EU RISK MANAGEMENT PLAN FOR

LEVETIRACETAM

250MG, 500MG, 750MG, 1000MG FILM-COATED TABLET

100MG/ML ORAL SOLUTION

100MG/ML CONCENTRATE FOR SOLUTION FOR INFUSION

Version 10.2

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ADMINISTRATIVE INFORMATION ON THE RISK MANAGEMENT PLAN

Risk Management Plan (RMP) Version number: 10.2

Data Lock Point for this RMP: 30 Nov 2023

Date of final sign off: 07 Oct 2024

Rationale for submitting an updated RMP, version-10.2:

This RMP is submitted to address the comments received from Joint Pharmacovigilance Risk Assessment Committee (PRAC)/Committee for Medicinal Products for Human Use (CHMP) Rapporteur's 2nd updated Responses Assessment Report, (Procedure number: EMEA/H/C/WS2529) for removal of important potential risk of "Medication error due to change in syringe volume (3mL to 5mL) for Keppra oral solution in children below 4 years of age" throughout the RMP, and to update Part III.1 "Routine pharmacovigilance activities" of the levetiracetam EU-RMP version 10.1.

Rationale for submitting an updated RMP, version 10.1:

- An updated EU-RMP, version 10.1, is submitted to address a few comments/suggestions/editorial changes received for Part II Module SIII; Part V Section 1, 2, and 3; and Annex of the levetiracetam EU-RMP, version 10.0, in the PRAC/ CHMP Rapporteur's Final Assessment Report, dated 11 Jul 2024 (Procedure number: EMEA/H/C/WS2529 and Reference number: EMA/CHMP/PRAC/229165/2024).
- As per PRAC Periodic Safety Update Report assessment report, dated 07 Jul 2022, the safety concern of "Deterioration of seizure control during pregnancy" was removed from the list of core safety concerns.
- To update Part II Module SII subsections on 'Reproductive/developmental toxicity' with information pertaining to pregnancy and 'Hepatotoxicity' relevance to human usage with wordings/information as per the current effective Summary of Product Characteristics (SmPC).

Summary of changes in RMP, version 10.2:

- Administrative page updated to reflect the updated EU-RMP version, date of approval, and the changes done in the RMP.
- Section III.1 "Routine pharmacovigilance activities" updated to remove proposed routine pharmacovigilance activities beyond adverse reaction reporting and signal detection for the important potential risk of medication error due to change in syringe volume from 3mL to 5mL for Keppra® (levetiracetam) oral solution in children below 4 years of age.
- The information pertaining to important potential risk "Medication error due to change in syringe volume (3mL to 5mL) for Keppra oral solution in children below 4 years of age" was removed from Part II Module SVII/Section SVII.3.2," "Part II Module SVIII/Table Part II–10, "PART V/Section V.1/Table Part V–1," "PART V/Section V.2.1, PART V Section V.3 Table Part V-3, and "Part VI/Section II.A/Table Part VI−1."

- Annex 6 updated to remove the additional risk minimization measure of DHPC for the important potential risk of Medication error due to change in syringe volume (3mL to 5mL) for Keppra oral solution in children below 4 years of age.
- Annex 8 updated with changes done in the RMP version 10.2.

Summary of significant changes in RMP, version 10.1:

- The rationale for the removal of the missing information "Deterioration of seizure control during pregnancy" from the list of safety concerns was included under Part II Module SIV Table Part II-6, Part II Module SVII.2, and removed information pertaining to safety concern (missing information) "Deterioration of seizure control during pregnancy" from "Part II Module SII, Part II Module SIV/Section SIV.3/SIV3.3 and Section SIV.4/Table Part II–6," "Part II Module SVII/Section SVII.3.3," "Part II Module SVIII/Table Part II–11," "Part III/Section III.3/Table Part III−1," "PART V/Section V.1/Table Part V–2," "PART V/Section V.3/Table Part V–4," and "Part VI/Section II.B/Table Part VI−3."
- Part II Module SII; the few wordings under the subsection 'Reproductive/developmental toxicity' and 'Hepatotoxicity' relevance to human usage were updated to reflect the wording from the current and effective SmPC. Other minor editorial changes were also made in Part II Module SII Nonclinical part of the safety specification.
- Changes were made to the presentation of Table Part II−1 under Part II-SIII of the RMP. A footnote is also included below the table to clarify why the sum of the different lines is not matching the total.
- Updated title of Part V.2.1 Additional risk minimization measures to clarify that the Direct Healthcare Professional Communication (DHPC) is implemented for the important potential risk of "Medication error due to change in syringe volume from 3mL to 5mL for Keppra® (levetiracetam) oral solution in children below 4 years of age."
- The subsection of "Process Indicator" under Part V.2.1 was updated to summarize how the distribution of the DHPC will be determined.
- Information related to pictogram on the box and the box label updated in Table Part V-1, Table Part V-3, and Table Part VI-2 to indicate that a prominent red colour will reflect the new 5mL syringe size.
- In Annex 1, the text "Available in electronic format only" was replaced with "Not applicable."
- Annex 6 of the RMP was revised to reflect the most recent DHPC version updated based on Rapporteur's recommendation.
- The current RMP update is based on version EU-RMP version 10.0.

Other RMP version under evaluation:

None

Details of the currently approved RMP:

Version number: 9.2

Approved with procedure: EMEA/H/C/000277/WS1664

Date of approval (opinion date): 12 Nov 2020

Qualified Person for Pharmacovigilance (QPPV) name: Bart Teeuw

Please see the electronic signature of the European Economic Area QPPV or his deputy on the last page of this report.

LIST OF ABBREVIATIONS

ADR	adverse drug reaction
AE	adverse event
AED	antiepileptic drug
ALT	alanine transaminase
AST	aspartate aminotransferase
ALP	alkaline phosphatase
APD90	action potential duration at 90% repolarization
BMC	bone mineral content
BMD	bone mineral density
CCDS	company core data sheet
CHO	Chinese hamster ovary
CI	confidence interval
CNS	central nervous system
CTX-1	carboxyterminal cross-linking telopeptide of type I collagen
DHPC	Direct Healthcare Professional Communication
DLP	data lock point
EMA	European Medicines Agency
EMw	electromechanical window
ESRD	end-stage renal disease
EURAP	European and International Antiepileptic Drugs and Pregnancy Registry
FCD	focal cortical dysplasia
FTPC	free therapeutic plasma concentration
hERG	human-ether-à-go-go related gene
IQ	intelligence quotient
IQR	interquartile range
LLT	low level term
MAA	marketing application approval
MAH	marketing authorization holder
MedDRA®	Medical Dictionary for Regulatory Activities
MRHD	maximum recommended human dose
n	number
NAAPR	North American Antiepileptic Drug Pregnancy Registry
OPG	osteoprotegerin

PHT	phenytoin
PRAC	Pharmacovigilance Risk Assessment Committee
PSUR	periodic safety update report
PT	preferred term
QPPV	qualified person for pharmacovigilance
RMP	risk management plan
SmPC	summary of product characteristics
SUDEP	sudden unexplained death in epilepsy
SV2A	synaptic vesicle protein 2A
VPA	valproate
WHO	World Health Organization

PART I PRODUCT(S) OVERVIEW

Table Part I–1: Product overview

Active substance	Levetiracetam
Pharmacotherapeutic group	Antiepileptic medicinal product (N03AX14)
Marketing Authorization Holder	UCB Pharma S.A.
Medicinal products to which this Risk Management Plan refers	2
Invented names in the European Economic Area	Keppra®, Levetiracetam UCB®
Marketing authorization procedure	Centralized and mutual recognition
Brief description of the product	Pyrrolidone derivative (S-enantiomer of α-ethyl-2-oxo-1-pyrrolidine acetamide)
	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. *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 gamma-aminobutyric acid- 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 (SV2A), believed to be involved in vesicle fusion and neurotransmitter release. Levetiracetam and related analogs show a rank order of affinity for binding to the SV2A which correlates with the potency of their antiseizure protection in the mouse audiogenic model of epilepsy. This finding suggests that the interaction between levetiracetam and the SV2A seems to contribute to the antiepileptic mechanism of action of the drug.
	Important information about its composition: Not applicable
Hyperlink to the Product Information	emea-combined-h277-en-annotated emea-combined-h277-en-clean

Table Part I–1: Product overview

	mrp-h2831-fct-combined-pi-en-annotated mrp-h2831-osl-combined-pi-en-annotated mrp-h2831-iv-combined-pi-en-annotated mrp-h2831-fct-combined-pi-en mrp-h2831-osl-combined-pi-en mrp-h2831-iv-combined-pi-en
Indications in the EEA	Current: Levetiracetam is indicated as monotherapy: • in the treatment of partial onset seizures with or without secondary generalization in adults and adolescents 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 generalization in adults, adolescents, children, and infants from 1 month of age with epilepsy (from 4 years of age for levetiracetam 100mg/mL concentrate for solution for infusion) • in the treatment of myoclonic seizures in adults and adolescents from 12 years of age with juvenile myoclonic epilepsy • in the treatment of primary generalized tonic-clonic seizures in adults and adolescents from 12 years of age with idiopathic generalized epilepsy
	Proposed: • Not applicable
Dosage in the EEA	Current: All indications **Adults (≥18 years) and adolescents (12 to 17 years) weighing 50kg or more:** The initial therapeutic dose is 500mg twice daily (tablets, oral solution, and intravenous formulations). This dose can be started on the first day of treatment. However, a lower initial dose of 250mg twice daily may be given based on physician assessment of seizure reduction versus potential side effects. This can be increased to 500mg twice daily after 2 weeks. Depending upon the clinical response and tolerance, the daily dose can be increased up to 1500mg twice daily. Dose changes can be made in 250mg or

Table Part I–1: Product overview

500mg twice daily increments or decrements every 2 to 4 weeks.

