COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

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

NL/H/5923/001-004/DC

Date: 10 April 2024

This module reflects the scientific discussion for the approval of Levetiracetam Mylan 250 mg, 500 mg, 750 mg and 1000 mg, film-coated tablets. The procedure was finalised at 20 January 2012 in Germany (DE/H/5719/001-004/DC). After a transfer on 24 November 2023, the current RMS is the Netherlands. 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
EMA	European Medicines Agency
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
RMS	Reference Member State
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the MHRA granted Mylan Pharmaceuticals Limited Marketing Authorisations for the medicinal products Levetiracetam Mylan 250 mg, 500 mg, 750 mg and 1000 mg, film-coated tablets on 10 February 2012. The products are prescription-only medicines.
These are generic applications for Levetiracetam Mylan 250 mg, 500 mg, 750 mg and 1000 mg, film-coated tablets, submitted under Article 10(1) of Directive 2001/83 EC, as amended. The applications refer to the innovator products, Keppra 250 mg, 500 mg, 750 mg and 1000 mg film-coated tablets (EU/1/00/146/001-026, 028 and 029), authorised to UCB S.A. in September 2000, via the centralised procedure. Keppra 250 mg, 500 mg, 750 mg and 1000 mg film-coated tablets have been authorised in the UK for more than 10 years, thus the period of data exclusivity has expired.

Levetiracetam is indicated as mono therapy in the treatment of partial onset seizures with or without secondary generalisation in patients from 16 years of age with newly diagnosed epilepsy.
Levetiracetam 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-clinic seizures in adults and adolescents from 12 years of age with Idiopathic Generalised Epilepsy.

A comprehensive description of the up-to-date indications and posology is given in the SmPC.

The active substance, levetiracetam, is a pyrrolidone derivative (S-enantiomer of a-ethyl-2-oxo-1- pynolidine 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. Levetiracetam induces seizure protection in a broad range of animal models of partial and primary generalised seizures without having a pro-convulsant effect. The primary metabolite is inactive. No new non-clinical or clinical efficacy studies were conducted for these applications, which is acceptable given that the applications were £or generic versions of products that have been licensed for over 10 years.

The applications are supported by a bioequivalence study comparing the pharmacokinetic profile of the test product, Levetiracetam Mylan 1000 mg film-coated tablets, to that of the reference product, Keppra 1000 mg film-coated tablets (UCB S.A.). The bioequivalence study was carried out in accordance with Good Clinical Practice (GCP).
The RMS has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for this product type at all sites responsible for the manufacture and assembly of these products. Evidence of compliance with GMP has been provided for the named

manufacturing and assembly sites. For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.
For manufacturing sites outside the community, the RMS has accepted copies of current GMP Certificates or satisfactory inspection summary reports, 'close-out letters' or 'exchange of information' issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.

The MAH has provided adequate justification for not submitting a detailed Environmental Risk Assessment (ERA). These were applications for generic products and there is no reason to conclude that marketing of these products will change the overall use pattern of the existing market. There are no environmental concerns associated with the method of manufacture or formulation of the products.
The RMS considers that the pharmacovigilance system as described by the Marketing Authorisation Holder (MAH) fulfils the requirements and provides adequate evidence that the MAH has the services of a Qualified Person (QP) responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.
The MAH has provided adequate justification for not submitting a Risk Management Plan (RMP). As the applications are for generic versions of already authorised reference products, for which safety concerns requiring additional risk minimisation have not been identified, routine pharmacovigilance activities are proposed and a risk minimisation system is not considered necessary. The reference products have been in use for many years and the safety profile of the active is well-established.

The concerned member states (CMS) involved in this procedure were Northern Ireland, Portugal and Spain.

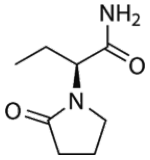
This product was originally authorised in several Members States of the European Union under the decentralised procedure UK/H/2895/001-004/DC with the United Kingdom as RMS. Subsequently, a RMS transfer to Germany (DE/H/25719/001-004/DC) took place. The current RMS is the Netherlands.

