EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

27 June 2019
EMA/CHMP/441053/2019
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Lacosamide UCB

International non-proprietary name: lacosamide

Procedure No. EMEA/H/C/005243/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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Administrative information

Name of the medicinal product:	Lacosamide UCB
Applicant:	UCB Pharma S.A. Allee de la Recherche 60 B-1070 Brussels BELGIUM
Active substance:	LACOSAMIDE
International Non-proprietary Name/Common Name:	lacosamide
Pharmaco-therapeutic group (ATC Code):	antiepileptics, other antiepileptics (N03AX18)
Therapeutic indication(s):	Lacosamide UCB is indicated as monotherapy and adjunctive therapy in the treatment of partial-onset seizures with or without secondary generalisation in adults, adolescents and children from 4 years of age with epilepsy
Pharmaceutical form(s):	Film-coated tablet; Solution for infusion; Syrup
Strength(s):	10 mg/ml, 50 / 100/ 150 / 200 mg, 50 mg, 100 mg, 150 mg and 200 mg
Route(s) of administration:	Intravenous use and Oral use
Packaging:	blister (PVC/PVDC/alu), bottle (glass) and vial (glass)
Package size(s):	14 tablets, 14 x 1 tablets (unit dose), 168 (3 x 56) tablets (multipack), 168 tablets, 28 tablets, 56 tablets, 56 x 1 tablets (unit dose), Treatment initiation pack: 14 tablets + 14 tablets + 14 tablets + 14 tablets, 1 bottle + 1 measuring cup + 1 oral syringe + 1 adaptor, 1 vial and 5 vials

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List of abbreviations

AED	Antiepileptic Drugs
CHMP	Committee for Medicinal Products for Human Use
CNS	Central Nervous System
CRMP-2	Collapsin Response Mediator Protein-2
EC	European Community
EMA	European Medicines Agency
EU	European Union
GCP	Good Clinical Practices
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practices
MAA	Marketing Authorisation Application
NA	Not applicable
SmPC	Summary of Product Characteristics.
VGSC	Voltage-Gated Sodium Channels
VNS	Vagus Nerve Stimulation

1. Background information on the procedure

1.1. Submission of the dossier

The applicant UCB Pharma S.A. submitted on 2 April 2019 an application for marketing authorisation to the European Medicines Agency (EMA) for Lacosamide UCB, through the centralised procedure under Article 3 (2)(a) of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 15 November 2018.

The applicant applied for the following indication:

Lacosamide UCB is indicated as monotherapy and adjunctive therapy in the treatment of partial-onset seizures with or without secondary generalisation in adults, adolescents and children from 4 years of age with epilepsy.

The legal basis for this application refers to:

Article 10(c) of Directive 2001/83/EC – relating to informed consent from a marketing authorisation holder for an authorised medicinal product

The application submitted is composed of administrative information, quality, non-clinical and clinical data with a letter from the MAH of Vimpat, UCB Pharma S.A. allowing the cross reference to relevant quality, non-clinical and/or clinical data.

This application is submitted as a multiple of Vimpat authorised on 29 August 2008 in accordance with Article 82.1 of Regulation (EC) No 726/2004.

Information on Paediatric requirements

Not applicable

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

New active Substance status

The applicant indicated the active substance lacosamide contained in the above medicinal product to be considered as a known active substance.

Scientific advice

The applicant did not seek Scientific advice at the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Filip Josephson Co-Rapporteur: N/A

The application was received by the EMA on	2 April 2019
The procedure started on	29 April 2019
The Rapporteur's first Assessment Report was circulated to all CHMP members on	4 June 2019
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	14 June 2019
The Rapporteurs circulated the updated CHMP Assessment Report on	20 June 2019
The Rapporteurs circulated the updated PRAC Assessment Report on	20 June 2019
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Lacosamide UCB on	27 June 2019

2. Scientific discussion

2.1. Problem statement

Lacosamide was synthesized as a member of a family of functionalized amino acids, more specifically, analogues of the endogenous amino acid and NMDA-receptor modulator D-serine.

