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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/P46/043

Note

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

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1. Introduction

On May 5 2022, the MAH submitted a completed paediatric study for lacosamide (Vimpat), in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

2. Scientific discussion

2.1. Information on the development program

N/A

2.2. Information on the pharmaceutical formulation used in the study

Intravenous (i.v.)

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for EP0155: Retrospective cohort study - pharmacokinetics and exposure outcome in neonates administered lacosamide

2.3.2. Clinical study

Retrospective cohort study - pharmacokinetics and exposure outcome in neonates administered lacosamide, report ep0155

Description

Methods

EP0155 was a retrospective cohort study that used electronic healthcare record (EHR) data from the Pediatric Network (PEDSnet) data network. The primary objectives were to evaluate pharmacokinetics (PK) and effectiveness outcomes in neonates exposed to any dose of LCM in clinical practice. The secondary objectives were to estimate the incidence of the selected medical events of interest (6 system organ classes and 2 Standardized Medical Dictionary for Regulatory Activities Queries).

EP0155 used EHR data from the PEDSnet multi-institutional database and University of Michigan C.S. Mott's Children's Hospital. Data from both databases are stored in the Patient-Centered Clinical Research Network (PCORnet®) database common data model (Version 5.1), where all elements are in a structured format.

Electronic healthcare record data from 01 Jan 2009 to 29 Feb 2020 were extracted from the PCORnet database. Patients were selected for inclusion in EP0155 based on LCM exposure only (ie, they did not have to have a diagnosis of epilepsy). Lacosamide could have been used as monotherapy or adjunctive to a prior antiepileptic drug (AED) therapy during an intensive care or in-hospital stay. Patients were followed for a maximum of 30 days.

Study participants

Inclusion criteria:

• Neonates <30 calendar days of age (or gestational age equivalent) on index date

• At least 35 weeks gestational age

• Treated with LCM (iv or oral, any dose) on index date

Exclusion criteria:

• Patients outside the neonatal age range at index date, as they did not fit the criteria of a neonate at treatment onset.

• Patients born very preterm (<35 weeks) as these babies did not have the same seizure etiology which would respond to AED.

Treatments

Objective(s)

Primary objectives:

1. To obtain measurements of pharmacokinetics of lacosamide (plasma concentration) by obtaining drug dosing with time stamps and blood tests with time stamps at any time during the first observable episode of exposure to lacosamide and thereafter up to 30 days.

2. To assess effectiveness outcomes in a noncomparative design, evaluating endpoints within 30 days of drug start.

Secondary objectives

1. To estimate the incidence of the selected medical events for 6 System Organ Classes (SOC) 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; vi) Blood and lymphatic system disorders.

2. Plus 2 Standardized Medical Dictionary for Regulatory Activities Queries (SMQs) namely: i) Drug rash - reaction with eosinophilia and systemic symptoms (DRESS) syndrome; ii) Severe cutaneous adverse reactions.

Outcomes/endpoints

Sample size

The study analyzed data from a convenience sample of patients from both databases. No formal sample size computation was done. A feasibility assessment identified at least 40 patients ever exposed to iv LCM who were < 30 days of age. The study selection criteria were not very restrictive, so it was assumed that the sample size would not be significantly reduced. This sample size was sufficient to evaluate the primary objective of the study which was purely descriptive in nature.

Randomisation and blinding (masking)

N/A

Statistical Methods

Results

Participant flow

Table 10.1: Study cohort attrition table

Step	Selection criterion	No of patients remaining (% Total)	No of patients excluded (% Prior step)
1	Total number of patients (in database)	8,664,168 (100%)	NA (NA)
2	Patients with LCM administration at <30 days of age (based on PCORnet database query)	54 (0.001%)	8,664,114 (99.999%)
3	Patients with LCM administration at <30 days of age (based on chart review determination)*	52 (0.001%)	[redacted]
4	Patients with gestational age >= 35 weeks (determined by chart review)	47 (0.001%)	5 (9.615%)

*=chart reviewers may determine patients didn't actually have LCM dose administration, then those patients would be excluded.
LCM=Lacosamide; NA = not applicable; PCORnet: Patient-Centred Clinical Research Network

Baseline data

Demographics

Table 10.5: Demographic characteristics of the study cohort

Characteristic	Study Cohort
Total number patients	47 (100%)
Age at index Date, days, mean (SD)	13.9 (9.4)
Birth weight, kg (mean, SD)	3.0 (0.6)
Gender, n (%)	
Male	20 (42.6%)
Female	27 (57.4%)