II. QUALITY ASPECTS

II.1 Drug Substance

Levetiracetam (S enantiomer)

Nomenclature:
INN: Levetiracetam
Chemical names: (S)-2-(2-oxopynolidin-1-yl)butanamide
Structure:



Molecular formula: C8H14N2O2
Molecular weight: 170.21 g/mol
CAS No: 102767-28-2
Physical form: White or almost white powder
Solubility: Very soluble in water, soluble in acetonitrile, practically insoluble in hexane

Manufacturing process

The active substance, levetiracetam, is the subject of a European Pharmacopeia (Ph. Eur) monograph. Synthesis of the active substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specifications are in place for all starting materials and reagents and these are supported by relevant Certificates of Analysis. Confirmation has been provided that the raw materials, intermediates and auxiliary agents used in synthesis of the active are not of animal, biological or genetically modified origin.

Quality control of drug substance

Appropriate specifications have been provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. Batch analysis data are provided and comply with the proposed specifications. Satisfactory Certificates of Analysis have been provided for reference standards used by the active substance manufacturers during validation studies.
The active substance is stored in appropriate packaging. Specifications and Certificates of Analysis have been provided for the packaging: materials used. The primary packaging in direct contact with the active substance complies with relevant Ph. Eur. requirements and satisfies Directive 2002/72/EC (as amended); it is suitable for contact with foodstuffs.

Stability of drug substance

Appropriate stability data have been generated for the active substance stored in the proposed commercial packaging. These data demonstrate the stability of the active substance and appropriate retest periods have been applied.

II.2 Medicinal Product

Levetiracetam Mylan 250 mg, 500 mg, 750 mg and 1000 mg, film-coated tablets are presented as white, film-coated, biconvex tablets with specified markings. Full descriptions of the individual tablets may be found by referring to the SmPCs or patient information leaflet. All of the tablets have a score line on one side. The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

Pharmaceutical development

Details of the pharmaceutical development of the medicinal products have been supplied and are satisfactory. The objective was to develop stable, generic, immediate-release, tablet formulations, bioequivalent to the innovator products, Keppra 250 mg, 500 mg, 7 50 mg and 1000 mg film-coated tablets (UCB S.A). Comparative dissolution and impurity data were provided for batches of the test products and appropriate reference products. The dissolution and impurity profiles were satisfactory.

Manufacturing process

A description and flow-chart of the manufacturing method has been provided. In-process controls are appropriate considering: the nature of the products and the method of manufacture. Process validation studies were conducted on pilot-scale batches and the results were satisfactory. The validation data demonstrated consistency of the manufacturing process. A commitment has been made by the MAH that full process validation will be conducted on commercial scale batches in accordance with the process validation protocol.

Control of excipients

Each tablet contains 250 mg, 500 mg, 750 mg or 1000 mg of the active ingredient levetiracetam. Other ingredients consist of pharmaceutical excipients, namely povidone (K29-32), microcrystalline cellulose, croscarmellose sodium, magnesium stearate, sodium laurilsulfate and colloidal anhydrous silica making up the tablet cores; and titanium dioxide (El71), polydextrose, hypromellose, triacetin, macrogol 8000 and macrogol 400 constituting the film-coatings. Appropriate justification for the inclusion of each excipient has been provided. All excipients of the tablet cores comply with their respective European Pharmacopoeia monographs. The film-coatings are constituted from pharmacopoeial ingredients and comply with satisfactory in-house specifications. Satisfactory Certificates of Analysis have been provided for all excipients. None of the excipients are sourced from genetically modified organisms. There were no novel excipients used.

Quality control of drug product

Finished product specifications are provided for both release and shelf-life and are satisfactory. Acceptance limits have been justified with respect to conventional pharmaceutical requirements and, where appropriate, safety. Test methods have been described and have been adequately validated, as appropriate. Satisfactory batch analysis data are provided and accepted. The data demonstrate that the batches are compliant with the proposed specifications. Certificates of Analysis have been provided for any reference standards used.

