an active substance supplier that is not involved in this procedure. The MAH has clarified that the active substance manufactured by this supplier adhered to the relevant regulations at the time of the manufacture of the drug product batches used for pharmaceutical development, manufacturing process validation, batch analysis and stability studies. As this supplier is not included in the dossier, and batches with this active substance are not being considered in support of the request for a biowaiver for the additional strengths, this clarification was considered adequate.

Stability of drug products

Stability data on the product have been provided for three pilot batches of each strength except for the 750 mg for which two were submitted. Stability studies were conducted on all of the batches at 25°C/60% RH (60 months) and at 40°C/75% RH (six months), in accordance with applicable European guidelines. At the accelerated conditions, dissolution data were failing to meet the “Q” point, i.e. the limit for the amount of dissolved active substance, when stored in aluminium/PVC blisters (all batches) and in aluminium/PVC/PVdC blisters (250 mg and 1000 mg batches). A photostability study was conducted in compliance with relevant European guidelines, which showed that there were no trends for any of the tested parameters when exposed directly to light.

On basis of the data submitted, a shelf life was granted of 60 months for all strengths when stored in aluminium/PVC blisters or aluminium/PVC/PVdC blisters. The labelled storage

conditions are: 'Do not store above 25°C.' When stored in HDPE bottles, a shelf life of 60 months without special storage conditions has been granted.

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 have a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished products.

No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Levetiracetam AMETAS are 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

The products are generic formulations of Keppra, which are available on the European market. Reference is made to the preclinical data obtained with the innovator products. 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 1000 mg, film-coated tablets (AMETAS medical GmbH, Germany) is compared with the pharmacokinetic profile of the reference product Keppra 1000 mg, film-coated tablets (UCB Pharma S.A., Belgium).

The choice of the reference product in the bioequivalence study has been justified by comparative dissolution 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.

Biowaiver

For the additional 250 mg, 500 mg and 750 mg product strengths a biowaiver was requested. The different product strengths comply with the following biowaiver criteria from CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **:

- The different product strengths are manufactured by the same manufacturing process;
- The products have the same qualitative composition;
- The products are quantitatively proportional;
- Appropriate *in vitro* dissolution data have confirmed the adequacy of waiving additional *in vivo* bioequivalence testing. The used dissolution method is acceptable in view of the recommendations for dissolution methods for biowaivers of additional strengths. For the 250 mg product, the MAH used multimedia dissolution data available for the finished product batch using active substance from the supplier that was not involved in this procedure, as a substitute for missing multimedia dissolution data. This has been justified by comparable physical-chemical characteristics of this active substance and the active substance from one of the involved active substance manufacturers.

Therefore, similarity can be accepted and a biowaiver for the 250 mg, 500 mg and 750 mg product strengths has been granted.

Bioequivalence study

Design

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 24 healthy adult subjects,

aged 18 - 43 years. Each subject received a single dose (1000 mg) of one of the two levetiracetam formulations. The tablet was orally administered with 240 ml water after an overnight fasting period of at least ten hours. There were two dosing periods, separated by a washout period of seven days.

Blood samples were collected pre-dose and at 0.16, 0.33, 0.50, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 4, 5, 6, 8, 12, 16, 24, 36 and 48 hours after administration of the products.

The design of the study is acceptable. One bioequivalence study with the highest strength is sufficient for these drug products with respect to the pharmaceutical form and immediate release formulation. A study under fasting conditions is appropriate.

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
Out of the 24 subjects, 22 subjects were eligible for pharmacokinetic analysis. One subject was withdrawn due to a positive alcohol breath test, and one subject was withdrawn for not reporting to the clinical facility for period II.

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

Treatment N=22	**AUC_{0-t} (ng.h/ml)**	**$AUC_{0-\infty}$ (ng.h/ml)**	**C_{max} (ng/ml)**	**t_{max} (h)**
Test	335.47 ± 37.27	342.44 ± 39.52	34.47 ± 6.21	0.75 (0.50 - 1.25)
Reference	342.00 ± 42.86	351.50 ± 47.04	35.08 ± 6.43	0.75 (0.50 - 2.02)
***Ratio (90% CI)**	0.982 (0.957 – 1.008)	--	0.983 (0.936 - 1.033)	--

$AUC_{0-\infty}$ 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. The MAH demonstrated through a bioequivalence study that the pharmacokinetic profile of the highest product strength is similar to the pharmacokinetic profile of the respective reference product strength.

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

Patients aged 1 month to less than 4 years	
Important identified risks	None
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.
Patients aged 4 years and older	
Important identified risks	None
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. • Worsening of seizure control during pregnancy

The MAH committed to perform routine pharmacovigilance activities and routine risk minimisation measures, which is also sufficient for the areas of missing information. This has been agreed upon by the member states.

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator products Keppra. No new clinical studies were conducted. The MAH demonstrated through a bioequivalence study that the pharmacokinetic profile of the 1000 mg product is similar to the pharmacokinetic profile of the respective reference product, and a biowaiver has been granted for the additional strengths. Risk management is adequately addressed. These generic medicinal products can be used instead of the reference products.

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 products 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 250 mg, 500 mg, 750 mg and 1000 mg, film-coated tablets have a proven chemical-pharmaceutical quality and are generic forms of Keppra 250 mg, 500 mg, 750 mg and 1000 mg, film-coated tablets. Keppra are well-known medicinal products with established favourable efficacy and safety profiles.

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 products, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 10 June 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