Summary of risk management plan for lacosamide

This is a summary of the risk management plan (RMP) for lacosamide (LCM). The RMP details important risks of LCM, how these risks can be minimized, and how more information will be obtained about LCM risks and uncertainties (missing information).

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

This summary of the RMP for LCM should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all 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 LCM RMP.

1 THE MEDICINE AND WHAT IT IS USED FOR

Lacosamide is authorized as monotherapy and adjunctive therapy in the treatment of partial-onset seizures with or without secondary generalization in adults, adolescents and children from 4 years of age with epilepsy (see Summary of Product Characteristics [SmPC] for the full indication). Lacosamide is also indicated as adjunctive therapy in the treatment of primary generalized tonic-clonic seizures in adults, adolescents, and children from 4 years of age with idiopathic generalized epilepsy. It contains LCM as the active substance and it is given by oral tablet in the following strengths: 50mg, 100mg, 150mg, and 200mg film-coated tablets, or by 10mg/mL syrup, or by injection of 10mg/mL solution for infusion.

Further information about the evaluation of LCM benefits can be found in LCM EPAR, including in its plain-language summary, available on the European Medicines Agency website, under the medicine's webpage: https://www.ema.europa.eu/en/medicines/human/EPAR/vimpat.

2 RISKS ASSOCIATED WITH THE MEDICINE AND ACTIVITIES TO MINIMIZE OR FURTHER CHARACTERISE THE RISKS

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

Measures to minimize 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;
- 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 (eg, with or without prescription) can help to minimize its risks.

Together, these measures constitute routine risk minimization measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including periodic safety update report assessment so that prompt action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

If important information that may affect the safe use of LCM is not yet available, it is listed under 'missing information' in Table 2-1 below.

2.1 List of important risks and missing information

Important risks of LCM 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 LCM. 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 2–1: List of important risks and missing information

Important identified risks	Cardiac AEs that may be potentially associated with PR interval prolongation or sodium channel modulation
Important potential risks	None
Missing information	Pregnant or lactating women Impact on long-term growth, long-term neurodevelopment, and on puberty in pediatric population aged 4 to < 16 years

AE=adverse event

2.2 Summary of important risks

Table 2–2: Summary of important risks

Important identified risk: Cardiac AEs that may be potentially associated with PR interval prolongation or sodium channel modulation	
Evidence for linking the risk to the medicine	Prolongations in PR interval with lacosamide (LCM) have been observed in clinical studies. A phase 1 study revealed a small dose related increase in the mean PR interval with LCM treated subjects. Nonclinical studies revealed an interaction with LCM and cardiac sodium channels which could potentially affect normal cardiac electrophysiology. This risk was upgraded by UCB from important potential risk to important identified risk based on a cumulative analysis of postmarketing data which indicated a causal relationship with LCM.
Risk factors and risk groups	The risk factors for developing AEs related to PR prolongation include a presence of pre-existing heart failure or a recent myocardial infarction or known conduction abnormalities (Ryvlin et al, 2013; Strzelczyk et al, 2008; Rocamora et al, 2003).

Table 2–2: Summary of important risks

	Studies on the risk factors for AEs related to PR prolongation have been done in the general population. The incidence of atrial fibrillation increases with age (Friberg et al, 2010). Other risk factors for atrial fibrillation include a history of hypertension, cardiac diseases including valvular, ischemic and congestive heart failure (Krahn et al, 1995).The frequency of cardiac syncope also increases with age from approximately 1.1% in people less than 40 years to 16% in individuals more than 75 years of age (Rvylin et al, 2013; Olde et al, 2009; Ungar et al, 2006). Ictal bradycardia is most prevalent in individuals with temporal lobe epilepsy (Monté et al, 2007; Reeves et al, 1996). There is no data available on the risk factors specific to antiepileptic drugs (AEDs). Lacosamide should be used with caution in patients with underlying proarrhythmic conditions such as patients with known cardiac conduction problems or severe cardiac disease (eg, myocardial ischemia/ infarction, heart failure, structural heart disease or cardiac sodium channelopathies) or patients treated with medicinal products affecting cardiac conduction, including antiarrhythmics and sodium channel blockers. Older age (>65 years) and/or iv therapy were not identified as independent risk factors.
Risk minimization measures	Routine risk minimization measures: Summary of Product Characteristics (SmPC) Section 4.2 (Posology and method of administration - iv formulation), SmPC Section 4.3 (Contraindications), SmPC Section 4.4 (Special warnings and precautions for use), SmPC Section 4.5 (Interaction with other medicinal products and other forms of interaction), SmPC Section 4.8 (Undesirable effects), SmPC Section 5.3 (Preclinical safety data) Available by prescription only Additional risk minimization measures: None
Missing information: Pregnant or lactating women	
Risk minimization measures	Routine risk minimization measures: SmPC Section 4.6 (Fertility, pregnancy and lactation), SmPC Section 5.3 (Preclinical safety data) Additional risk minimization measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: participation in and sponsorship of pregnancy registries (European and International Registry of AEDs in Pregnancy [EURAP] and North American AED Pregnancy Registry [NAAPR]) See Section 2.3.2 of this summary for an overview of the post-authorization development plan.
Missing information: Impact on long-term growth, long-term neurodevelopment, and on puberty in pediatric population aged 4 to < 16 years	
Risk minimization measures	Routine risk minimization measures: No additional wording in SmPC Available by prescription only. Additional risk minimization measures: None

Table 2–2: Summary of important risks

Additional pharmacovigilance activities	Additional pharmacovigilance activities: ongoing pediatric studies with a follow-up of up to 2 years in SP848/EP0034 and of up to 5 years in EP0012 (according to the actual study protocols). See Section 2.3.2 of this summary for an overview of the post-authorization development plan.

AE=adverse event; AED=antiepileptic drug; EURAP=European and International Registry of AEDs in Pregnancy; LCM=lacosamide; NAAPR=North American AED Pregnancy Registry; SmPC=summary of product characteristics

2.3 Postauthorization development plan

2.3.1 Studies which are conditions of the marketing authorisation

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

2.3.2 Other studies in post-authorisation development plan

Additional pharmacovigilance activities include the following:

- Registry studies to monitor pregnancy outcomes: participation in and sponsorship of European and International Registry of Antiepileptic Drugs (AEDs) in Pregnancy (EURAP) and in the North American AED Pregnancy Registry (NAAPR).

Activities include provision of requested data from UCB to the registries 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 and North American AED Pregnancy Registry. References to registries are included on the pregnancy follow-up letter, US Call Center script, and on information for Medical Science Liaisons.

- Ongoing clinical trials in pediatric patients (ie, studies SP848, EP0034) with a follow-up of up to 2 years. Study EP0012 includes pediatric patients, who are followed for up to 5 years. (according to the actual study protocols):
  - Endocrinology, body weight, height, and calculated BMI will be measured in the studies per protocol. In addition, EP0034 will collect head circumference.Neurodevelopmental maturation will be assessed in the pediatric studies as per protocol by the investigator using physical examination and neurodevelopmental validated scales including: Achenbach CBCL, BRIEF/BRIEF-P, Tanner staging.

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