Adolescents (12 to 17 years) weighing below 50kg 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 *Pediatric population* section for dosing adjustments based on weight.

Pediatric population:

Infants from 1 month to less than 6 months:

The initial therapeutic dose is 7mg/kg twice daily. Depending upon the clinical response and tolerability, the dose can be increased by 7mg/kg twice daily every 2 weeks up to recommended dose of 21mg/kg twice daily. Dose changes should not exceed increases or decreases of 7mg/kg twice daily every 2 weeks. The lowest effective dose should be used.

Infants should start the treatment with levetiracetam 100mg/mL oral solution.

Dosage recommendations for infants less than 6 months:

Weight	Starting dose (dose for oral solution): 7mg/kg twice daily	Maximum dose (dose for oral solution): 21mg/kg twice daily
4kg	28mg (0.3mL) twice daily	84mg (0.85mL) twice daily
5kg	35mg (0.35mL) twice daily	105mg (1.05mL) twice daily
7kg	49mg (0.5mL) twice daily	147mg (1.5mL) twice daily

Infants aged 6 to 23 months, children (2 to 11 years) and adolescents (12 to 17 years) weighing less than 50kg:

The initial therapeutic dose is 10mg/kg twice daily. Depending upon the clinical response and tolerability, the dose can be increased by 10mg/kg twice daily every 2 weeks up to 30mg/kg twice daily. Dose changes should not exceed increments

Table Part I–1: Product overview

<table>
<tr><td></td><td>or decrements of 10mg/kg twice daily every 2 weeks. The lowest effective dose should be used.
Dosage in children 50kg or greater is the same as in adults.
Dosage recommendations for infants from 6 months of age, children, and adolescents:
<table>
<tr><th>Weight</th><th>Starting dose: 10mg/kg twice daily</th><th>Maximum dose: 30mg/kg twice daily</th></tr>
<tr><td>6kg</td><td>60mg twice daily</td><td>180mg twice daily</td></tr>
<tr><td>10kg</td><td>100mg twice daily</td><td>300mg twice daily</td></tr>
<tr><td>15kg</td><td>150mg twice daily</td><td>450mg twice daily</td></tr>
<tr><td>20kg</td><td>200mg twice daily</td><td>600mg twice daily</td></tr>
<tr><td>25kg</td><td>250mg twice daily</td><td>750mg twice daily</td></tr>
<tr><td>From 50kg</td><td>500mg twice daily</td><td>1500mg twice daily</td></tr>
</table>
Note: Children 20kg or less should preferably start the treatment with levetiracetam 100mg/mL oral solution. Dosage in children and adolescents 50kg or more is the same as in adults.</td></tr>
<tr><td></td><td>Proposed: Not applicable</td></tr>
<tr><td>Pharmaceutical forms and strengths</td><td>Film-coated tablets: 250mg, 500mg, 750mg, 1000mg
Oral solution: 100mg/mL
Concentrate for solution for infusion: 100mg/mL</td></tr>
<tr><td>Is/will the product be subject to additional monitoring in the European Union?</td><td>No</td></tr>
</table>

EEA=European Economic Area; SV2A=synaptic vesicular protein 2A

PART II SAFETY SPECIFICATION

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

SI.1 Epilepsy

SI.1.1 Incidence

Patients aged 1 month to less than 4 years with partial onset seizures

Overall, the incidence of epilepsy in children up to 15 years of age ranges between 30 and 397 per 100,000 person-years (Hunter et al, 2020; Dura-Trave et al, 2008; Forsgren et al, 2005a; Cowan, 2002). In Europe, the incidence of epilepsy in children ranges between 35 and 256 per 100,000 person-years (Forsgren et al, 2005a). The crude annual incidence of early-onset epilepsy was 60.2 (95% confidence-interval [CI] 44.8–75.5) per 100,000 per year for children aged 0–59 months (Hunter et al, 2020). Partial or localization-related epilepsies account for 20 to 66% of incidence epilepsies in population-based studies, representing the most predominant seizure type both in children and adults (Banerjee et al, 2009, Kotsopolous et al, 2002; Forsgren et al, 1996). In most children with epilepsy (approximately 55% to 75%), the cause is unknown (Cowan, 2002), and for the rest of the cases, causes include congenital malformations, metabolic disorders, trauma and central nervous system infections (Olafsson et al, 2005; Oun et al, 2003; Forsgren et al, 1996).

Patients aged 4 years and older

Overall, the age-adjusted incidence rate of epilepsy ranges from 16 to 111 cases per 100,000 person years (Banerjee et al, 2009). In Europe, the incidence rate of epilepsy ranges between 35 and 256 per 100,000 person-years (Banerjee et al, 2009; Forsgren et al, 2005a). The estimated number of new cases per year amongst European adults 20 to 64 years is 96,000 (incidence rate 30 per 100,000) and 85,000 in the elderly 65 years and older, with an incidence rate of 100 per 100,000 (Forsgren et al, 2005a). An overall annual incidence of epilepsy of 0.65 per 100 000 children (95% CI 0.52-0.81) was reported in children (aged <16 years) from the United Kingdom and Ireland (Abdel-Mannan and Sutcliffe, 2020). In the US, the overall incidence of epilepsy ranges from 35.5 to 48 per 100,000 person-years (Theodore et al, 2006). The incidence rate is approximately 45 per 100,000 person-years in adolescents and young adults and approximately 30 per 100,000 in older adults (Hauser et al, 1993). About 70% of individuals with epilepsy achieve long-term remission, most within 5 years of diagnosis (MacDonald et al, 2000).

SI.1.2 Prevalence

Patients aged 1 month to less than 4 years with partial onset seizures

The prevalence of epilepsy in children up to 15 years of age ranges from 400 to 4,000 per 100,000 children (Cowan, 2002). In Europe the prevalence of active epilepsy in children ranges between 320 and 510 per 100,000 population (Forsgren et al, 2005a).

Patients aged 4 years and older

Overall, the age-adjusted prevalence of epilepsy ranges from 270 to 410 per 100,000 population (Banerjee et al, 2009). In Europe, the prevalence rate of active epilepsy ranges from 320 to 780 per 100,000 population (Forsgren et al, 2005a). It is estimated that the number of adults (individuals aged 20 to 64 years) in Europe with active epilepsy is 1.9 million (prevalence 6 per 1,000) and 0.6 million in ages 65 years and older (prevalence 7 per 1,000). In the US the prevalence of epilepsy ranges from 470 to 680 per 100,000 (Theodore et al, 2006). The prevalence of epilepsy was reported to be 0.67% in Danish people (aged >18 years) in Dec 2016 (Christensen et al, 2023).

SI.1.3 Demographics of the population in the epilepsy indication–age, gender, racial and/or ethnic origin, and risk factors for the disease

Patients aged 1 month to less than 4 years with partial onset seizures

The incidence and prevalence of epilepsy in children varies by age. The incidence is highest in the first year of life and declines throughout childhood. Within the first year of life, the incidence rates range between 153 and 256 per 100,000 whereas in children aged between 10 and 19 years, the incidence rate ranges between 35 and 58 per 100,000 (Dura-Trave et al, 2008; Forsgren et al, 2005a). Studies have reported differences in the incidence and prevalence of epilepsy by gender with most studies reporting higher rates in boys compared with girls (Forsgren et al, 2005a). The difference varies by age; before the age of 5 years, the incidence rates are approximately 30% to 60% higher in girls while the rates tend to be 10% to 20% higher in boys through the later childhood and adolescence (Annegers et al, 1999; Hauser et al, 1993). Some studies have reported that socioeconomic status has no impact on the risk of epilepsy in children (Hesdorffer et al, 2005). Data on the effect of race/ethnicity on the risk of epilepsy in children is very scarce. As per Hunter et al (2020), ascertainment-adjusted annual incidence rates per 100,000 children (95% CI) was 61.7 (46.2-77.3) for age 0-59 months, with 73.5 (49.8-97.3) and 49.5 (29.6-69.4) for males and females, respectively. Scotland age- and ascertainment-adjusted annual incidence rate for children 0-59 months was 63.4 (95% CI 47.6-79.2) per 100,000 children per year. Most children with White British Isles (46.5%), non-White British Isles (50.0%), and Asian (57.1%) descents had epilepsy of unknown origin. All the African/Caribbean children had epilepsy of structural etiology.

