EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Vimpat

lacosamide

Procedure no: EMEA/H/C/000863/P46/045

Note

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

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1. Introduction

Lacosamide is a member of a series of functionalized amino acids that were specifically synthesized as anticonvulsive drug candidates.

Lacosamide has been approved as monotherapy and adjunctive treatment in patients with partial onset seizures in the EU (2 years and older for tablets, oral solution [syrup], and intravenous [iv] infusion), US (1 month and older for tablets, oral solution [syrup], and iv infusion), Canada (18 years and older for tablets and iv infusion), and Japan (4 years and older for tablets, dry syrup, and iv infusion).

Lacosamide has also been approved as adjunctive treatment of primary generalized tonic clonic seizures in patients with idiopathic generalized epilepsy in the EU (4 years and older for tablets, oral solution [syrup], and iv infusion), US (4 years and older for tablets, oral solution [syrup], and iv infusion), and Japan (4 years and older for tablets, oral solution [dry syrup], and iv infusion).

As of 31 Aug 2022, LCM has been approved worldwide in over 70 countries.

On 28 November 2022, the MAH submitted a completed paediatric study for Vimpat, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical expert overview has also been provided.

The MAH is of the opinion that no change is deemed necessary to the Vimpat Product Information in view of the data submitted in this application.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that study title and number(s) is ***EP0148:*** *Retrospective cohort study describing treatment pathways through care and estimating potential adverse events in neonatal seizures.* This is a stand-alone study.

2.2. Information on the pharmaceutical formulation used in the study.

The medical chart data were extracted from all patients exposed to oral LCM (n=<11), identified in the CDM. The oral LCM data were combined with the neonates exposed to iv LCM (n=28) from another UCB sponsored study (EP0147) with similar follow up.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report(s) for:

- **EP0148:** Retrospective cohort study describing treatment pathways through care and estimating potential adverse events in neonatal seizures.

EP0148 was a retrospective cohort neonatal study conducted using structured data from the PEDSnet database from 01 Jan 2009 until 30 Jun 2020 (study observation period), including limited medical chart extraction (unstructured data) of 250 patients to identify the adverse events (AEs) or adverse drug reactions in patients treated with UCB compounds (LCM, levetiracetam [LEV], and brivaracetam [BRV]). The primary objective of the study was to describe AED treatment pathways including lines of therapy, dose, time on drugs, medical conditions, and concomitant non-AED prescribing.

The PEDSnet database is a national pediatric clinical research network (CRN) in the United States. All neonates (<30 days at index dose) with a diagnosis code for seizure and/or newborn seizure, treated with any AED during the index hospitalization, taking the first ever prescription issued, were followed for up to 180 days for studying the treatment pathways.

To obtain the 250 patient charts, chart extraction was done for all LCM patients and the remaining patients were selected by simple random sampling for LEV and BRV. For estimating the AEs in the sample, the subjects were followed up for up to 37 days.

The final data tables were delivered on 21 June 2022 and the first version of final report of study results was approved on 15 July 2022.

2.3.2. Clinical study

Description

Methods

Study design

A retrospective descriptive cohort study was conducted using data from PEDSnet database (01 Jan 2009 to 30 Jun 2020), a national pediatric clinical research network (CRN) that collects standardized electronic health record (EHR) data for children in the USA.

All neonates (<30 days at index dose) with a diagnosis code for seizure and/or newborn seizure, treated with any AED during the index hospitalization, taking the first ever prescription issued, were followed for up to 180 days for studying the treatment pathways.

For estimating the AEs, a sample of 250 patients selected for chart review and treated with UCB compounds (LCM, LEV, BRV) were followed up for up to 37 days.

The study was carried out in two steps:

Step I: The study population was initially extracted from the PEDSnet database via SNOMED- CT (Systematized Nomenclature of Medicine-Clinical Terms) codes for seizure and/or newborn seizure and AED prescription codes using the RxNorm terminology for the years 01 Jan 2009 until 30 Jun 2020. Step I addressed the Primary Objective.

Step II: To study the AEs, further patient data were extracted from a sample of 250 medical charts at member hospitals by trained medical personnel. Step II addressed the Secondary Objectives.

Study participants

EP0148 was a retrospective cohort neonatal study conducted using structured data from the PEDSnet database from 01 Jan 2009 until 30 Jun 2020 (study observation period), including limited medical chart extraction (unstructured data) of 250 patients to identify the adverse events (AEs) or adverse drug reactions in patients treated with UCB compounds (LCM, levetiracetam [LEV], and brivaracetam [BRV]).

