EU Risk Management Plan

For

[redacted]

Levetiracetam Accord 250, 500, 750 and 1000 mg Film-coated tablets

[redacted]

(Levetiracetam)

RMP version to be assessed as part of this application:

RMP Version number	7.0
Data lock point for this RMP	14-Jan-2025
Date of final sign off	11-Apr-2025

Rationale for submitting an updated RMP: This RMP has been updated in line with EPAR Risk-management-plan of Keppra (Levetiracetam) (Version 10.2, dated 07-Oct-2024) published by the EMA on 06-Jan-2025.

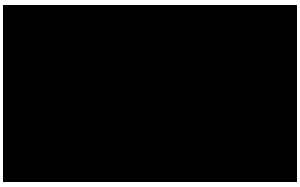
Summary of significant changes in this RMP: Significant changes have been made in following sections of RMP: Part I, Part II (Module SVII and Module SVIII), Part VI and Part VII (Annex 7 and Annex 8).

Other RMP versions under evaluation: Not applicable

Details of the currently approved RMP:

Version	Approved with procedure	Date of approval (opinion date)
6.0	[redacted] [redacted] EMEA/H/C/002290/IB/003	08-Jun-2021

QPPV name: Arletta Werynska

QPPV signature: 

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Part I: Product(s) Overview

Table 1: Product Overview

Active substance(s) **(INN or common name)**	Levetiracetam
Pharmacotherapeutic group(s)(ATC Code)	**Pharmacotherapeutic group(s):** Antiepileptics, other antiepileptics. **ATC code**: N03AX14
Marketing Authorisation Holder	Accord Healthcare S.L.U., Spain
Medicinal products to which this RMP refers	6
Invented name(s) in the European Economic Area (EEA)	[redacted] Levetiracetam Accord 250, 500, 750 and 1000 mg Film-coated tablets [redacted]
Marketing authorisation procedure	[redacted] [redacted] Levetiracetam Accord 250, 500, 750 and 1000 mg Film-coated tablets EMEA/H/C/002290 [redacted] [redacted]

Brief description of the product	Chemical class: Antiepileptics, Other antiepileptics The active substance, levetiracetam, is a pyrrolidone derivative (S-enantiomer of α-ethyl-2-oxo-1-pyrrolidine acetamide), chemically unrelated to existing antiepileptic active substances.
	Summary of mode of action: The mechanism of action of levetiracetam still remains to be fully elucidated. In vitro and in vivo experiments suggest that levetiracetam does not alter basic cell characteristics and normal neurotransmission. *In vitro* studies show that levetiracetam affects intraneuronal Ca^{2+} levels by partial inhibition of N-type Ca^{2+} currents and by reducing the release of Ca^{2+} from intraneuronal stores. In addition it partially reverses the reductions in GABA- and glycine-gated currents induced by zinc and β-carbolines. Furthermore, levetiracetam has been shown in *in vitro* studies to bind to a specific site in rodent brain tissue. This binding site is the synaptic vesicle protein 2A, believed to be involved in vesicle fusion and neurotransmitter exocytosis. Levetiracetam and related analogs show a rank order of affinity for binding to the synaptic vesicle protein 2A which correlates with the potency of their anti-seizure protection in the mouse audiogenic model of epilepsy. This finding suggests that the interaction between levetiracetam and the synaptic vesicle protein 2A seems to contribute to the antiepileptic mechanism of action of the medicinal product.
	Important information about its composition: [redacted]

[redacted]

	[redacted] Levetiracetam Accord 250, 500, 750 and 1000 mg Film-coated tablets: *Levetiracetam Accord 250 mg film-coated tablets* Each film-coated tablet contains 250 mg levetiracetam *Levetiracetam Accord 500 mg film-coated tablets* Each film-coated tablet contains 500 mg levetiracetam *Levetiracetam Accord 750 mg film-coated tablets* Each film-coated tablet contains 750 mg levetiracetam *Excipient with known effect:* Each film-coated tablet contains 0.013 mg of sunset yellow FCF (E110) *Levetiracetam Accord 1000 mg film-coated tablets* Each film-coated tablet contains 1000 mg levetiracetam [redacted]
Hyperlink to the Product Information	Please refer Module 1.3.1 for SmPC and PIL.

Indication(s) in the EEA *Current*	[redacted] Levetiracetam Accord 250, 500, 750 and 1000 mg Film-coated tablets It 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. It 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. [redacted]

	[redacted]
Dosage in the EEA *Current*	**Posology** [redacted] Levetiracetam Accord 250, 500, 750 and 1000 mg Film-coated tablets [redacted] Levetiracetam therapy can be initiated with [redacted] oral administration. Conversion to or from oral to intravenous administration can be done directly without titration. The total daily dose and frequency of administration should be maintained. *Partial onset seizures* The recommended dosing for monotherapy (from 16 years of age) and adjunctive therapy is the same; as outlined below. *All indications* *Adults (≥18 years) and adolescents (12 to 17 years) weighing 50 kg or more:* The initial therapeutic dose is 500 mg twice daily. This dose can be started on the first day of treatment. However, a lower initial dose of 250 mg twice daily may be given based on physician assessment of seizure reduction versus potential side effects. This can be increased to 500 mg twice daily after two weeks. Depending upon the clinical response and tolerability, the daily dose can be increased up to 1,500 mg twice daily. Dose changes can be made in 250 mg or 500 mg twice daily increases or decreases every two to four weeks. *Adolescents (12 to 17 years) weighing below 50 kg and children from 1 month of age* The physician should prescribe the most appropriate pharmaceutical form, presentation and strength according to weight, age and dose. Refer to *Paediatric population* section for dosing adjustments based on weight.