Patients aged 4 years and older

The burden of epilepsy is higher in developing countries than in developed countries. The median lifetime prevalence of epilepsy in developed countries is 5.8 per 1,000 population (5th to 95th percentile range 2.7 to 12.4) whilst in developing countries it is 15.4 per 1,000 (5th to 95th percentile range 4.8 to 49.6) (Ngugi et al, 2010). The median incidence rate in developed countries is 45.0 per 100,000 person-years (interquartile range (IQR) 30.3 to 66.7) whilst in developing countries it is 81.7 per 100,000 person-years (IQR 28.0 to 239.5) (Ngugi et al, 2011). The median prevalence of active epilepsy in developed countries is 4.9 per 1,000 (5th to 95th percentile range 2.3 to 10.3) whilst in developing countries it is 12.7 per 1,000 (5th to 95th percentile 3.5 to 45.5) (Ngugi et al, 2010). The incidence of epilepsy varies with age. The incidence is highest in the first year of life and declines throughout childhood (Forsgren et al, 2005a). The prevalence increases with age ranging from 200 to 300 per 100,000 children and in the elderly ranging from 300 to 730 per 100,000 (Forsgren et al, 2005a). The incidence of

epilepsy has been reported to be higher in adult males compared with females even after adjusting for risk factors for epilepsy such as head injury, stroke and central nervous system infections (Kotsopoulos et al, 2002). Christensen et al (2023), reported the prevalence of epilepsy in males and females as 0.69% and 0.65%, respectively. Individuals from socioeconomically deprived classes have also been reported to have a higher prevalence of epilepsy compared with higher socioeconomic classes (Benn et al, 2008; Noronha et al, 2007; Birbeck et al, 2007). Studies have reported conflicting results on the association between ethnicity/race and the incidence of epilepsy (Benn et al, 2008).

SI.1.4 The main existing treatment options

Patients aged 1 month to less than 4 years with partial onset seizures

The primary focus of care for children with epilepsy is the prevention of further seizures. Antiepileptic drugs (AEDs) are the mainstay of treatment. The choice of AED is primarily based on evidence of efficacy and effectiveness for the individual's seizure type and other patient-specific factors, including age, adverse-effect profile, comorbidities, and concomitant medications are also needed to be considered (Perucca and Tomson, 2011). Monotherapy is generally recommended for patients with newly diagnosed epilepsy. Combination therapy is initiated upon unresponsiveness to monotherapy. More than 70% of patients who are treated achieve long-term remission or freedom from seizures, usually within 5 years of diagnosis (Kwan and Sander, 2004).

If AEDs are not successful in controlling seizures, nonpharmacological treatments such as surgery, a ketogenic diet, or vagus nerve stimulation may be tried. Surgery is usually performed in patients with refractory epilepsy that is associated with a localised focal lesion that can be resected. The ketogenic diet is a special high-fat, low-carbohydrate diet that helps to control seizures in some people with epilepsy. The vagus nerve stimulator is an internalised implantable device which is implanted in the patient's left upper chest under the skin and connected via electrodes to the left vagus nerve in the neck. The device is programmed to deliver intermittent nerve stimulation every 3 to 5 minutes. The benefits of epilepsy surgery vary with the procedure type and location of the lesion (Tellez Zentenoet al, 2005).

Patients aged 4 years and older

The primary focus of care for epilepsy patients is the prevention of further seizures. AEDs are the mainstay of treatment for the majority of epileptic patients. The choice of AED is primarily based on evidence of efficacy and effectiveness for the individual's seizure type and other patient-specific factors, including age, sex, childbearing potential, adverse-effect profile, comorbidities, and concomitant medications are also needed to be considered (Perucca and Tomson, 2011). Monotherapy is generally recommended for patients with newly diagnosed epilepsy. Combination therapy is initiated upon unresponsiveness to monotherapy. More than 70% of patients who are treated achieve long-term remission or freedom from seizures, usually within 5 years of diagnosis (Kwan and Sander, 2004).

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SI.1.5 Natural history of the indicated condition in the untreated population, including mortality and morbidity

The estimated cumulative mortality at the age of 50 years was 3.1% (95% CI=3.0-3.1) for persons without epilepsy and schizophrenia, 10.7% (95% CI=9.7-11.8) for persons with epilepsy, 17.4% (95% CI=16.0-18.8) for persons with schizophrenia, and 27.2% (95% CI=15.7 40.1) for persons with both disorders (Andersen et al, 2019).

In children who experience a first unprovoked focal or generalized tonic-clonic seizure, the cumulative risk of recurrence is 42% at 8 years follow-up, with only 3% of all recurrences occurring after 5 years (Shinnar et al, 1996). About 63% to 70% of individuals with epilepsy achieve long-term remission, most within 5 years of diagnosis (Kwan and Sander, 2004; MacDonald et al, 2000).

The ability to achieve remission of seizures or to discontinue antiepileptic medication varies by type of epilepsy, etiology, the presence of other neurological disorders, and initial response to treatment. The higher the number of years before entering 5-year remission, the higher was the annual risk of relapse. Those with cryptogenic or symptomatic generalized epilepsy, West syndrome, and those with Lennox-Gastaut syndrome had the lowest proportions of terminal remission (Sillanpaa and Schmidt, 2006).

Estimates indicate that 10 years of life are lost for people whose epilepsy has a known cause, and 2 years are lost for people with epilepsy from an unknown cause (Gaitatzis et al, 2004a). Studies have consistently reported higher mortality rates in epilepsy compared with general populations (Neligan et al, 2011; Sillanpaa and Shinnar, 2010; Shackleton et al, 2002; Callenbach et al, 2001; Lindsten et al, 2000).

The highest mortality rates occur during the first years after seizure onset, mainly due to the underlying conditions causing the epilepsy (Neligan et al, 2010; Forsgen et al, 2005b). However, a significant excess mortality has also been recorded, even many years after the diagnosis of epilepsy (Neligan et al, 2011). Studies of cause-specific mortality rates in patients with epilepsy have shown excess mortality from cerebrovascular disease, heart disease, neoplasms, and pneumonia (Neligan et al, 2011; Forsgren et al, 2005b). One of the factors contributing to the increased mortality is the occurrence of sudden unexpected death in people with epilepsy with an estimated incidence of 2 per 10,000 person-years in children with epilepsy (Donner et al, 2001). Frequency of generalized tonic–clonic seizures is a well-established risk factors for sudden unexplained death in epilepsy (SUDEP; Harden et al, 2017).

In the study done by Hunter et al (2020), focal epilepsy was reported in 21/59 (35.6%); generalized epilepsy in 32/59 (54.2%); and combined type epilepsy in 6/59 (10.2%) children with early onset of epilepsy (number [n]=59) aged 0-59 months. The onset of generalized and focal seizures between 0-59 months was reported in 33/59 (55.9%) and 26/59 (44.1%) children with early onset of epilepsy, respectively (Hunter et al, 2020). The estimated annual incidence of childhood epilepsy deaths was 0.65 per 100,000 children aged 0-15 years (95% CI: 0.52-0.81). Age at death ranged from 3 months to 15 years 11 months, median age at death was 8.0 years (IQR: 3-12), and median age of onset of epilepsy was 1 years (IQR: 0.5-4). Of all the deaths in children (n=88), epilepsy-related deaths including SUDEP occurred in 25% children and nonepilepsy-related deaths occurred in 75% children. Most common cause of seizure-related deaths was SUDEP (76%) where males and white children accounted for 62% and 77%, respectively (Abdel-Mannan and Sutcliffe, 2020).

SI.1.6 Important comorbidities

Patients aged 1 month to less than 4 years with partial onset seizures

The prevalence of psychiatric disorders including depression, anxiety, attention deficit hyperactivity disorder (ADHD), behavioral and development disabilities are higher in children with epilepsy compared with the general population (Pellock, 2004; Gaitatzis et al, 2004c; Lin et al, 2012). One study found that children with epilepsy had increased prevalence of depression (8% versus 2%), anxiety (17% versus 3%), ADHD (23% versus 6%), conduct disorder (16% versus 3%), developmental delay (51% versus 3%), autism spectrum disorder (16% versus 1%), social problems (relative risk (RR) 2.16, 95% CI 1.61 to 2.90), and parental aggravation (2.19, 95% CI 1.44to3.32) compared with children without epilepsy (Russ et al, 2012). Studies have also found that children with uncomplicated epilepsy had lower verbal intelligence quotient (IQ), full scale IQ than did healthy control individuals (Rantanen et al, 2010).

Patients aged 4 years and older

Adults with epilepsy also have a significantly higher prevalence of some psychiatric and somatic conditions compared with the general population. As per Christensen et al (2023), 37.4% patients with epilepsy were diagnosed with comorbid psychiatric disorder or prescription of antipsychiatric drugs. The prevalence of depression in epilepsy has been reported to range from 20% to 55% (Téllez-Zenteno et al, 2007; Victoroff et al, 1994). Other psychiatric conditions that have been reportedly high in epilepsy patients include anxiety (11%) and psychoses in 9% (Hesdorffer et al, 2012; Rai et al, 2012; Gaitatzis et al, 2004c). Studies have also reported a higher prevalence of ADHD in adults with epilepsy (30% to 40%) compared to 15% in the general population (Hamed, 2011). Additionally, studies have reported a high incidence of cognitive impairment including learning disability, intellectual disability, and academic underachievement in patients with epilepsy (Snoeijen-Schouwenaars et al, 2021; van Blarikom et al, 2006). Ninety percent of children with epilepsy had comorbidities, with cerebral palsy and neonatal encephalopathy as the most common ones (Abdel-Mannan and Sutcliffe, 2020). The most common comorbid medical conditions that have been reported among adults with prevalent epilepsy include fractures, ischemic heart disease and heart failure. The risk of fractures in epileptic patients is elevated approximately two-fold compared with the general population; the fractures result directly from seizure-induced injury or the reduction in bone mineral density associated with use of enzyme-inducing AEDs (Wirrell, 2006). Among older adults, the occurrence of either stroke or epilepsy is associated with an increased risk for the other condition (Cleary et al, 2004; Hauser et al, 1993). Studies involving adults with epilepsy aged at least 18 years have also reported sleep disturbance conditions including increased latency to sleep onset, increased number and duration of awakenings and increased duration of sleep stages 1 and 2 (van Golde et al, 2011). Although epilepsy does not increase the risk of cancer, patients with cancer have an increased risk of developing epileptic seizures in the course of their disease. The lifetime risk of patients with brain tumors to have epileptic seizures is 20 to 80% (van Breemen et al, 2007). The risk of having epileptic seizures is higher in patients with primary brain tumors than in those with brain metastasis. Seizures can occur in patients with cancer in the absence of CNS involvement. Even when a brain lesion is present, it may not be cause of seizures. Other factors that cause seizures in these patients include medications, metabolic disturbances, stroke, and infection (Singh et al, 2007).