Most common conditions documented before index date by SNOMED-CT code*	
Condition	Study Cohort, n (%)
Seizure disorder	16 (34.0%)
Convulsions in the newborn	15 (31.9%)
Thrombocytopenic disorder	<11
Status epilepticus	<11
Neonatal respiratory failure	<11
Low blood pressure	<11
Nutritional deficiency disorder	<11
Hypoxic ischemic encephalopathy	<11
Blood coagulation disorder	<11
Pulmonary hypertension	<11
Respiratory failure	<11
Respiratory insufficiency	<11
Meconium aspiration syndrome	<11
Small-for-dates baby	<11
Hypoglycemia	<11
Disseminated intravascular coagulation	<11

SCHIP= State Children's Health Insurance Program; SD=Standard deviation; SNOMED-CT= Systematized Nomenclature of Medicine-Clinical Terms

Table 10.7: Seizure history of the cohort

Characteristic	Study Cohort
Total number patients	47 (100.0)
Etiology of first seizure (patients may have >1), n (%)	
HIE	<11
ICH	13 (27.7)
Meningitis	<11
Metabolic/Genetic disorder	<11
Neonatal-onset epilepsy	<11
Other	27 (57.4%)
Perinatal asphyxia	<11
Sepsis	<11
Stroke (ischemic)	<11
Suspected epilepsy/seizure	16 (34.0%)
Age at earliest prior status epilepticus, in days*	
Mean (SD)	9.1 (9.6)
Median (IQR)	3.0 (2.0 - 15.0)
Minimum	0.0
Maximum	27.0
History of seizure before index date, n (%)	44 (93.6%)
History of status epilepticus before index date, n (%)	19 (40.4%)
History of cooling on index date, n (%)	<11
Patients with status epilepticus on the index date, n (%)	<11

Table 10.6: Medication patterns in the study cohort

Characteristic	Study Cohort
Total number patients	47 (100%)
Weight (at index Date), n (%)	
<4kg	38 (80.9%)
4 to 10kg	<11
Count of LCM administrations, n (%)	
1	<11
2	<11
3	<11
4+	29 (61.7%)
Line of therapy – LCM used as what line of therapy among non-benzodiazepine AEDs*	
Median (IQR)	<11
Line 1, n (%)	<11
Line 2, n (%)	17 (36.2%)
Line 3, n (%)	16 (34.0%)
Line 4, n (%)	<11
Line 5, n (%)	<11

Efficacy results

Table 10.3: Follow-up for Effectiveness Evaluation

Characteristic	Study Cohort
Total number patients	47 (100%)
Duration of follow-up period, days	
Mean (SD)	5.5 (7.9)
Median (IQR)	1.0 (1.0 - 6.0)
Minimum	1.0
Maximum	30.0
Reason for censoring at follow-up, n/%**	
LCM cessation if the patient had a break in LCM administration ≥1 calendar day	13 (27.7%)
Addition of any benzodiazepine after the index date	13 (27.7%)
Addition of any new AED that they were not previously taking on or before the index date	<11
End Date was 7 days after the patient's last administered LCM dose	<11
Patient died	<11
Patient reached the end of the maximum 30-day follow-up period	<11
Patient was discharged to home/discharged from in-patient care	<11
Patient was transferred to another hospital	<11

**For censoring, the first censoring event that occurred for the patient was what censored them. The total number of reasons for censoring should add up to the study cohort total.
AED=Antiepileptic drugs; IQR=Interquartile range; LCM=Lacosamide; SD=Standard deviation

In most cases, electroencephalography (EEG) data were only available for up to 3 days, as this was what was deemed clinically necessary for these patients. Therefore, it was considered more appropriate to define outcomes as EEG outcomes rather than effectiveness outcomes.

Electroencephalography data were available for 34 patients on Day 1, for 26 patients on Day 2, and for 21 patients on Day 3, respectively.

On Day 1, in the 31 patients with electrographic seizures, the effectiveness assessment showed that <11 patients had any improvement, <11 patients had no change, and 13 patients (42.0%) had unknown responses. A total of <11 patients had an improvement in seizure burden of >50%.

On Day 2, in the 17 patients with electrographic seizures, <11 patients showed improvement, <11 patients showed no change, and <11 patients had unknown responses.

On Day 3, in the 12 patients with electrographic seizures, <11 patients showed no change in seizure burden, and the response was unknown in the remaining <11 patients.

PK results

Pharmacokinetic data were not available in patient charts for most patients (ie, only <11 patients had any PK data). Given the small number of values, a meaningful analysis of PK data was not possible.