The mechanism of action of lacosamide has to be considered still not fully elucidated. *In vitro* electrophysiological studies have shown that lacosamide selectively enhances slow inactivation of voltage-gated sodium channels (VGSC), resulting in stabilization of hyperexcitable neuronal membranes..

Lacosamide showed an antiepileptic activity in different rodent seizure models for generalized and complex partial-onset seizures and status epilepticus.

2.1.1. Disease or condition

Epilepsy which is defined by the recurrence of spontaneous/unprovoked seizures – i.e. seizures not provoked by systemic, metabolic or toxic disorders – constitutes a vast ensemble of very diverse clinical situations which differ by age of onset, type of seizures, aetiological background, resulting handicap, prognosis and response to treatment.

2.1.2. Epidemiology

More than 50 million adults and children are estimated to suffer from epilepsy world-wide. The two highest peaks of incidence are in children and in the elderly population (above 65 years). A prevalence estimate of epilepsy in the total population varies from 4 to 8 per 10000 subjects.

2.1.3. Clinical presentation, diagnosis

The classification of epileptic seizures is based on clinical manifestation. The 3 main types are generalized, partial-onset (which may become secondarily generalized), and unclassified. Partial-onset epilepsies, associated with a local cerebral lesion, are the most frequent, representing approximately 60% of cases. Generalized epilepsies represent approximately 30% of cases. In the remaining 10% of seizures, the classification is uncertain.

2.1.4. Management

Although some forms of epilepsy may benefit from surgical treatment and others may not require any treatment at all, most patients with epilepsy require chronic pharmacological therapy. In the past decade, several new options for the medical treatment of epilepsy have been introduced, including novel antiepileptic drugs (AEDs) and vagus nerve stimulation (VNS). The new AEDs differ from older agents in several important ways, including mechanism of action, spectrum of activity, and pharmacokinetics. However, more than 30% of patients still have inadequate seizure control or experience significant adverse drug effects on currently available AEDs. Therefore, there is still a need for AEDs with improved effectiveness and tolerability.

2.2. About the product

Lacosamide is a member of a series of functionalized amino acids that were specifically synthesized as anticonvulsant drug candidates. The mechanism of action for lacosamide is incompletely known but is thought to involve an enhancement of the slow inactivation of sodium channels, resulting in stabilization of hyperexcitable physiological neuronal excitability.

Lacosamide was authorised in 2008 with the indication "Adjunctive therapy in the treatment of partial onset seizures with or without secondary generalization in patients with epilepsy aged 16 years and older". The approval comprised three different pharmaceutical formulations:

- film-coated tablets containing 50, 100, 150 and 200 mg of lacosamide as active substance,
- oral solution containing 15 mg/ml of lacosamide as active substance,
- solution for infusion containing 10 mg/ml of lacosamide as active substance

The indication has been changed twice. In 2017, lacosamide was approved for monotherapy in the treatment of partial onset seizures with or without secondary generalization in patients with epilepsy aged 16 years and older, and later in the same year a paediatric indication was approved. Since then, the indication is

Monotherapy and adjunctive therapy in the treatment of partial-onset seizures with or without secondary generalisation in adults, adolescents and children from 4 years of age with epilepsy.

The 15 mg/ml oral solution was withdrawn from the marked in 2011 because of precipitation and in the end of 2011, 10 mg/ml oral solution was approved.

Type of Application and aspects on development

Lacosamide UCB is submitted under an informed consent application, article 10(c) of directive 2001/83/EC with reference made to Vimpat.

This informed consent application is a complete true duplicate of Vimpat including the same indication, all pharmaceutical forms, strengths and presentations as approved for Vimpat.