Part II Module SII Nonclinical part of the safety specification

Key safety findings from nonclinical studies and relevance to human usage:

Toxicity

- Acute or repeat-dose toxicity

Levetiracetam was evaluated in repeat toxicity studies up to 52 weeks in rats and dogs. Liver and kidneys were identified as target organs in rats.

- Kidney changes (hyaline droplet deposition, regenerative urinary tubules, and chronic progressive nephropathy) were caused by male rat-specific α2-microglobulin accumulation in renal tubular epithelium.

  Relevance to human usage: This α2-microglobulin accumulation is specific to male rats and is considered of no concern for humans.

- Liver changes consisted of increased liver weight, increased liver enzyme levels in plasma, centrilobular hepatocyte hypertrophy, and vacuolation considered to be adaptive.

  Relevance to human usage: Liver changes were not observed in humans. This has been outlined in Summary of Product Characteristics (SmPC) Section 5.3.

- Reproductive/developmental toxicity

Levetiracetam was evaluated for its effects on reproduction in rats and rabbits. No maternal abnormal findings were observed in rats. In rabbits, neuromuscular signs, inappetence, poor general condition, or abortions were observed in dams. In rat and rabbit fetuses, growth retardation (low body weight) and increased incidence of skeletal anomalies or variations were observed. Levetiracetam did not influence fertility, maintenance of pregnancy, or parturition in rats. In offspring, transient suppression of body weight gain was observed, followed by recovery and transient reduction of survival rate up to day 8, but no effect was observed on growth, development, and reproductive functions. In addition, levetiracetam did not show teratogenicity in mice and did not potentiate the adverse teratogenic effects of sodium valproate (VPA) in this species.

Relevance to human usage: Available data in use during pregnancy does not suggest teratogenic effect. However, additional data is required on a larger number of levetiracetam-exposed pregnancies. Levetiracetam can be used during pregnancy, if after careful assessment it is considered clinically needed. Levetiracetam is excreted in human breast milk. Therefore, breastfeeding is not recommended. However, if levetiracetam treatment is needed during breastfeeding, the benefit/risk of the treatment should be weighed considering the importance of breastfeeding. This has been outlined in SmPC Section 4.6 and Section 5.3.

Developmental toxicity:

Neonatal and juvenile studies performed in rats and dogs indicated that levetiracetam is at least as well tolerated in neonatal rats and juvenile pups as it is in adult animals. No adverse effects were seen in any of the standard developmental or maturation endpoints at doses up to 6 to 17-fold the maximum recommended human dose (MRHD) on an mg/m² basis.

Relevance to human usage: This has been outlined in SmPC Section 5.3

- Nephrotoxicity:

  Kidney changes (hyaline droplet deposition, regenerative urinary tubules, and chronic progressive nephropathy) were caused by male rat-specific α2-microglobulin accumulation in renal tubular epithelium.

  Relevance to human usage: This α2-microglobulin accumulation is specific to male rats and is considered of no concern for humans.

- Hepatotoxicity:

  Liver changes were observed in the rat and in a lesser extent in the mouse and consisted of increased liver weight, increased liver enzymes in plasma, centrilobular hepatocyte hypertrophy, and vacuolation considered to be adaptive.

  Relevance to human usage: Levetiracetam adverse reactions include uncommon liver function tests abnormalities, and rare hepatic failure and hepatitis. This has been outlined in SmPC Section 4.8.

- Genotoxicity

  No evidence of genotoxicity in vitro was observed in both bacteria and eukaryotic systems and in vivo in the mouse micronucleus test.

  Relevance to human usage: No hazard for humans was noted. This has been outlined in SmPC Section 5.3.

- Carcinogenicity

  No evidence of carcinogenic potential was observed in 2-year carcinogenicity studies in rats and mice.

  Relevance to human usage: No hazard for humans was noted. This has been outlined in SmPC Section 5.3.

Safety pharmacology

- Cardiovascular (including potential for QT interval prolongation):

  Levetiracetam did not prolong cardiac action potential duration or QT corrected for heart rate in dogs. Levetiracetam induces short-lasting hemodynamic changes including increased pulmonary arterial pressure in dogs after intravenous (i.v) injection, an effect attributed to hemorheological effects at the high concentrations injected, particularly after bolus injection.

  In human-ether-à-go-go related gene (hERG) potassium channel stably expressed in Chinese hamster ovary (CHO) cells, the Cardiac Safety Index of levetiracetam was 30-fold higher than free therapeutic plasma concentration (FTPC) in man. Similarly, levetiracetam did not significantly inhibit the cardiac ion currents up the highest tested concentration (30-fold higher than FTPC) on 7 cardiac ion channels ($Na_V1.5$, $Ca_V1.2$, $K_V1.5$, $K_V4.3$, $K_V7.1$/minK, $K_{ir}2.1$, and hyperpolarization activated cyclic nucleotide gated potassium channel 4) stably transfected in CHO or Human Embryonic Kidney-293. Levetiracetam does not have effects on hERG trafficking.

In another in vitro study, LEV (0.25, 0.75, 2.5, and 7.5mM) did not induce either early-after depolarization or the field potential duration corrected for beat rate prolongation (a surrogate for proarrhythmia) in human-induced pluripotent stem cell-derived cardiomyocyte up the highest tested concentration (30-fold higher than FTPC). There were no significant and/or concentration-dependent changes in cell index, beating rate, or contractility amplitude indicating that levetiracetam did not have an impact on human-induced pluripotent stem cell-derived cardiomyocyte function over the 24-hour treatment.

An in-silico study was performed to simulate the effects of levetiracetam (concentration range: 0.25, 0.75, 2.5, and 7.5mM) on virtual human cardiomyocytes using different risk conditions. Three populations of virtual cardiomyocyte models were constructed to mimic a healthy control population (n=270 cells), a population with large up-/downregulations of ion channels which could be compatible with underlying conditions or genetic mutations (n=283 cells), and a high-risk population specifically designed with a low repolarization reserve (n=322 cells) to maximize the risk to develop drug-induced early-after depolarizations associated with proarrhythmic risk. No relevant changes were observed in the action potential and calcium transient biomarkers for up to 7.5mM LEV in the 3 populations of virtual human cells (control, large variability, or high risk), compared to control conditions (no drug), at normal pacing (1Hz). Most biomarker changes remained far below 5%. Further, action potential duration at 90% of repolarization (APD90) prolongation and electromechanical window (EMw) shortening at 10-fold free therapeutic plasma concentration (3.1% and -4.2%, respectively) were both below the safety thresholds defined as biologically meaningful to identify a proarrhythmic risk, ie, ΔAPD90>6% and ΔEMw<-10%.

Relevance to human usage: No hazard for humans was noted. This has been outlined in SmPC Section 5.3.

- Nervous system

  There were central nervous system adverse effects in any safety pharmacology study.

  Relevance to human usage: This has been outlined in SmPC Section 5.3.

Mechanisms for drug interactions:

- Levetiracetam metabolism is not dependent on any liver cytochrome P450 isoenzymes and did not show inhibition in vitro. Only a mild induction of CYP CYP2B6 and CYP3A4 was observed at concentrations >10-fold the C_{max} at MRHD.

  Relevance to human usage: Levetiracetam is not associated with clinically significant pharmacokinetic interactions with other drugs, including other antiepileptic drug (AEDs). This has been outlined in SmPC Section 4.5.

Other toxicity-related information or data

- Dependence:

  Levetiracetam did not produce behavioral signs of withdrawal after oral administration in rats or forced iv infusion in monkeys. No reinforcement after iv self administration was observed in monkeys.

  Relevance to human usage: No hazard for humans was noted.

Additional nonclinical data

Three articles addressed the effects of levetiracetam on the bones of Wistar rats after 3-month oral administration. Nissen-Meyer et al (2007) evaluated the effects of levetiracetam (50 and 150mg/kg, gavage) on bone mass, biomechanical strength, and bone turnover in female rats and compared them with those of other AEDs (phenytoin [PHT] 50mg/kg and VPA 300mg/kg). Dissected femurs were analyzed using dual energy X-ray absorptiometry, 3-point cantilever bending, and histomorphological evaluation. Serum levels of biochemical bone turnover markers were monitored using immunoassay quantification. The authors found that PHT and VPA reduced bone mineral density (BMD) and bone mineral content (BMC) in 1 or more bone compartments, whereas levetiracetam did not. Valproate induced increased bone turnover, whereas modest changes were observed with PHT. Furthermore, low-dose levetiracetam was associated with reduced biomechanical strength of the femoral neck (mainly trabecular bone). In addition, low-dose levetiracetam treatment resulted in significantly reduced levels of serum osteocalcin, a marker of bone formation. Histomorphological analyses indicated increased retention of cartilage remnants at the growth plate metaphysis of rats treated with low-dose levetiracetam versus controls. The authors concluded that PHT, VPA, and levetiracetam exert differential effects on bone mass and strength, suggesting different mechanisms of action. The weakening effect of low-dose levetiracetam on the femoral neck, despite a constant BMD, suggests a primary effect on bone quality. According to the authors, these findings warrant further human studies of possible adverse effects of levetiracetam on bone development and growth, particularly in children and adolescents.

