25 May 2023
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Human Medicines Division

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/P46/046

Note

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

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Status of this report and steps taken for the assessment				
Current step[1]	**Description**	**Planned date**	**Actual Date**	**Need for discussion[2]**
☐	Start of procedure	27 Mar 2023	27 Mar 2023	☐
☐	CHMP Rapporteur Assessment Report	02 May 2023	03 May 2023	☐
☐	CHMP members comments	15 May 2023	n/a	☐
☐	Updated CHMP Rapporteur Assessment Report	17 May 2023	n/a	☐
☒	CHMP adoption of conclusions:	25 May 2023	25 May 2023	☐

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1. Introduction

On the 27th of March, the MAH submitted a completed paediatric study for lacosamide, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

These data are also submitted as part of the post-authorisation measure(s) <specific obligation(s)>?

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that Lacosamide to treat neonatal seizures EPO149 is a standalone study.

2.2. Information on the pharmaceutical formulation used in the study<ies>

IV lacosamide was given in 82% of the cases, the rest enteral.

2.3. Clinical aspects

2.3.1. Clinical study

Lacosamide to treat neonatal seizures EPO149

Description

EP0149 was a single arm retrospective chart review study to evaluate the use of LCM to treat neonatal seizures in tertiary care centers, assessing its safety and possible effectiveness. The primary objectives were the characterization of the population of newborns whose seizures were treated with LCM and the response of neonatal seizures to LCM treatment. The secondary objective was to characterize the rate and type of adverse events (AEs).

Methods

Patient records of patients born from 2008 to 2020 were reviewed. Chart review data was collected and managed using electronic data capture tools such as Research Electronic Data Capture hosted at Boston Children's Hospital.

For the collection of AEs, patients were followed for up to 30 days from the index date (first exposure to enteral or iv LCM) provided they remained on LCM. For the assessment of effectiveness outcomes, patients were followed during continuous exposure, which was defined as exposure to LCM without the addition of another antiseizure medication (ASM) and without breaks in administration of more than 1 calendar day estimated using time stamps for drug administration.

Due to multiple drug exposure and the historical nature of the data, it was not possible to attribute the cause of an AE to LCM unless stated at the time by the treating physician in the medical chart.

Study participants

Patients were selected for inclusion in EP0149 if they were <44 weeks postmenstrual age (PMA) at seizure onset and LCM treatment for seizures was initiated by 48 weeks PMA. Neonates with a transient cause for seizures (eg, mild hypoglycemia, hyponatremia, hypocalcemia with no associated brain injury) for whom the primary treatment of seizures was the correction of the underlying metabolic abnormality were excluded from the study. The study was a multicenter effort in order to collect a sufficient number of patients to achieve meaningful results (only a few neonates were treated at most centers).

Among 62 patients, the median (interquartile range [IQR]) PMA at index date was 40.3 (39.1, 43.1) weeks and the median (IQR) gestational age was 37.1 (35.6, 39.3) weeks. Sixty-three percent of neonates were born full term (≥37 weeks). Most of the patients were White (69%), female (60%).

Treatments

Lacosamide was given to neonates having seizures. The median (IQR) PMA at seizure onset was 39.2 (37.1, 40.6) weeks. The primary seizure etiologies included presumed or confirmed underlying genetic etiologies (22%), hypoxic ischemic encephalopathy (18%), disorders of cerebral dysgenesis (18%), intracranial hemorrhage (<18%), infection (<18%), ischemic or hemorrhagic neonatal stroke (<18%), and others (<18%). Almost half of the patients (47%) had status epilepticus before the index date, and around one-fifth of the patients each had status epilepticus on the index date (19%) and after the index date (21%). The majority of patients (60%) received ≥4 ASMs before LCM; all patients (100%) received phenobarbital before LCM, and almost all patients (98%) received levetiracetam before LCM.