Container Closure System

Levetiracetam Mylan 250 mg, 500 mg, 750 mg and 1000 mg, film-coated tablets are licensed for marketing in High Density Polyethylene (HDPE) bottles with polypropylene (PP) closures, or child-resistant polypropylene (PP) closures, in pack sizes of 60, 100, 120, 200 and 500 film-coated tablets. The HDPE bottle pack may either be placed in an outer cardboard carton or provided without a carton, based on market requirement. The tablets are also licensed in aclar··-polyvinylchloride (PVC)- aluminium blister strips, which are packaged with the Patient Information Leaflet (PIL) into cardboard outer cartons in pack sizes of 20, 30, 50, 60, 90, 100, 120 and 200.

Finally, the tablets are licensed in aclar··-polyvinylchloride (PVC)-aluminium perforated unit-dose blisters, which are packaged with the Patient Information Leaflet (PIL) into cardboard outer cartons in pack sizes of 30 x 1 and 60 x 1. The MAH has stated that not all pack sizes may be marketed. Satisfactory specifications and Certificates of Analysis for all packaging components used have been provided. All primary product packaging complies with EU legislation, Directive 2002/72/EC (as amended), and is suitable for contact with foodstuffs.

Stability of drug product

Finished product stability studies have been conducted in accordance with current guidelines, using product stored in the packaging proposed for marketing. These data support the applied shelf-life of 2 years. These medicinal products do not require any special storage conditions. For the HDPE bottle packs, the instructions are: 'Use within 3 months of opening. Once open, keep bottle tightly closed' .

Product Information

The approved Summaries of Product Characteristics (SmPCs), Patient Information Leaflet (PIL) and labelling are satisfactory. Mock-ups of the PIL and labelling have been provided. The labelling fulfils the statutory requirements for Braille.

The PIL is in line with the SmPCs and is satisfactory. PIL user-testing has been accepted based on bridging to the successful user-testing of the 'parent' PIL for Keppra 250 mg, 500 mg, 750 mg and 1000 mg film-coated tablets (UCB S.A). The text, content and layout of the proposed PIL are considered to be sufficiently similar to the approved PIL for the stated products. The design and layout of the proposed PIL are also consistent with the applicant's approved in-house style. The bridging is accepted. The MAH has stated that not all licensed pack sizes may be marketed. They have committed to submitting mock-ups for marketed pack sizes to the relevant regulatory authorities for approval before those packs are commercially marketed.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

The magnesium stearate has been confirmed as being of vegetable origin. The applicant has provided a declaration confirming that there are no materials of human or animal origin contained in or used in the manufacturing process for the proposed product.

Conclusion

A satisfactory quality overall summary is provided and has been prepared by an appropriately qualified expert. The CV of the expert has been supplied. All pharmaceutical issues have been

resolved and the quality grounds for these applications are considered adequate. There are no objections to approval of Levetiracetam Mylan from a pharmaceutical point of view.

III. NON-CLINICAL ASPECTS

III.1 Introduction

Specific non-clinical studies have not been performed, which is acceptable considering that these are applications for generic versions of products that have been licensed for over 10 years. The non- clinical overview provides a satisfactory review of the pharmacodynamic, pharmacokinetic and toxicological properties of levetiracetam, a widely used and well-known active substance. The CV of the non-clinical expert has been supplied. For generic applications of this nature, the need for repetitive tests on animals and humans is avoided. Reference is made to the innovator products, Keppra 250 mg, 500 mg, 750 mg and 1000 mg film-coated tablets (UCB S.A).

III.2 Ecotoxicity/environmental risk assessment (ERA)

The Marketing Authorisation Holder has provided adequate justification for not submitting an Environmental Risk Assessment (ERA).

III.3 Discussion on the non-clinical aspects

There are no objections to approval of Levetiracetam Mylan 250 mg, 500 mg, 750 mg and 1000 mg, film-coated tablets from a non-clinical point of view.

IV. CLINICAL ASPECTS

IV.1 Introduction

Levetiracetam induces seizure protection in a broad range of animal models of partial and primary generalised seizures without having a pro-convulsant effect. The primary metabolite is inactive. In man, an activity in both partial and generalised epilepsy conditions (epileptiform discharge/photoparoxysmal response) has confirmed the broad spectrum pharmacological profile of levetiracetam.