Safety results

Table 10.2: Follow-up for Adverse Event Evaluation

Characteristic	Study Cohort
Total number patients	47 (100%)
Duration of follow-up period, days*	
Mean (SD)	15.3 (10.6)
Median (IQR)	12.0 (7.0 - 28.0)
Minimum	0.0
Maximum	29.0
Reason for censoring at follow-up, n/%	
End Date was 7 days after the patient's last administered LCM dose	15 (31.9%)
Patient died	<11
Patient reached the end of the maximum 30-day follow-up period	<11
Patient was discharged to home/discharged from in-patient care	11 (23.4%)
Patient was transferred to another hospital	<11

*Range of chart review was from index day through day 29 (30 days total)
IQR=Interquartile range; LCM=Lacosamide; SD=Standard deviation

Among the adverse events of special interest (AESIs) for LCM, cardiac arrest was observed in <11 patient; the crude incidence rate per 1000 person-days was <11

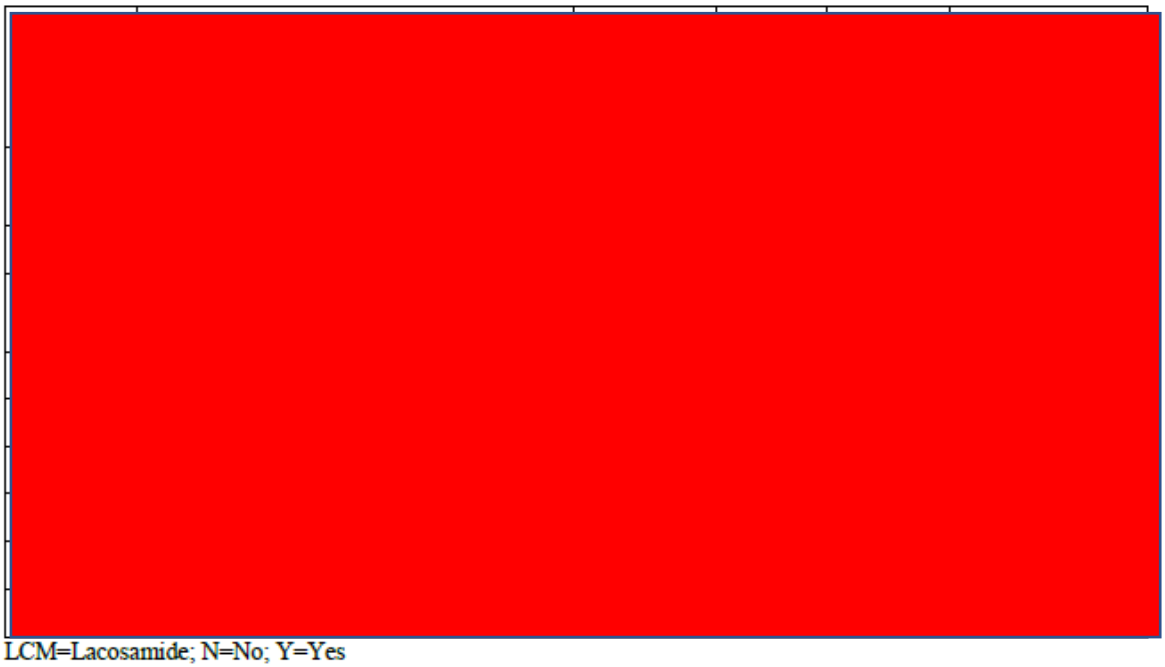
Individual AEs:

DVT (<11 pt), portal vein thrombosis (<11), cardiac arrest (<11), congestive heart failure (<11), hypertension (<11), left ventricular systolic dysfunction (<11), hypotension (<11), systolic murmur (<11), acute injury of the kidney (<11), adrenal cortical hypofunction (<11), diabetes insipidus (<11), electrolytes abnormal (<11), gastritis (<11), hypernatremia (<11), AST (<11), large liver (<11), Necrotizing enterocolitis in fetus or newborn (<11), Pneumothorax (<11), serum creatinine increased

(<11), cerebral ischemia (<11), cerebral ventriculomegaly (<11), thalamic infarction (<11), broken skin (<11), candidiasis of skin (<11), cellulitis of upper limb (<11)

The median duration of follow up for safety evaluations was 12.0 days. During the follow-up period, <11 patients died; none of the deaths were ascribed to LCM in the patients' charts.

Table 10.4: Description of fatal events during the follow-up period in neonates



LCM=Lacosamide; N=No; Y=Yes
* Cause of Death was based on chart reviewer findings as death certificate data was not available. In some cases only immediate or preliminary cause of death was given. When possible, the most specific diagnosis was selected from the chart reviewers' findings as decided by PEDSnet clinician review.
** Time to death was days after index date that patient died. A time of 0 indicated death on the day of the index date

Among the AESI for LCM, cardiac arrest was observed in <11 patient, with a crude incidence rate per 1000 person-days of 1.39 (95% CI: 0.04 to 7.74). For other adverse event categories, crude incidence rates per 1000 person-days ranged from 2.81 (95% CI: 0.34 to 10.16) each for blood or lymphatic system disorders and nervous system disorders to 12.46 (95% CI: 5.38 to 24.55) for morbidity diagnoses. No adverse events were attributed to LCM by the treating physician.