2.3. Quality aspects

Lacosamide UCB is submitted under an informed consent application, article 10(c) of directive 2001/83/EC. Reference is made to Vimpat (EU/H/C/000863). The applicant refers to module 3 of Vimpat MA. Therefore, the quality data in support of Lacosamide UCB MAA are identical to the up-to-date quality data of Vimpat dossier, which have been assessed and authorised by the CHMP. No new quality data have been submitted.

2.4. Non-clinical aspects

2.4.1. Introduction

Lacosamide UCB is submitted under an informed consent application, article 10(c) of directive 2001/83/EC. Reference is made to Vimpat (EU/H/C/000863). The applicant refers to module 4 of Vimpat MA. Therefore, the non-clinical data in support of Lacosamide UCB MAA are identical to the up-to-date non-clinical data of the Vimpat dossier, which have been assessed and authorised by the CHMP. No new non-clinical data have been submitted.

2.4.1. Ecotoxicity/environmental risk assessment

According to the applicant, no increase in the population exposed to Lacosamide UCB and Vimpat compared to the exposure to Vimpat alone is expected because of generic substitution.

Further, the applicant concludes that a possible significant increase of the environmental exposure to the drug substance, is not expected following the launch of Lacosamide UCB product as a generic to the already approved Vimpat, and it is therefore justified not to provide a full ERA with this informed consent application.

2.5. Clinical aspects

Lacosamide UCB is submitted under an informed consent application, article 10(c) of directive 2001/83/EC. Reference is made to Vimpat (EU/H/C/000863) including all indications, pharmaceutical forms, strengths and presentations, authorised and granted in the EU. The applicant refers to module 5 of Vimpat MA. Therefore, the clinical data in support of Lacosamide UCB MAA are identical to the up-to-date clinical data of Vimpat dossier, which have been assessed and authorised by the CHMP. No new clinical data have been submitted.

2.6. Risk Management Plan

The applicant has submitted a common RMP for Vimpat and Lacosamide UCB which was updated as part of the informed consent procedure (version 14.0, DLP 30 Nov 2015, signed 12 Mar 2019).

Safety concerns

Summary of safety concerns	
Important identified risks	Cardiac AEs that may be potentially associated with PR interval prolongation or sodium channel modulation Suicidality Dizziness
Important potential risks	Potential for hepatotoxicity Potential for worsening of seizures Potential for abuse as a CNS-active product Potential for off-label use of a loading dose in acute conditions such as status epilepticus
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

Pharmacovigilance plan

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

- Specific adverse reaction follow-up questionnaires for cardiac AEs that may be potentially associated with PR interval prolongation or sodium channel modulation to facilitate prompt follow-up of relevant information.

- Other forms of routine pharmacovigilance activities:
    - An independent Data Monitoring Committee is in place for study SP0982 to review the safety data related to the risk of absence and/or myoclonic seizures of patients with idiopathic generalized epilepsy with generalized tonic-clonic seizures.

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.

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, and EP0012) 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):
    - Endocrinology, body weight, height, calculated BMI, and head circumferences will be measured in the pediatric studies as per protocol.
    - 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, BRIEFP/BRIEF, Tanner staging.

Risk minimisation measures

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Cardiac AEs that may be potentially associated with PR interval prolongation or sodium channel modulation	**Routine risk minimization measures:** 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	**Routine PhV activities beyond adverse reactions reporting and signal detections:** specific cardiac follow-up query. **Additional PhV activities:** None