	There is no experience with administration of intravenous levetiracetam for longer period than 4 days. Discontinuation [redacted] Levetiracetam Accord 250, 500, 750 and 1000 mg Film coated tablets If levetiracetam has to be discontinued it is recommended to withdraw it gradually (e.g. in adults and adolescents weighing more than 50 kg: 500 mg decreases twice daily every two to four weeks; in infants older than 6 months, children and adolescents weighting less than 50 kg: dose decrease should not exceed 10 mg/kg twice daily every two weeks; in infants (less than 6 months): dose decrease should not exceed 7 mg/ kg twice daily every two weeks). [redacted] **Method of administration** [redacted] Levetiracetam Accord 250, 500, 750 and 1000 mg Film-coated tablets The film-coated tablets must be taken orally, swallowed with a sufficient quantity of liquid and may be taken with or without food. After oral administration the bitter taste of levetiracetam may be

	experienced. The daily dose is administered in two equally divided doses. [redacted]
Pharmaceutical form(s) and strengths *Current*	[redacted] **Pharmaceutical form:** Film-coated tablets **Strengths:** 250, 500, 750 and 1000 mg [redacted]
Is the product subject to additional monitoring in the EU?	No

Part II: Safety specification

Module SI – Epidemiology of the indication(s) and target population(s)

Not applicable

Module SII – Non-clinical part of the safety specification

Not applicable

Module SIII – Clinical trial exposure

Not applicable

Module SIV – Populations not studied in clinical trials

SIV.1 Exclusion criteria in pivotal clinical studies within the development programme

Not applicable

SIV.2 Limitations to detect adverse reactions in clinical trial development programmes

Not applicable

SIV.3 Limitations in respect to populations typically under-represented in clinical trial development programmes

Not applicable

Module SV – Post-authorisation experience

SV.1 Post-authorisation exposure

Not applicable

Module SVI – Additional EU requirements for the safety specification

Potential for misuse for illegal purposes

Not applicable - there is no potential for misuse for illegal purposes.

Module SVII – Identified and potential risks

The safety concerns of this RMP have been updated as per EPAR RMP summary available for product Keppra (levetiracetam), (Version 10.2, dated 07-Oct-2024) published by the EMA on 06-Jan-2025. There is no change proposed by MAH in this safety concern mentioned in Module SVIII which is in line with reference product.

Hence, this section remains "Not applicable".

SVII.1 Identification of safety concerns in the initial RMP submission

SVII.1.1 Risks not considered important for inclusion in the list of safety concerns in the RMP

Not applicable

SVII.1.2 Risks considered important for inclusion in the list of safety concerns in the RMP

Not applicable

SVII.2 New safety concerns and reclassification with a submission of an updated RMP

Not applicable

SVII.3 Details of important identified risks, important potential risks, and missing information

SVII.3.1 Presentation of important identified risks and important potential risks

Not applicable

SVII.3.2 Presentation of the missing information

Not applicable

Module SVIII – Summary of the safety concerns

Table 2: Summary of safety concerns

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

Part III: Pharmacovigilance Plan (including post-authorisation safety studies)

III.1 Routine pharmacovigilance activities

Routine pharmacovigilance activities including collection and reporting of adverse reactions and signal management as stated in pharmacovigilance system master file are sufficient for the safety concerns listed in module SVIII.

III.2 Additional pharmacovigilance activities

None proposed

III.3 Summary Table of additional Pharmacovigilance activities

Not applicable

Part IV: Plans for post-authorisation efficacy studies

Not applicable

Part V: Risk minimisation measures (including evaluation of the effectiveness of risk minimisation activities)

The safety information in the proposed product information is aligned to the reference medicinal product.

V.1 Routine Risk Minimisation Measures

Not applicable

V.2 Additional Risk Minimisation Measures

None proposed

V.3 Summary of risk minimisation measures

Not applicable

Part VI: Summary of the risk management plan

Summary of risk management plan for [redacted] Levetiracetam Accord 250, 500, 750 and 1000 mg Film-coated tablets [redacted]

This is a summary of the risk management plan (RMP) for [redacted], Levetiracetam Accord 250, 500, 750 and 1000 mg Film-coated tablets [redacted]. Throughout this summary, the product name has been referred as Levetiracetam Accord. The RMP details important risks of Levetiracetam Accord, how these risks can be minimised, and how more information will be obtained about Levetiracetam Accord's risks and uncertainties (missing information).

Levetiracetam Accord's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Levetiracetam Accord should be used.

This summary of the RMP for Levetiracetam Accord should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all of which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Levetiracetam Accord's RMP.

I. The medicine and what it is used for

[redacted] Levetiracetam Accord 250, 500, 750 and 1000 mg Film-coated tablets

It 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.

It 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.

It contains levetiracetam as the active substance and it is given by oral route.

[redacted]

Further information about the evaluation of Levetiracetam Accord's benefits can be found in Levetiracetam Accord's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage https://www.ema.europa.eu/en/medicines/human/EPAR/levetiracetam-accord.

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of Levetiracetam Accord, together with measures to minimise such risks and the proposed studies for learning more about Levetiracetam Accord's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;

[redacted]

- The authorised pack size - the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status - the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation measures*.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities.*

If important information that may affect the safe use of Levetiracetam Accord is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of Levetiracetam Accord are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Levetiracetam. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine).

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 children exposed in utero

II.B Summary of important risks

The safety information in the proposed Product Information is aligned to the reference medicinal product.

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of Levetiracetam Accord.

II.C.2 Other studies in post-authorisation development plan

There are no studies required for Levetiracetam Accord.