Fekete et al (2013) evaluated the effects of levetiracetam by diet admix (giving plasma exposures corresponding to a dose level of 160mg/kg) on BMD, BMC, bone marker body composition, and bone mechanical strength in an orchidectomized rat model. Bone mineral density was measured by dual energy X-ray absorptiometry at the whole body, lumbar spine, and femur. Bone marker concentrations were examined for osteoprotegerin (OPG) and insulin-like growth factor 1 in serum and amino-terminal propeptide of procollagen type I, carboxyterminal cross-linking telopeptide of type I collagen (CTX-I), bone alkaline phosphatase, and bone morphogenetic protein 2 in bone homogenate. The femurs were used for biomechanical testing. Compared to the control group's lower fat mass, lower BMD in the area of the left femur, and lower BMC in both femurs, a reduced concentration of OPG and an increased concentration of CTX-I of borderline statistical significance ($p=0.0661$) was seen in the levetiracetam-treated group. Biomechanical parameters did not differ between groups. The authors concluded that significant loss of BMD or BMC was seen at the left and right femur area in the levetiracetam-treated group with significantly decreased levels of OPG (marker of bone formation) in serum and increased levels of CTX-I (marker of bone resorption) in bone homogenate, but the data did not reveal any change in biomechanical bone strength. They stated that further studies in animals and humans will be needed to confirm these findings.

Parveen et al (2018) confirmed adverse effects on the bone following AEDs in female rats. Further, the results demonstrated, for the first time, that these effects are more pronounced in ovariectomized animals. Treatment with AEDs displayed changes in the serum levels of wnt inhibitors, and hence, modulation of wnt inhibitors might be involved in adverse effects on the bone. The results have translational significance for postmenopausal epileptic women. This was also indicated in a paper published by Fekete et al (2013) regarding the potential adverse effects of levetiracetam on the bones in male orchidectomized rat models.

The nonclinical safety of levetiracetam had been investigated with a full package of UCB-sponsored toxicology studies, which were submitted for Marketing Application Approval (MAA) to the European Medicines Agency and Food and Drug Administration. This included chronic toxicology studies in which rats and dogs received levetiracetam for 12 months, at oral doses up to 1800mg/kg/day in rats and 1200mg/kg/day in dogs. Histopatholgical examination of the femur and sternum of these animals indicated no microscopic changes to the bone structure. The MAA package of studies also included those in neonatal rats and juvenile dogs at doses up to 1800mg/kg/day. Rats aged 4 days were treated orally for 7 weeks, while dogs aged 3 weeks were treated for 4 weeks. The study failed to show any change in femoral bone geometry or biomechanical strength.

Therefore, the relevance of these published findings can be questioned on the basis of the artificial osteoporosis model used in the papers published by Fekete et al (2013) and Parveen et al (2018), the inconsistent findings in changes in BMD (left, not right, femur affected), the nonsignificant change in the biomarker CTX-I, as well as the conflicting data from another research group (Nissen-Meyer et al, 2007). Furthermore, there were no bone findings in UCB-sponsored good laboratory practice toxicology studies with levetiracetam in rats and dogs at higher doses administered for longer treatment periods. Moreover, Kanda et al (2017) presented no effect of levetiracetam on bone strength, bone mass, and bone turnover in rats treated with 50 or 200mg/kg doses daily for 12 weeks. These data are in agreement with the UCB data in juvenile animals.

Part II Module SIII Clinical trial exposure

Overall, 15,008 study participants have received Investigational Medicinal Product in the levetiracetam development program by UCB since the Developmental International Birth Date up to the DLP. Of these, a total of 11,146 study participants were exposed to levetiracetam in ongoing and completed studies. Keppra and levetiracetam-UCB are manufactured on the same production line, i.e. have identical active pharmaceutical ingredient but are packaged differently. However, marketing authorization holder recognizes these as separate medicinal products. No clinical studies were required to be performed with levetiracetam-UCB because it was registered as a generic based on Keppra as the reference product. Therefore, no table of exposure to levetiracetam-UCB is presented.

The cumulative numbers of study participants from ongoing and completed clinical studies exposed to the investigational drug or placebo and/or active comparator(s) during the drug development program through the DLP are presented in Table Part II–1. The estimates are based on actual exposure data from completed and ongoing clinical studies.

Table Part II–1: Estimated cumulative study participants exposure from ongoing and completed clinical studies

Treatment	Number of study participants[a]
Levetiracetam	11,146
Comparator	1909
Placebo	4344
Total (Unique) [b]	**15,008**

Note: Implementation of a modified calculation method which avoided multiple counting of study participants who were exposed to more than 1 treatment out of the categories of levetiracetam, comparator or placebo, as compared to the last version of the RMP, led to a decrease of the overall count of exposed participants even after adding participant counts from past completed studies that had not been included before and adding newly exposed participants. As the updated calculation was not applicable to the count of participants exposed to levetiracetam, the change in this number only reflects the addition of the mentioned participants and therefore increased, as expected, compared to the last report.

[a] Data from ongoing and completed clinical trials as of 30 Nov 2023

[b] Presents count of unique participants. Participants could be exposed to more than 1 treatment of "levetiracetam", "comparator" and "placebo" (e.g., sequentially). Such participants are counted for each of these 3 rows but only once for the "Total" row so that the count in this row is lower than the sum of counts of the rows above.

Cumulative summary tabulation from completed clinical studies of the demographics data are presented by age and sex in Table Part II–2 and by racial/ethnic group in Table Part II–3. The total number of study participants who have received investigational medicinal product as reported in Table Part II–1 (referred to as “Overall” in the beginning of this section) is greater than the total in Table Part II–2 and Table Part II–3 because Table Part II–1 summarizes exposure data for levetiracetam, active comparators and placebo. Furthermore, Table Part II–1 includes ongoing studies whereas Table Part II–2 and Table Part II–3 only include completed studies. For the given report the second factor is not applicable as at the DLP no study was ongoing, which means that the number of 11,146 of participants exposed to levetiracetam per Table Part II–1 agrees with the total number of participants reported in Table Part II–2 and Table Part II–3.

Table Part II–2: Cumulative study participant exposure to the investigational drug from completed clinical trials by age and sex

Number of study participants[a]				
Age range	**Male**	**Female**	**Unknown sex**	**Total**
0-<28 days	2	0	0	2
28 days-<2 years	117	114	0	231
2-<12 years	201	154	0	355
12-<18 years	222	219	0	441
18-<65 years	4671	4602	5	9278
65-<85 years	367	373	0	740
≥85 years	17	60	0	77
Missing	12	10	0	22
Total	**5609**	**5532**	**5**	**11,146**

[a] Data from completed clinical studies as of 30 Nov 2023

Table Part II–3: Cumulative study participant exposure to the investigational drug from completed clinical trials by racial/ethnic group

Racial group	**Number of study participants**[a]
Asian	2051
Black	305
Caucasian	7040
Other	557
Unknown	1193
Total	**11,146**

[a] Data from completed clinical studies as of 30 Nov 2023

Part II Module SIV Populations not studied in clinical trials

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

Table Part II–4 presents the exclusion criteria for the studies in the pediatric population aged 1 month to 16 years.

Table Part II–4: Exclusion criteria for studies in the pediatric population (1 month to 16 years)

Study number	No of patients exposed to levetiracetam	Age range	Exclusion criteria for study
N01009	60	1 month to <4 years	Pediatric patients were excluded from the study if they: • were on a ketogenic diet • received any other investigational drug/device within 30 days of Day –8 • had clinically significant deviations in laboratory parameters • had clinically significant acute or chronic illness, a history of pseudoseizures, a terminal illness, or any disorder which may have interfered with the absorption, distribution, metabolism, or excretion of drugs, experienced status epilepticus 1 month prior to Day -8 (except for status epilepticus occurring in the first 10 days of life), epilepsy secondary to a progressing cerebral disease or any other progressively neurodegenerative disease, or a current diagnosis of Lennox-Gastaut syndrome • had an allergy to pyrrolidine derivatives • were taking any medication which may have interfered with concomitant antiepileptic drugs (AEDs) or levetiracetam or influenced the central nervous system (CNS) • underwent prior treatment with levetiracetam • had any medical condition that might interfere with the subject's study participation

Table Part II–4: Exclusion criteria for studies in the pediatric population (1 month to 16 years)

Study number	No of patients exposed to levetiracetam	Age range	Exclusion criteria for study
N01052	13	1 month to <4 years	Pediatric patients were excluded from the study if they: • were on a ketogenic diet • received any other investigational drug/device within 30 days of selection visit • had clinically significant deviations in laboratory parameters • had clinically significant acute or chronic illness, a history of pseudoseizures, a terminal illness, or any disorder which may have interfered with the absorption, distribution, metabolism, or excretion of drugs, experienced status epilepticus 2 weeks prior to selection visit, epilepsy surgery 1 year prior to selection visit, epilepsy secondary to a progressing cerebral disease, or any other progressively neurodegenerative disease • had an allergy to pyrrolidine derivatives • were taking any medication which may have interfered with concomitant AEDs or levetiracetam or influenced the CNS • had any medical condition that might interfere with the subject's study participation
N157	238 14 in the 1 month to <4 year group	1 month to 16 years	Pediatric patients were excluded from the study if they: • had seizures to close together to count accurately • were on a ketogenic diet • received any other investigational drug/device • had clinically significant deviations in laboratory parameters • had clinically significant acute or chronic illness
N01148	255 152 in the 1 month to <4 year group	1 month to 16 years	Pediatric patients were excluded from the study if they: • were on a ketogenic diet • received any other investigational drug/device within 30 days of selection visit • had clinically significant deviations in laboratory parameters • had clinically significant acute or chronic illness, a history of pseudoseizures, terminal illness, or any disorder which may have interfered with the absorption, distribution, metabolism, or excretion