Suicidality	**Routine risk minimization measures:** SmPC Section 4.4 (Special warnings and precautions for use) SmPC Section 4.8 (Undesirable effects) Available by prescription only Packaging **Additional risk minimization measures:** None	**Routine PhV activities beyond adverse reactions reporting and signal detection:** None **Additional PhV activities:** None
Dizziness	**Routine risk minimization measures:** SmPC Section 4.2 (Posology and method of administration) SmPC Section 4.4 (Special warnings and precautions for use) SmPC Section 4.7 (Effects on ability to drive and use machines) SmPC Section 4.8 (Undesirable effects) **Additional risk minimization measures:** None	**Routine PhV activities beyond adverse reactions reporting and signal detection:** None **Additional PhV activities:** None
Potential for hepatotoxicity	**Routine risk minimization measures:** SmPC Section 4.8 (Undesirable effects), SmPC Section 5.3 (Preclinical safety data) Available by prescription only **Additional risk minimization measures:** None	**Routine PhV activities beyond adverse reactions reporting and signal detection:** None **Additional PhV activities:** None
Potential for worsening of seizures	**Routine risk minimization measures:** SmPC Section 4.4 (Special warnings and precautions for use), SmPC Section 4.8 (Undesirable effects) Available by prescription only **Additional risk minimization measures:** None	**Routine PhV activities beyond adverse reactions reporting and signal detection:** Independent Data Monitoring Committee for study SP0982 to review the safety data related to the risk of absence and/or myoclonic seizures of patients with idiopathic generalized epilepsy with generalized tonic-clonic seizures. **Additional PhV activities:** None
Potential for abuse as a CNS-active product	**Routine risk minimization measures:** SmPC Section 4.8 (Undesirable effects) Available by prescription only. Packaging **Additional risk minimization measures:** None	**Routine PhV activities beyond adverse reactions reporting and signal detection:** None **Additional PhV activities:** None

Potential for off-label use of a loading dose in acute conditions such as status epilepticus	**Routine risk minimization measures:** SmPC Section 4.2 (Posology and method of administration) Available by prescription only **Additional risk minimization measures:** None	**Routine PhV activities beyond adverse reactions reporting and signal detection:** None **Additional PhV activity:** None

Conclusion

The CHMP and PRAC considered that the risk management plan version 14.0 is acceptable.

2.7. Pharmacovigilance

Pharmacovigilance system

The applicant certifies that necessary means to fulfil the tasks and responsibilities listed in Title IX of the Directive 2001/83/EC amended by Directive 2010/84/EU are available, and that the applicant has the services of a qualified person responsible for pharmacovigilance.

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.8. Product information

The proposed PI (separately attached) is identical with the currently approved PI for Vimpat.

Consultation with target patient groups

The applicant has submitted the user test for Vimpat syrup and bridging reports for Vimpat solution for infusion, film-coated tablets and film-coated tablets titration pack. A Bridging statement confirming that the content and layout are identical to Vimpat has been provided. Lacosamide UCB being an informed consent application and its product information being consistent with VIMPAT product information, reference to the last user testing results for Vimpat is sufficient.

Braille

The applicant has committed to express in Braille the tradename and strength on the printed outer cartons for the film-coated tablets and syrup. As the solution for infusion is an intravenous formulation meant to be administered by health professionals only, there will be no braille inscription on the carton.

3. Benefit-Risk Balance

The current application for Lacosamide UCB is an informed consent application according to article 10(c) of Directive 2001/83/EC as amended and Article 82(1) of Regulation (EC) No 726/2004 , making reference to the original product Vimpat (film-coated tablets, syrup and solution for infusion) for which a marketing authorisation was granted in the EU under EMA reference number EMEA/H/C/000863, to the same MAH UCB Pharma S.A, since 29 August 2008.

This informed consent application is a complete true duplicate of Vimpat including the same indication, all pharmaceutical forms, strengths and presentations as approved for Vimpat.

The quality, nonclinical, and clinical data for Lacosamide UCB are identical to Vimpat. No new quality, nonclinical or clinical data have been submitted and no new data are needed.

Overall, the benefit/risk balance of the current procedure is considered favourable.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Lacosamide UCB is favourable in the following indication:

Lacosamide UCB is indicated as monotherapy and adjunctive therapy in the treatment of partial-onset seizures with or without secondary generalisation in adults, adolescents and children from 4 years of age with epilepsy

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP

presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.