14 December 2023
EMA/575249/2023
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/P46/048

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	16-10-2023	16-10-2023	☐
☐	CHMP Rapporteur Assessment Report	20-11-2023	20-11-2023	☐
☐	CHMP members comments	04-12-2023	n/a	☐
☐	Updated CHMP Rapporteur Assessment Report	07-12-2023	n/a	☐
☒	CHMP adoption of conclusions:	14-12-2023	14-12-2023	☐

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1. Introduction

On October 2, 2023, the MAH submitted a completed paediatric study for EP0081, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that EP0081 study: Drug Use-results Survey on Vimpat Tablet 50 mg, Vimpat Tablet 100 mg and Vimpat Dry syrup 10% is a stand alone study.

2.2. Information on the pharmaceutical formulation used in the study

VIMPAT tablets 50mg, VIMPAT tablets 100mg, and VIMPAT dry syrup 10% used in routine clinical practice were used in this study.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report(s) for:

- EP0081 study: Drug Use-results Survey on Vimpat Tablet 50 mg, Vimpat Tablet 100 mg and Vimpat Dry syrup 10%

2.3.2. Clinical study

EP0081 study: Drug Use-results Survey on Vimpat Tablet 50 mg, Vimpat Tablet 100 mg and Vimpat Dry syrup 10%

Description

EP0081 was a postmarketing survey intended to determine whether there were any concerns with the safety and effectiveness of VIMPAT tablets 50mg, VIMPAT tablets 100mg, and VIMPAT dry syrup 10% (hereinafter referred to as "the Survey Drug") in routine clinical practice settings.

Methods

Study participants

Patients with epilepsy who had newly initiated treatment with the Survey Drug as an adjunctive therapy in the treatment of POS with or without secondary generalization and who had not obtained sufficient response to other antiepileptic drugs (AEDs) were observed over a period of 52 weeks. The

defined evaluation points were 16 weeks and 52 weeks. The patients were followed as per current clinical practices for their condition.

A total of 3000 patients (including pediatric patients who were 16 to <18 years of age) were planned in the survey.

Assessor's comment

No specific inclusion/exclusion criteria were introduced.

Treatments

EP0081 was conducted using a central registration system. The physician registered each patient who had started treatment with LCM. Registration did not occur more than 14 days after the start of treatment. With regard to patients who were observed for less than 16 weeks or 52 weeks (due to drug discontinuation, without visiting medical institutions, etc), the observation periods were considered to be ended on the last Survey Drug intake. In patients who had an operation (such as surgery or vagal nerve stimulation performed for epilepsy treatment), the observation period stopped at the day before the operation. Patients whose treatment with the Survey Drug was discontinued were followed up for 2 weeks after discontinuation of the Survey Drug. The patients were monitored for withdrawal symptoms and rebound phenomenon.

Objective(s)

The main objectives of the EP0081 survey were to detect and understand any issues surrounding safety and the effectiveness of the Survey Drug under routine clinical practice; these included: (1) unexpected/unknown adverse drug reactions (ADRs); (2) ADRs when used in routine clinical practice; (3) factors that may affect safety; and (4) factors that may affect effectiveness.

Outcomes/endpoints

Effectiveness evaluations included:

- Global improvement rating

☐ Assessment was conducted at Week 16 and Week 52 or upon drug withdrawal.

☐ Global improvement rating: Evaluation on a 3-point scale, consisting of "Improved," "Unchanged," and "Worsened" during the observation period. Patients rated as "Improved" were considered as responders.

- Seizure freedom

☐ Presence or absence of seizures during the observation period.

☐ Seizure-free patients were defined as patients who had no seizures throughout the observation period.

Frequency of epileptic seizure

☐ Number of seizures for each seizure type noted within the past 4 weeks, at each time point of Baseline, Week 16, and Week 52, or at drug withdrawal.

Safety

 Adverse events; Presence of adverse event, name of event, date of onset, seriousness, action taken with this drug, treatment of adverse event, outcome, date of outcome, causal relationship with this drug and other potential factor than this drug

 Laboratory results Test item (hematology, clinical chemistry, and others), date of test, test result and presence of abnormality ➢ Measurements of AED levels in blood (if measured); Presence of measurement, date of measurement, name of drug, time from previous dosing and blood level ➢ Withdrawal/ rebound (if treatment is discontinued)

This survey was conducted as a use-results survey in accordance with the Good Post-marketing Study Practice (GPSP) ordinance. Potential confounding bias cannot be ruled out because the survey was performed as an observational study under daily clinical practice without strict patient eligibility criteria.