Table Part II–4: Exclusion criteria for studies in the pediatric population (1 month to 16 years)

Study number	No of patients exposed to levetiracetam	Age range	Exclusion criteria for study
			of drugs, experienced status epilepticus 1 month prior to Visit 1 (except for status epilepticus occurring in the first 10 days of life) prior to selection visit, epilepsy or epilepsy secondary to a progressing cerebral disease or any other progressively neurodegenerative disease, or a current diagnosis of Lennox-Gastaut syndrome • had current psychiatric diagnosis of severe attention deficit hyperactivity disorder • had an allergy to pyrrolidine derivatives • had any medical condition that might have interfered with the subject's study participation
EP0100	25	1 month to <4 years	Subjects are not permitted to enroll in the study if any of the following criteria are met: • Subject has been taking any medication (other than their concomitant AEDs) that influences the CNS, for which they had not been on a stable regimen for at least 1 month prior to Visit 1. • Subject is taking any medication that may interfere with the absorption, distribution, metabolism, or excretion of the concomitant AEDs or levetiracetam during the course of the study. • Subject has received any investigational medication or device within 30 days prior to Visit 1. • Subject has taken LEV prior to the study. • Subjects using felbamate who have presented with clinically significant abnormalities for white blood cells, red blood cells, platelets, and/or hepatic function during felbamate treatment, and subjects who are taking felbamate <1 year from the date of Visit 1. • Subject has a history of status epilepticus requiring hospitalization during the 30 days prior to Visit 1, except for status epilepticus occurring during the first 10 days of life. • Subject has a treatable seizure etiology (ie, febrile seizures).

Table Part II–4: Exclusion criteria for studies in the pediatric population (1 month to 16 years)

Study number	No of patients exposed to levetiracetam	Age range	Exclusion criteria for study
			• Subject is on a ketogenic diet (concomitantly or within 30 days prior to Visit 1). • Subject has epilepsy secondary to progressing cerebral diseases. • Subject has a current diagnosis of Rasmussen's syndrome, Landau-Kleffner disease, or Lennox-Gastaut syndrome. • Subject has clinically significant deviations from reference range values for renal function or any of the other laboratory parameters required for this study, as determined by the investigator. • Subject has any clinically significant acute or chronic illness (as determined during the physical examination or from other information available to the investigator). • Subject has an allergy to pyrrolidine derivatives or a history of multiple drug allergies. • Subject is known to have a terminal illness. • Subject has a disorder or condition that may interfere with the absorption, distribution, metabolism, or excretion of medications. • Subject has a history of or presence of pseudoseizures. • Subject has any medical condition that might interfere with the subject's study participation (ie, serious infection, scheduled elective surgery, severe scalp eczema, etc.). • Subject has ≥3× the upper limit of normal (ULN) of any of the following: alanine aminotransferase (ALT), aspartate, aminotransferase (AST), alkaline phosphatase (ALP), or >ULN total bilirubin (≥1.5×ULN total bilirubin if known Gilbert's syndrome). • Subject has elevations only in total bilirubin that are >ULN and <1.5×ULN, fractionate bilirubin to identify possible undiagnosed Gilbert's syndrome (ie, direct bilirubin <35%). • For randomized subjects with a baseline result >ULN for ALT, AST, ALP, or total bilirubin, a baseline diagnosis and/or the cause of any

Table Part II–4: Exclusion criteria for studies in the pediatric population (1 month to 16 years)

Study number	No of patients exposed to levetiracetam	Age range	Exclusion criteria for study
			clinically meaningful elevation must be understood and recorded in the electronic case report form. • If subject has >ULN ALT, AST, or ALP that does not meet the exclusion limit at screening, repeat the tests, if possible, prior to dosing to ensure there is no further ongoing clinically relevant increase. In case of a clinically relevant increase, inclusion of the subject must be discussed with the medical monitor. • Tests that result in ALT, AST, or ALP up to 25% above the exclusion limit may be repeated once for confirmation. This includes rescreening.

AED=antiepileptic drug; ALT=alanine aminotransferase; AST=aspartate aminotransferase; ALP=alkaline phosphatase; CNS=central nervous system; LEV=levetiracetam; ULN=upper limit of normal

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

The clinical development program was unlikely to detect certain types of adverse reactions such as rare adverse reactions (occurring > 1/10,000 to < 1/1000), adverse reactions due to prolonged exposure, or those caused by cumulative effects, and those, which have a prolonged latency period.

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

SIV.3.1 Children

In total, 168 pediatric patients aged 1 month to <4 years were observed in 4 open-label and placebo-controlled clinical studies; the enrolled subjects are representative of the target population. Additional data on the use of E-Keppra® oral solution in routine clinical practice were collected in 101 infants younger than 12 months of age in N01357, a noninterventional sentinel sites postauthorization safety study. Levetiracetam has been approved in children ≥4 years since 2005 and in children 1 month to <4 years since 2009. Safety information continues to be collected during routine pharmacovigilance activities in patients aged <16 years. Further data in patients aged 1 month to <4 years are being collected in Japan from an ongoing levetiracetam efficacy and safety study (EP0100).

SIV.3.2 Elderly

Levetiracetam has been approved in adult population ≥16 years of age since 1999. Safety information continues to be collected during routine pharmacovigilance activities on elderly patients.

SIV.3.3 Pregnant or breastfeeding women

Data on use during pregnancy was not collected during clinical studies. Exposure of levetiracetam in pregnant women has been collected since launch during routine pharmacovigilance activities as well as in pregnancy registries.

SIV.3.4 Patients with hepatic impairment

No dose adjustment is needed in patients with mild to moderate hepatic impairment. In patients with severe hepatic impairment, the creatinine clearance may underestimate the renal insufficiency. Therefore, a 50% reduction of the levetiracetam daily maintenance dose is recommended when the creatinine clearance is <60 mL/min/1.73m^2.

SIV.3.5 Patients with renal impairment

The administration of levetiracetam to patients with renal impairment may require dose adaptation. In patients with severely impaired hepatic function, assessment of renal function is recommended before dose selection. In Japanese subjects, N01373 demonstrated that the simulated levetiracetam plasma concentration vs time profiles in the subjects with mild, moderate, or severe renal impairment and subjects with end-stage renal disease (ESRD) were in the simulated concentration range of the subjects with normal renal function, confirming that levetiracetam dose adjustments (as mentioned in the Japanese Package Insert) are applicable to Japanese subjects with mild, moderate, and severe renal impairment and subjects with ESRD.

SIV.3.6 Patients with other relevant comorbidity

Pediatric patients with acute or chronic illness or a concomitant condition which may have affected the absorption, distribution, metabolism, or excretion of drugs were excluded from clinical studies. Data on dosing adjustments are available in the SmPC.

SIV.3.7 Subpopulations carrying known and relevant polymorphisms

UCB has conducted a Keppra vs Older Monotherapy in Epilepsy Trial with an exploratory assessment of the correlation between SV2A gene variations and treatment response in subjects treated with levetiracetam compared to older AEDs. However, there were insufficient numbers of subjects to draw any meaningful conclusions.

SIV.3.8 Patients of different racial and/or ethnic origin

Across the 5 completed clinical studies in pediatric patients aged 1 month to <4 years, the majority of patients were Caucasian (69.8%), followed by black (20.8%), mixed race (7.5%), and Asian (1.9%) patients. No clinically relevant interactions related to treatment-emergent adverse events leading to permanent discontinuation were noted with regard to race; however, the number of subjects in some of the subgroups and the number of discontinuations was too small to draw any meaningful conclusions.

In the previously submitted pooled population aged 4 to 16 years (variation file EMEA/H/C/000277/0044), most of the children were Caucasian (162 [67.8%]). The 77 non-Caucasians comprised Hispanic (31 [13.0%]), black (30 [12.6%]), and Asian (3 [1.3%]) races as well as 13 patients (5.4%) designated as other. The average daily dose on an mg/kg basis and the duration of exposure to levetiracetam were comparable. Adverse events wherein differences between the races were observed (ie, occurring in a higher proportion of Caucasians as compared to non-Caucasians) were as follows: accidental injury, asthenia, headache, infection, pain, diarrhea, convulsions, emotional lability, insomnia, personality disorder, sinusitis, and rash.

However, when comparing the subgroups within the N159 randomized population, adverse events have been reported with a higher incidence in the subjects treated with levetiracetam compared to placebo in Caucasian and not in non-Caucasian (asthenia, anorexia, hostility, nervousness, somnolence and cough increased), while pain, emotional lability, and rhinitis were more frequent with levetiracetam than placebo in the non-Caucasian subjects. Accidental injury has been the only AE consistently reported in more patients treated with levetiracetam than placebo in both subgroups.