IV.2 Indications

Levetiracetam is indicated as mono therapy in the treatment of partial onset seizures with or without secondary generalisation in patients from 16 years of age with newly diagnosed epilepsy.

Levetiracetam 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.

The indications are consistent with those for the innovator products and are satisfactory.

IV.3 Posology and method of administration

Full details concerning the posology are provided in the SmPCs. The posology is consistent with that for the innovator products and is satisfactory.

IV.4 Toxicology

The toxicology of levetiracetam is well-known. No new data have been submitted and none are required for applications of this type.

IV.5 Clinical pharmacology

The clinical pharmacology of levetiracetam is well-known. With the exception of the bioequivalence study, no new pharmacodynamic or pharmacokinetic data are supplied and none are required for these applications.

IV.6 Pharmacokinetics

The applications are supported by a bioequivalence study comparing the pharmacokinetic profile of the test product, Levetiracetam 1000 mg Film-coated Tablets, to that of the reference product, Keppra 1000 mg film-coated tablets (UCB S.A). The study was of an appropriate design and was conducted to principles of Good Clinical Practice (GCP). Certificates of Analysis were provided for the test and reference products.

<u>Bioequivalence studies</u>

This was an open-label, randomised, two-treatment, two-sequence, two-period, single dose crossover bioequivalence study conducted in healthy adult human subjects under fasting conditions. Following an overnight fast of at least 10 hours, a single 1000 mg dose of the investigational products was administered orality to each subject in each period. A satisfactory washout period of 7 days was maintained between the two dosing days in each group.

Blood samples were taken pre-dose and at specified time points up to 36.0 hours after administration of test or reference product. Plasma levels of levetiracetam were detected by

a validated HPLC-MS method. The primary pharmacokinetic parameters for the study were Cmax, AUC0-t, and AUC0-∞.
Bioequivalence of the test product versus the reference product was concluded if the 90% Confidence Intervals (CI) of the ratio of the test and reference products fell within the acceptance range, 0.80-1.25 (80%-125%), for log-transformed Cmax, AUC0-t, and AUC0-∞ for levetiracetam.

Results
An appropriate number of subjects completed the study and were included in the pharmacokinetic evaluation and statistical analysis.

Safety - The safety analysis shows that the treatments were well tolerated. Headache and dizziness were the most reported adverse events (AEs). All AEs were reported as mild or moderate in severity. There were no deaths or serious or significant adverse events. The summary of the results of the bioequivalence study are tabulated below.

Summary pharmacokinetic data for levetiracetam for a randomised, 2-way, single-dosed crossover study; healthy subjects, dosed fasted; t=36 hours. Wash-out period: 7 days.

Parameter	Arithmetic Mean (%CV) A = Levetiracetam; Mylan	Arithmetic Mean (%CV) B = Keppra®; UCB	LSMEANS Ratio (A/B)	90 % Confidence Interval
AUC0-t (µg · hr/mL)	264.34 (21.72%)	269.72 (21.82%)	0.98	97.00%-98.96%
AUC0-∞ (µg · hr/mL)	274.93 (21.89%)	280.80 (22.04%)	0.98	96.84%-98.94%
CPEAK (µg/mL)	28.78 (26.95%)	29.40 (23.09%)	0.97	93.30%-101.46%

AUC0-t area under the plasma concentration-time curve from time zero to t hours AUC0-∞ area under the plasma concentration-time curve from time zero to infinity C_{max} (CPEAK) maximum plasma concentration

Conclusion on Bioequivalence study
The results of the bioequivalence study show that the 1000 mg strength test and reference products are bioequivalent, under fasting conditions, as the confidence intervals for Cmax, AUC0-t, and AUC0-∞ fall within the acceptance criteria ranges of 80-125%. Satisfactory justification is provided for a bio- waiver for Levetiracetam Mylan 250 mg, 500 mg, 750 mg and 1000 mg, film-coated tablets. As Levetiracetam Mylan 250 mg, 500 mg, 750 mg and 1000 mg, film-coated tablets meet the criteria specified in the "Note for Guidance on the Investigation of Bioavailability and Bioequivalence" (CPMP/EWP/QWP/1401/98), the results and conclusions of the bioequivalence study on the 1000 mg strength can be extrapolated to the 250 mg, 500 mg and 750 mg strength tablets.