The median (range) index LCM dose was 5.0 (0.8, 25.1) mg/kg. The route of first LCM administration was iv in 82% of patients. Ninety-five percent of patients received their first dose of LCM in an intensive care unit.

The median (range) length of LCM inpatient treatment was 11 (1, 157) days

Objective(s)

To characterize the population of newborns whose seizures were treated with lacosamide and the response of neonatal seizures to lacosamide treatment

The secondary objective was to characterize the rate and type of adverse events

Outcomes/endpoints

Sample size

62 neonates

Randomisation and blinding (masking)

No, this study was a single arm retrospective chart review study

Statistical Methods

Results

Participant flow

Recruitment

Baseline data

Number analysed

Efficacy results

Among 20 patients, EEG evidence of seizure cessation during exposure to LCM (regardless of the introduction of another drug post LCM initiation) demonstrated that 45% of patients were seizure free at 1 day and by 30 days each. Among 11 patients, EEG evidence of seizure cessation during continuous exposure to LCM (without introduction of another drug post LCM initiation) demonstrated that 46% and 45% patients were seizure free at 1 day and by 30 days, respectively. Lacosamide continuation, the patient still receiving iv or enteral lacosamide at the end of the 30 days follow up period was observed in 53%. 72% of the patients were discharged home or transferred to another clinic on Lacosamide suggesting the clinicians may have attributed a beneficial effect to lacosamide

Safety results

The median (IQR) duration of follow up for AE and effectiveness evaluations were 15 (7, 30) days and 4 (2, 9) days, respectively.

During the AE follow-up period, 11 deaths were observed. None of the deaths were attributed to LCM. In < 11 patients the reason of death was the withdrawal of medical technology

From the currently available safety data for lacosamide, there was no evidence of any new safety concern. During the median (IQR) follow up of 15 (7, 30) days, the incidence rates per 1000 patient days for each AE were as follows: cardiac disorders (5.2), skin and subcutaneous tissue disorders (1.0), nervous system disorders (2.0), blood and lymphatic system disorders (9.9), other AEs (22.9) and mortality (10.6). The incidence rate by specific AEs were atrial arrhythmia (1.0), bradycardia (5.2), cardiac arrest (2.0), rash (1.0), encephalopathy (1.0), moderate encephalopathy

(1.0), band neutrophil count decreased (1.0), band neutrophil percentage decreased (1.0), eosinopenia/eosinophil count decreased (2.0), lymphopenia/lymphocyte count decreased (1.0), neutropenia/ neutrophil count decreased (4.1), white blood cell count decreased (4.1), other AEs (22.9) and mortality (10.6). None of the AEs were attributed to LCM by the treating physicians

2.3.2. Discussion on clinical aspects

Due to multiple drug exposure, and the historical nature of the data, it is not possible to attribute cause of an AE to LCM unless stated at the time by the treating physician in the medical chart.
• Bias: Channeling by severity may occur as patients who have refractory seizures may be more likely to get LCM and these neonates are more likely to have a greater morbidity burden. This phenomenon means that such patients taking such drugs may appear to have greater numbers of AEs occurring post exposure, even though none are likely to be directly attributable to said drug based on attribution and reporting requirements.
Safety findings (ie, the number of AEs) in neonates exposed to LCM in specialist treatment centers may thus be biased upwards beyond the rate usually observed in less refractory patients treated at non-specialist centers.
• Historical data: Chart extraction are reliant on the original data quality and care taken by the recorder

3. CHMP overall conclusion and recommendation

The CHMP agrees with the conclusion of the study when it comes to the suggested effectiveness although it is hard to determine the effect of a certain AED, especially if it is given in addition to several other AEDs. The CHMP also concurs concerning AEs and think there is no need to change the indications applicable to Lacosamide, neither is it raising any new safety concerns. The MAH suggest that there will be no change in the SmPC text and the CHMP agrees with that opinion.

☒ **Fulfilled:**