Among 250 patient charts, chart extraction was done for all LCM patients, and the remaining patients were selected by simple random sampling for LEV and BRV.

Data were collected in 2 steps. During step I data collection, data elements within the PEDSnet database were examined. The PEDSnet database comprised structured data extracted from electronic healthcare records (EHRs). The step I data addressed the primary objective. During step II data

collection, data not available in the PEDSnet database, such as AEs, were collected via chart reviews of the EHRs. The step II data addressed the secondary objectives.

This study did not plan to differentiate between acute seizure treatment and prophylactic treatment, as many neonates start treatment with 1 drug and may continue with that drug even though the reasons for the prescribing change, eg, from symptom control to prevention of further seizures.

Objective(s)

The **primary objective** of this study was to describe antiepileptic drug (AED) treatment pathways, including lines of therapy, dose, time on drugs, medical conditions, and concomitant non AED prescribing.

Based on the characteristics of the three UCB compounds (LCM, LEV, and BRV) with known safety risk profiles in adults and older children, the AEs were estimated in a sample of 250 patients selected for medical chart review and treated with UCB compounds (LCM, LEV, and BRV) to assess similar risk in neonates.

The **secondary objectives** were as follows:

- To estimate the incidence of the selected medical events for 6 system organ classes, namely i) Cardiac disorders, ii) Skin and subcutaneous tissue disorders, iii) Nervous system disorders, iv) Metabolism and nutrition disorders, v) Administration site conditions and injury, and vi) Blood and lymphatic system disorders.
- To estimate the incidence of 2 Standardized Medical Dictionary for Regulatory Activitie Queries, namely i) Drug rash - reaction with eosinophilia and systemic symptoms (DRESS) syndrome and ii) Severe cutaneous adverse reactions.
- To estimate the incidence of any other medical events including morbidities.

Variables and data sources

Descriptive analysis of frequencies, proportions were conducted to describe the treatment pathways.

The PEDSnet database contains data stored in a structured format. During step I, primary outcome variables were studied using the PEDSnet database.

Chart reviews of unstructured data were used to collect data on AE outcome variables in step II.

Results

The original data file in the PEDSnet database consisted of 6,925,908 patients. After using selection criteria, patients born on or after 01 Jan 2009, had at least one hospitalization within 30 days of birth, diagnosed with seizure code and administered an AED within 30 days of birth, and ≥35 weeks of gestational age, 2369 patients were included.

Table 2-1: Attrition table for the study cohort

Step	Selection criterion	Number of patients remaining (% total) n (%)	Number of patients excluded (% prior step) n (%)
1	Total number of patients in PEDSnet database	6,925,908 (100)	NA

Table 2-1: Attrition table for the study cohort

Step	Selection criterion	Number of patients remaining (% total) n (%)	Number of patients excluded (% prior step) n (%)
2	All patients born on or after 01 Jan 2009	2,960,275 (42.742)	3,965,633 (57.258)
3	All patients with at least 1 hospitalization	595,548 (8.599)	2,364,727 (79.882)
4	All patients hospitalized within 30 days of birth	237,057 (3.423)	358,491 (60.195)
5	All hospitalized patients administered an AED within 30 days of birth (administration can be in ED or during hospitalization)	16,229 (0.234)	220,828 (93.154)
6	All patients with diagnosis code for seizure and/or newborn seizure associated with the hospitalization where they received AED therapy	3762 (0.054)	12,467 (76.819)
7	All patients with gestational age ≥35 weeks[a]	2369 (0.034)	1393 (37.028)

AED=antiepileptic drug; ED=emergency department; NA=not applicable
[a]Only patients with gestational age data were included. If gestational age data were unknown or unavailable, those patients were excluded. Data source: EP0148 Table 10-1

Among these 2369 patients with median (interquartile range, IQR) follow up period of 14.0 (6.00, 31.0) days, 1 to 11 AEDs per patient were prescribed and the median (IQR) number of unique AEDs prescribed was 2.00 (1.00, 3.00). Of 2369 patients, 1124 (47.4%) and 33 (1.4%) patients received at least one dose of UCB drugs, ie, LEV and LCM, respectively *(one patient in the LCM group had missing dosing information)*. None of the patients received BRV.

Subjects and study size, including dropouts

Step I:

- In the PEDSnet database after applying selection criteria, 2369 neonates (<30 days) were eligible for the study.

Step II:

- As part of the step II data collection, the medical chart data were extracted from all patients exposed to oral LCM (n=<11), identified in the CDM.
- The oral LCM data were combined with the neonates exposed to iv LCM (n=28) from another UCB sponsored study (EP0147) with the similar follow up. *(The study EP0147 was previously assessed in Procedure No. EMEA/H/C/WS2049/G)*
- The remaining 244 neonates were randomly sampled from those exposed to LEV, later <11 LEV patients were excluded due to their unknown gestational age.