IV.7 Clinical efficacy

No new data have been submitted and none are required. The reference products are established and the applications are supported by the demonstration of bioequivalence. Efficacy is reviewed in the clinical overview. The efficacy of levetiracetam is well established from its extensive use in clinical practice.

IV.8 Clinical safety

No new data have been submitted and none are required for applications of this type. No new or unexpected safety concerns arose from these applications. Safety is reviewed in the clinical overview. The safety profile of levetiracetam is well-known.

IV.9 Clinical overview

A satisfactory clinical overview is provided and has been prepared by an appropriately qualified expert. The CV of the clinical expert has been supplied.

IV.10 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 Mylan 250 mg, 500 mg, 750 mg and 1000 mg, film-coated tablets.

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

Important identified risks	None
Important potential risks	None
Missing information	None

IV.11 Discussion on the clinical aspects

Sufficient clinical information has been submitted to support these applications. The risk-benefit of the products is considered favourable from a clinical perspective. The grant of Marketing Authorisations was, therefore, recommended.

V. USER CONSULTATION

Summary of Product Characteristics (SmPC)
The approved SmPCs are consistent with those of the innovator products and are acceptable.

Patient Information Leaflet
The final PILs are in line with the approved SmPCs and are satisfactory. . PIL user-testing has been accepted based on bridging to the successful user-testing of the PIL for Keppra 250 mg, 500 mg, 750 mg and 1000 mg film-coated tablets (UCB S.A). The results show that the 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.

Labelling
The labelling is satisfactory.
The approved labelling artwork complies with statutory requirements. In line with current legislation, the name of the product in Braille appears on the outer packaging and sufficient space has been included for a standard UK pharmacy dispensing label. The MAH has stated that not all licensed pack sizes may be marketed. They have committed to submitting mock-ups for unmarketed pack sizes to the relevant regulatory authorities for approval before those packs are commercially marketed.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Quality
The important quality characteristics of Levetiracetam Mylan 250 mg, 500 mg, 750 mg and 1000 mg, film-coated tablets are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

Non-clinical
No new non-clinical data were submitted and none are required for applications of this type.

Clinical
Bioequivalence has been demonstrated between the applicant's Levetiracetam 1000 mg Film-coated Tablets and the reference product, Keppra 1000 mg film-coated tablets (UCB S.A). As Levetiracetam Mylan 250 mg, 500 mg, 750 mg and 1000 mg, film-coated tablets meet the criteria specified in the ''Note for Guidance on the Investigation of Bioavailability and Bioequivalence" (CPMP/EWP/QWP/1401/98), the results and conclusions of the bioequivalence study on the 1000 mg strength were extrapolated to the 250 mg, 500 mg and 750 mg strength tablets, and omission of further bioequivalence studies on the lower strengths can be accepted. No new or unexpected safety concerns arise from these applications.

Benefit-risk assessment
The quality of the products is acceptable and no new non-clinical or clinical safety concerns have been identified. The bioequivalence study and its conclusions support the claim that the applicant's Levetiracetam Mylan 250 mg, 500 mg, 750 mg and 1000 mg, film-coated tablets are generic versions of the reference products, Keppra 250 mg, 500 mg, 750 mg and 1000 mg film-coated tablets (UCB S.A). Extensive clinical experience with levetiracetam is considered to have demonstrated the therapeutic value of the active substance. The benefit-risk ratio is considered to be positive.
The application is approved. For intermediate amendments see current product information.

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
1052309-12	RMS Tranfer from DE/H/5719/001-004/DC to NL/H/5923/001/004/DC	Yes	24 November 2023	Approved	N.A.
NL/H/5923/001-4/IB/032	Changes in the Summary of Product Characteristics, Labelling, or Package Leaflet of a generic medicinal product following assessment of the same change for the reference product: – - Implementation of change(s) for which no new additional data is required to be submitted by the MAH.	Yes	2 April 2024	Approved	N.A.