In addition, levetiracetam has been studied and approved in Asian populations, including Japanese and Chinese.

SIV.4 Conclusions on the populations not studied and other limitations of the clinical development program

Missing information for patients aged 1 month to <4 years and patients aged 4 years and older is summarized in Table Part II–5 and Table Part II–6, respectively.

Table Part II–5: Missing information for patients aged 1 month to less than 4 years

Safety concerns due to limitations of the clinical program		**Considered to be included as missing information**
Safety concern	**Comment**	**Yes/No**
Long-term effects on learning, intelligence, growth, endocrine function, puberty, and childbearing potential in children with epilepsy or in children exposed in utero	Not adequately assessed during clinical studies	Yes

Table Part II–6: Missing information for patients aged 4 years and older

Safety concerns due to limitations of the clinical program		Considered to be included as missing information	Additional comment
Safety concern	**Comment**	**Yes/No**	
Deterioration of seizure control during pregnancy	Not adequately assessed during clinical studies	No	The Pharmacovigilance Risk Assessment Committee (PRAC) in its Periodic Safety Update Report assessment report dated 07 Jul 2022 (Procedure no. EA/H/C/PSUSA/00001846/202111) concluded that the information collected over many year consistently is aligned with the wording already documented in Product Information (same wording are listed in the Company Core Data Sheet too). The information was considered adequate and sufficient to mitigate the risk, and the PRAC therefore requested to delete this missing information from the list of safety concerns.

Table Part II–6: Missing information for patients aged 4 years and older

Safety concerns due to limitations of the clinical program		Considered to be included as missing information	Additional comment
Safety concern	**Comment**	**Yes/No**	
Decreased bone mineral density after prolonged levetiracetam exposure	Limited data are available from clinical studies regarding the impact on bone mineral density after prolonged levetiracetam exposure	No	The topic is no longer considered missing information due to the new Good Pharmacovigilance Practices Module V Rev. 2 requirements (further characterization of this missing information via routine pharmacovigilance only) Of note, "Decreased bone mineral density after prolonged levetiracetam exposure" will remain missing information in Periodic Safety Update Reports.
Long-term effects on learning, intelligence, growth, endocrine function, puberty, and childbearing potential in children with epilepsy or in children exposed in utero	Not adequately assessed during clinical studies	Yes	-
Use during pregnancy	Not adequately assessed during clinical studies	No	It was thoroughly re-evaluated during the postmarketing phase (EMEA/H/C/000277/LEG/084); therefore, it is no longer considered missing information.

PRAC=Pharmacovigilance Risk Assessment Committee

Part II Module SV Postauthorization experience

SV.1 Postauthorization exposure

SV.1.1 Method used to calculate exposure

A conservative view was adopted by assuming that all patients receive complete dosage regimens at the time of treatment. Patient exposure is estimated using the available UCB sales data from 01 Dec 2007 to 30 Nov 2023 for the cumulative time interval. Note that sales data are only available to UCB on a monthly basis.

The total amount of product sold during the cumulative reporting interval is 9,887,320,955,184mg, as derived from the UCB sales data reported.

The defined daily dose (DDD) for levetiracetam is assumed to be 1500mg/day according to the World Health Organization. It was also assumed that 1-year corresponds to 365.25 days. The patient exposure time is calculated using the following formula:

$$\text{Patient years} = \frac{(\text{total milligrams of product distributed})/\text{DDD}}{365.25 \text{ days in year}}$$

0.25 is added to account for leap years.

SV.1.2 Exposure

Patient exposure before 01 Dec 2007 based on historical data obtained from Periodic Safety Update Reports (PSURs) including the period from Apr 2000 to 30 Nov 2007 was estimated at 2,199,328 patient-years. Patient exposure from 01 Dec 2007 to 30 Nov 2023 estimated using the available sales data is 17,986,314 patient-years.

Cumulative patient exposure from Apr 2000 to 30 Nov 2023 is then estimated at approximately 20,185,642 patient-years.

Data on cumulative exposure by region are presented in Table Part II−7. The historical data before 01 Dec 2007 are not available in milligrams and by markets and are, therefore, not included in this table.

Table Part II−7: Patient exposure by region cumulatively (01 Dec 2007 to 30 Nov 2023)

Region	Country	Patient-years cumulatively
European Economic Area (EEA)	[redacted]	[redacted]
	[redacted]	[redacted]
	[redacted]	[redacted]
	[redacted]	[redacted]
	[redacted]	[redacted]
	[redacted]	[redacted]

Table Part II‒7: Patient exposure by region cumulatively (01 Dec 2007 to 30 Nov 2023)

Region	Country	Patient-years cumulatively
	[redacted]	[redacted]
	[redacted]	[redacted]
	[redacted]	[redacted]
	[redacted]	[redacted]
	[redacted]	[redacted]
	[redacted]	[redacted]
	[redacted]	[redacted]
	[redacted]	[redacted]
	[redacted]	[redacted]
	[redacted]	[redacted]
	[redacted]	[redacted]
	[redacted]	[redacted]
	[redacted]	[redacted]
	[redacted]	[redacted]
	[redacted]	[redacted]
	[redacted]	[redacted]
	[redacted]	[redacted]
	[redacted]	[redacted]
	[redacted]	[redacted]
Europe (non-EEA)[a]		[redacted]
	[redacted]	[redacted]
	[redacted]	[redacted]
[redacted]		[redacted]
[redacted]		[redacted]
[redacted]		[redacted]
[redacted]		[redacted]
[redacted]		[redacted]
Total		**17,986,314**

Table Part II−7: Patient exposure by region cumulatively (01 Dec 2007 to 30 Nov 2023)

Region	Country	Patient-years cumulatively

EEA=European economic area

[a] The UK withdrew from the European Union and European Economic Area on 31 Jan 2020. As of 14 Apr 2021, UK exposure data is presented in the Europe/non-European Economic Area category instead of the Europe/European Economic Area category. Therefore, cumulative exposure data for Europe/European Economic Area may be different from prior versions of this report.

Data on cumulative exposure by formulation are presented in Table Part II–8. Historical data before 01 Dec 2007 are not available in milligrams and by formulations and are, therefore, not included in this table.

Table Part II–8: Patient exposure by formulation cumulatively (01 Dec 2007 to 30 Nov 2023)

Formulation	Patient-years cumulatively
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
Total	**17,986,314**

[a] Not marketed in the European Union

Part II Module SVI Additional EU requirements for the safety specification

SVI.1 Potential for misuse for illegal purposes

Due to the nature of this drug, the potential for misuse for illegal purposes is considered to be low.

Part II Module SVII Identified and potential risks

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

As Section SVII.1 applies only to an initial RMP, this section is not applicable to levetiracetam.

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

As Section SVII.1 applies only to an initial RMP, this section is not applicable to levetiracetam.

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

The PRAC in its PSUR assessment report (Procedure number: EMEA/H/C/PSUSA/00001846/202111), dated 07 Jul 2022, suggested the deletion of missing information “Deterioration of seizure control during pregnancy” from the list of safety concerns in future PSURs. As per the PRAC PSUR assessment report, the information collected over many years consistently confirmed the wording already documented in the PI, ie that physiological changes associated with pregnancy may affect levetiracetam blood concentration and effectiveness. This effect may be more pronounced in the last trimester, and careful monitoring of levetiracetam treatment should be exercised in pregnant women. This information is considered adequate and sufficient to mitigate the risk. Hence the details with regards to safety concern (missing information) “Deterioration of seizure control during pregnancy” has been removed from all sections of this RMP.

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

None, for the population aged 4 years and older.

SVII.3.2 Important potential risk in children below 4 years of age

None

SVII.3.3 Presentation of the missing information

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 1 month to less than 4 years:

Evidence source:

There are no adequate data regarding the use of levetiracetam on long-term effects on learning, intelligence, growth, endocrine function, puberty, and childbearing potential in children with epilepsy or in children exposed in utero.

Population in need of further characterization:

Pediatric patients will be further characterized for the following safety concerns: growth, neurodevelopment, intelligence, endocrine function, puberty, and reproduction.

Patients aged 4 years and older

Evidence source:

There are no adequate data regarding the use of levetiracetam on long-term effects on learning, intelligence, growth, endocrine function, puberty, and childbearing potential in children with epilepsy or in children exposed in utero.

Population in need of further characterization:

All the patients (pediatric, adult and geriatric) will be further characterized for the following safety concerns: growth, neurodevelopment, intelligence, endocrine function, puberty, and reproduction.

Part II Module SVIII Summary of the safety concerns

Table Part II–9: Summary of safety concerns for patients aged 1 month to less than 4 years

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

Table Part II–10: Summary of safety concerns for patients aged 4 years and older

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 POSTAUTHORIZATION STUDIES)

III.1 Routine pharmacovigilance activities

There are no routine pharmacovigilance activities beyond adverse reactions reporting and signal detection.

III.2 Additional pharmacovigilance activities

Additional pharmacovigilance activities include the following:

- Registry studies to monitor pregnancy outcomes of European and International Antiepileptic Drugs and Pregnancy Registry (EURAP) and North American Antiepileptic Drug Pregnancy Registry (NAAPR).

  Activities include provision of requested data from registries to the UCB and regular review of interim outputs from the registries. The protocols for EURAP and NAAPR include possible activities to follow-up on children.

  Prescribers and reporters of pregnancy cases are encouraged to register pregnant women exposed to AEDs into the EURAP and NAAPR.

  Tabulated summary of ongoing and completed pharmacovigilance activities are provided in EU-RMP Part VII Annex 2.