- Overall, 244 chart reviewed patients treated with oral LCM (n=<11) and LEV (n=238) were eligible to include in the study.
- None of the patients were identified in Step I, who were treated with BRV.

Efficacy results

Efficacy was not formally assessed in EP0148.

Safety results

Adverse events were identified using the medical charts, and the medical charts were reviewed in the second part of the study (step II data collection). The step II study results suggest that the study population is critically ill.

The LCM chart reviewed patients (n=34) were aged between 2 and 28 days; the median age (IQR) at the index date was 17.0 (5.2-24.0) days.

The initial dose of LCM was given in the intensive care unit (ICU) for 97.1% of patients, and the mean (SD) initial, maximum, and final daily doses (mg/kg) were 4.0 (3.6), 7.3 (5.0), and 4.4 (2.9), respectively. Most of the patients had ≥3 lines of therapies (70.6%). Most patients had ≥4 LCM administrations (58.8%), and the median (IQR) number of LCM administrations was 27.0 (2.0-57.0). Before the index date, the patients were treated with non-benzodiazepine (BZD) and BZD drugs; 55.9% patients received ≥3 non-BZD AEDs, and 35.3% patients received 2 BZD AEDs. In 91.2% and 73.6% of patients, concomitant use of at least 1 non-BZD AED and 1 BZD AED was observed, respectively.

Among the 34 LCM chart reviewed patients, the median (IQR) duration of follow up period was 25.5 (10.0-33.0) days. During the follow up period, <11 deaths were observed in 34 LCM patients (<32%), 38.2% were discharged from acute inpatient care to rehabilitation level of service, <32% were discharged to home from acute inpatient care, and <32% were given LCM until the end of the follow up period.

Out of the <11 fatalities in LCM chart reviewed patients (n=34), none of the deaths were attributed to LCM by the treating physicians, though <11 patients were on LCM at the time of death. Time after the index date to death ranged from 0 to 15 days. The age at death ranged from 5 to 38 days.

In LCM chart reviewed patients, the incidence rates of adverse events (per 1000 patient days) by diagnostic categories ranged from 1.41 (95% CI 00.4-7.84) for blood and lymphatic system disorders to 7.65 (95% CI 2.49-17.84) for cardiac conditions. None of these events were attributed by the treating physicians to LCM.

There were no patients with events within the following AE diagnostic categories: Skin and subcutaneous tissue disorders, Morbidity diagnoses, Procedural complications, Investigations of ECG indicating long PR, DRESS syndrome, and Severe cutaneous adverse reactions.

2.3.3. Discussion on clinical aspects

The MAH has submitted a report of the results of study EP0148: a retrospective cohort study describing treatment pathways through care and estimating potential adverse events in neonatal seizures. The primary objective of this study was to describe antiepileptic drug treatment pathways in neonates. The efficacy of the different treatments was not formally tested in this study.

As part of the step II data collection, the medical chart data were extracted from all patients exposed to oral LCM (n=<11), identified in the CDM. The step II study results suggest that the study population is critically ill.

The oral LCM data were combined with the neonates exposed to iv LCM (n=28) from another UCB sponsored study (EP0147) with the similar follow up. The study EP0147 was previously assessed in Procedure No. EMEA/H/C/WS2049/G.

The majority (97 %) of the LCM treated patients received the first dose in the intensive care unit. During the follow up period, <11 deaths were observed in 34 LCM patients. Out of the <11 fatalities in LCM chart reviewed patients (n=34), none of the deaths were attributed to LCM by the treating physicians.

In LCM chart reviewed patients, the incidence rates of adverse events (per 1000 patient days) by diagnostic categories ranged from 1.41 (95% CI 00.4-7.84) for blood and lymphatic system disorders to 7.65 (95% CI 2.49-17.84) for cardiac conditions. None of these events were attributed by the treating physicians to LCM.

The MAH is of the opinion that no change is deemed necessary to the Vimpat Product Information in view of the data submitted. This is agreed. The descriptive results of the current study do not impact the current benefit-risk balance of LCM and no evidence of new safety concerns was found.

3. CHMP overall conclusion and recommendation

The results of the current study do not impact the current benefit-risk balance of LCM and no evidence of new safety concerns was found.

The results of EP0148 are being submitted in accordance with Article 46 of Regulation (EC) No 1901/2006 (The Paediatric Regulation).

☒ **Fulfilled:**

No regulatory action required.