No adverse events were attributed to LCM by the treating physicians.

Overall, no new safety concerns were observed, and the results of the study do not impact the current benefit-risk balance of LCM.

2.3.3. Discussion on clinical aspects

In this retrospective study, effectiveness and safety of LCM was evaluated in the acute treatment of neonatal seizures.

Forty-seven neonates (<30 days of age) met the study eligibility criteria. Almost all of the neonates received their first dose of LCM in the ICU (n=46; 97.9%), and three-fifths of patients (n=29; 61.7%) received more than four administrations of LCM. The median (IQR) number of

days on LCM was 10.0 (1.0 - 28.0) days. Phenobarbital (n=37; 78.7%), fosphenytoin (n=29; 61.7%) and LEV (n=27; 57.4%) were the most commonly used AEDs before index date.

Approximately 94% and 40% of the study patients had history of seizure and status epilepticus, respectively, before index date. About 21% of patients had status epilepticus on the index date. Reported underlying conditions were suspected epilepsy or seizure (n=16; 34%), intracranial hemorrhage (27.7%), sepsis (<11%), and meningitis (<11%).

In most cases, EEG data were available for up to 3 days, as this was what was deemed clinically necessary for these patients. EEG data were available on day 1, day 2 and day 3 for 34, 26 and 21 patients, respectively. In patients who were on LCM and did not receive any new AED,electrographic seizures were present on days 1, 2 and 3 in 31, <11 and <11patients, respectively. On days 1 and 2, any improvement in seizures was observed in <11 neonates and <11 neonate, respectively.

The population included in this study was critically ill. During the median duration of follow up, ie, 12.0 (7.0 - 28.0) days, <11 patients died. Cardiac arrest was observed in one patient.

Various AEs occurred, the majority only in one patient. Hypotension and adrenal cortical hypofunction were reported in <11 patients each, congestive heart failure, hypertension, acute injury of the kidney and diabetes insipidus in <11 patients each. None of these events or deaths were attributed by the treating physician to LCM. No evidence of new safety concerns was found.

The current study has limitations, ie, retrospective design, small sample size and the lack of a control arm. Comparative studies are required to enable any conclusions on the effectiveness and safety of LCM in neonatal seizures.

3. Rapporteur's CHMP overall conclusion and recommendation

In accordance with Article 46, the MAH has provided the final study report of "Retrospective cohort study - pharmacokinetics and exposure outcome in neonates administered lacosamide". In this retrospective study the primary objectives were to evaluate pharmacokinetics (PK) and effectiveness outcomes in neonates exposed to any dose of LCM in clinical practice and the secondary objectives were to estimate the incidence of the selected medical events of interest.

Of the 47 patients in EP0155, the mean age at the index date was 13.9 days and the mean birthweight was 3.0 kg, respectively. The most common aetiology of first seizure was suspected epilepsy (34.0%), followed by intracranial haemorrhage (27.7%), and sepsis and hypoxic ischemic encephalopathy (<11%each). On the index date, <11%of patients had status epilepticus.

PK data was not available in the patient charts for most patients, only for <11 patients. No PK data is presented which is accepted, however in a future submission it is encouraged that the PK observations are reported.

The median (interquartile range [IQR]) duration of follow up for the effectiveness evaluation was 1.0 (1.0 to 6.0) days and the median (IQR) duration of follow up for the adverse event evaluation was 12.0 (7.0 to 28.0) days. Approximately 70% of patients had LCM used as a second or third line of therapy. The most commonly used (non-benzodiazepine) AEDs before the index date were phenobarbital (PB) (78.7%), fosphenytoin (61.7%), and levetiracetam (LEV) (57.4%). In most cases, electroencephalography (EEG) data were only available for up to 3 days, as this was what was deemed clinically necessary for these patients. The effectiveness based on EEG outcome was not possible to determine due to a small sample size and a high percentage of missing data.

During the safety follow-up period of a median 12 days, <11 patients died, however none of the deaths were deemed related to lacosamide treatment but probably related to the severe background diseases (see above) for which lacosamide was given.

The MAH considers that no change of the label is deemed necessary and that the results of the study do not impact the current benefit-risk balance of LCM. This is concurred.

The Rapporteur concludes that the MAH has fulfilled its obligation to submit data from this paediatric study in accordance with Art 46. However, the small sample size, effectiveness evaluation based only on EEG data and a short safety follow up do not allow any evaluation of effectiveness or safety and accordingly, the results do not have any impact on the B/R balance of lacosamide. No further actions are required.

☒ **Fulfilled:**

No regulatory action required.