  Protocols for ongoing studies in the pharmacovigilance plan are provided in EU-RMP Part VII Annex 3.

III.3 Summary table of additional pharmacovigilance activities

The summary of ongoing and planned additional pharmacovigilance activities is provided in Table Part III−1.

Table Part III−1: Ongoing and planned additional pharmacovigilance activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization				
Not applicable				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are specific obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
Not applicable				
Category 3 - Required additional pharmacovigilance activities				

Table Part III−1: Ongoing and planned additional pharmacovigilance activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Monitor pregnancy outcomes of European and International Antiepileptic Drug (AED) and Pregnancy Registry Ongoing	To evaluate and determine the comparative risk of major fetal malformations following the intake of AEDs (old and new) and their combinations during pregnancy	Missing information on long-term effects on learning, intelligence, growth, endocrine function, puberty, and childbearing potential in children with epilepsy or those exposed in utero	Start of data collection Completion of data collection Interim study report (semiannual)	Cumulative data appearing in these registries are discussed in Periodic Safety Update Reports (PSURs).
Monitor pregnancy outcomes of North American AED Pregnancy Registry Ongoing	To determine, from the outcomes of the pregnancies of each enrolled woman taking AEDs, the health status of her infant, with a particular focus on the occurrence of major malformations and growth restriction	Missing information on long-term effects on learning, intelligence, growth, endocrine function, puberty, and childbearing potential in children with epilepsy or those exposed in utero	Start of data collection Completion of data collection Interim study report (Annual)	Cumulative data appearing in these registries are discussed in PSURs.

AED=antiepileptic drug; PSUR=periodic safety update report

PART IV PLANS FOR POSTAUTHORIZATION EFFICACY STUDIES

There is no planned or ongoing imposed postauthorization efficacy studies that are conditions of the marketing authorisation or that are specific obligations for levetiracetam.

PART V RISK MINIMIZATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMIZATION ACTIVITIES)

RISK MINIMIZATION PLAN

V.1 Routine risk minimization measures

Description of routine risk minimization measures by safety concern are presented in Table Part V–1 and Table Part V–2.

Table Part V–1: Routine risk minimization measures by safety concern for patients aged 1 month to less than 4 years

Safety concern	Routine risk minimization activities
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	**Routine risk communication:** SmPC Section 4.4 (Special warnings and precautions) and Section 4.6 (Fertility, pregnancy and lactation) **Routine risk minimization activities recommending specific clinical measures to address the risk:** None **Other routine risk minimization measure beyond the product information:** Available by prescription only.

PL=package leaflet; SmPC=summary of product characteristics

Table Part V–2: Routine risk minimization measures by safety concern for patients aged 4 years and older

Safety concern	Routine risk minimization activities
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	**Routine risk communication:** Summary of Product Characteristics (SmPC) Section 4.4 (Special warnings and precautions) and SmPC Section 4.6 (Fertility, pregnancy and lactation) **Routine risk minimization activities recommending specific clinical measures to address the risk:** None **Other routine risk minimization measure beyond the product information:** Available by prescription only.

SmPC=summary of product characteristics

V.2 Additional risk minimization measures

Routine risk minimization activities as described in Part V.1 are sufficient to manage the safety concerns of the medicinal product. Additional risk minimization measures are not considered necessary.

V.3 Summary of risk minimization measures

Table Part V–3 and Table Part V–4 provides a summary table of pharmacovigilance activities and risk minimization activities by safety concerns.

Table Part V–3: Summary table of pharmacovigilance activities and risk minimization activities for patients aged 1 month to less than 4 years

Safety concern	Risk minimization measures	Pharmacovigilance activities
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	Routine risk minimization measures: Available by prescription only SmPC Section 4.4 (Special warnings and precautions) and Section 4.6 (Fertility, pregnancy and lactation) Additional risk minimization measures: None	Routine PhV: Signal detection efforts, including data mining of spontaneous reports, literature review, and review of UCB safety data summary line listings and cumulative tabulations. Additional PhV activities: European and International Registry of Antiepileptic Drugs and North American Antiepileptic Drug Pregnancy Registry

PhV=pharmacovigilance; PL=package leaflet; SmPC=summary of product characteristics

Table Part V–4: Summary table of pharmacovigilance activities and risk minimization activities for patients aged more 4 years

Safety concern	Risk minimization measures	Pharmacovigilance activities
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	Routine risk minimization measures: Available by prescription only Summary of Product Characteristics Section 4.4 (Special warnings and precautions) and Section 4.6 (Fertility, pregnancy and lactation) Additional risk minimization measures: None	Routine Pharmacovigilance (PhV): Signal detection efforts, including data mining of spontaneous reports, literature review, and review of UCB safety data summary line listings and cumulative tabulations. Additional PhV activities: European and International Registry of Antiepileptic Drugs and Pregnancy and North American Antiepileptic Drug Pregnancy Registry

PhV=pharmacovigilance

PART VI SUMMARY OF THE RMP

SUMMARY OF THE RMP FOR KEPPRA/LEVETIRACETAM UCB

This is a summary of the RMP for Keppra®/Levetiracetam UCB. The RMP details important risks of Keppra/Levetiracetam UCB, how these risks can be minimized, and how more information will be obtained about levetiracetam's risks and uncertainties (missing information).

The SmPC of Keppra/Levetiracetam UCB and its package leaflet give essential information to healthcare professionals and patients on how Keppra/Levetiracetam UCB should be used.

This summary of the RMP for Keppra/Levetiracetam UCB 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 Keppra/Levetiracetam UCB's RMP.

I The medicine and what it is used for

Keppra/Levetiracetam UCB is authorized as a monotherapy for treatment of partial-onset seizures with or without secondary generalization in adults and adolescents from 16 years of age with newly diagnosed epilepsy and as an adjunctive therapy for partial-onset seizures with or without secondary generalization in adults, children, and infants from 1 month of age with epilepsy, myoclonic seizures in adults and adolescents from 12 years of age with juvenile myoclonic epilepsy, and primary generalized tonic-clonic seizures in adults and adolescents from 12 years of age with idiopathic generalized epilepsy (see SmPC for the full indication). Keppra contains levetiracetam as the active substance and is given via oral routes in the following strengths: tablets: 250mg, 500mg, 750mg, 1000mg; oral solution: 100mg/mL; and concentrate for solution for infusion: 100mg/mL.

Further information about the evaluation of Keppra/Levetiracetam UCB benefits can be found in Keppra/Levetiracetam UCB 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/keppra.

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

Important risks of Keppra/Levetiracetam UCB, together with measures to minimize such risks and the proposed studies for learning more about Keppra/Levetiracetam UCB risks, are outlined below.

Measures to minimize the risks identified for medicinal products can be as follows:

- 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
- The authorized pack size: the amount of medicine in a pack is chosen so as to ensure that the medicine is used correctly

- The medicine's legal status: the way a medicine is supplied to the patient (eg, with or without prescription) can help minimize its risks

Together, these measures constitute routine risk minimization measures.

In the case of Keppra/Levetiracetam UCB, these measures are supplemented with additional risk minimization measures mentioned under relevant important risks, below.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including periodic safety update report assessment 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 Keppra/Levetiracetam UCB is not yet available, it is listed under "missing information" below.

II.A List of important risks and missing information

Important risks of Keppra/Levetiracetam UCB are risks that need special risk management activities to further investigate or minimize 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 Keppra/Levetiracetam UCB. 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 (eg, on the long-term use of the medicine).

Table Part VI−1: List of important risks and missing information

List of important risks and missing information for 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
List of important risks and missing information for 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

II.B Summary of important risks and missing information

Table Part VI–2: Summary of important risks and missing information (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	
Risk minimization measures	Routine risk minimization measures: Available by prescription only SmPC Section 4.4 (Special warnings and precautions) and Section 4.6 (Fertility, pregnancy and lactation) Additional risk minimization measures: None
Additional pharmacovigilance activities	European and International Registry of Antiepileptic Drugs and Pregnancy and North American Antiepileptic Drug Pregnancy Registry

PL=package leaflet; SmPC=summary of product characteristics

Table Part VI−3: Summary of important risks and missing information (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	
Risk minimization measures	Routine risk minimization measures: Available by prescription only Summary of Product Characteristics Section 4.4 (Special warnings and precautions) and Section 4.6 (Fertility, pregnancy and lactation) Additional risk minimization measures: None
Additional pharmacovigilance activities	European and International Registry of Antiepileptic Drugs and Pregnancy and North American Antiepileptic Drug Pregnancy Registry

II.C Postauthorization development plan

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

There are no studies which are conditions of the marketing authorization or specific obligation of Keppra/Levetiracetam UCB.

II.C.2 Other studies in postauthorization development plan

Additional pharmacovigilance activities include the following:

Registry studies to monitor pregnancy outcomes: support of EURAP and NAAPR.

Activities include provision of requested data from registries to UCB and regular review of interim outputs from the registries. The protocols for EURAP and NAAPR include possible activities to follow-up on the children.

Prescribers and reporters of pregnancy cases are encouraged to register pregnant women exposed to AEDs into the EURAP or NAAPR. Also, women can register themselves directly with the NAAPR, and they are encouraged to do so in the US Medication Guide.

PART VII ANNEXES

ANNEX 4 SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

Not applicable

ANNEX 6 DETAILS OF PROPOSED ADDITIONAL RISK MINIMIZATION ACTIVITIES

Not applicable