Sample size

Subjects of the survey Epilepsy patients who have newly initiated the use of this drug as "adjunctive therapy with antiepileptic drugs (AEDs) for the treatment of partial-onset seizures with or without secondary generalization in patients with epilepsy who have not obtained sufficient response to other AEDs" ➢ Sample size of the survey 3,000 subjects ➢ Number of survey sites by specialty 500 – 600 sites of mainly neurology, psychiatry, and neurosurgery.

Statistical Methods

Summary statistics such as ratio, mean, standard deviation, two-sided 95% confidence interval, minimum, 25th percentile, median, 75th percentile, and maximum were calculated.

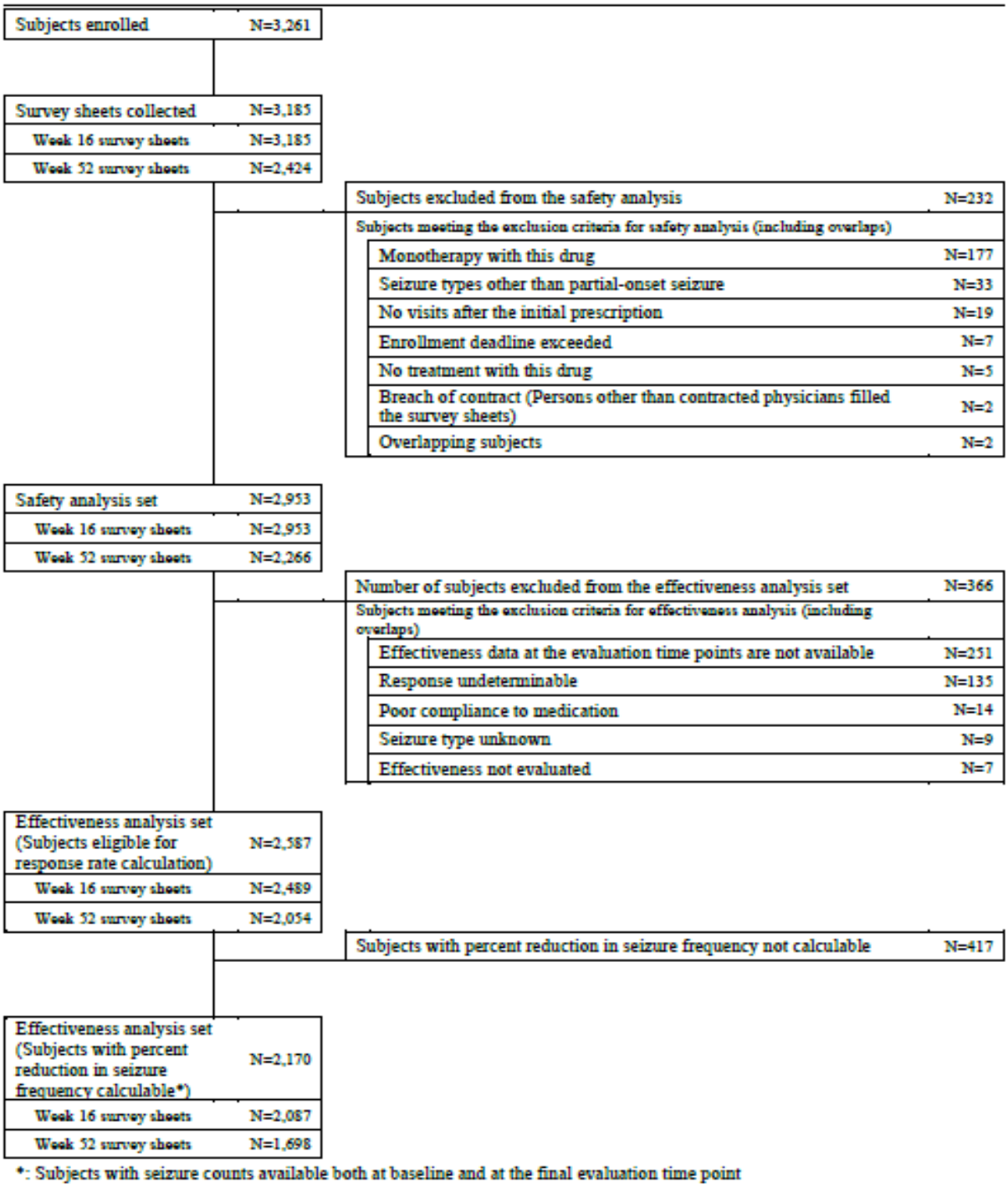
Statistical tests were performed in subgroup analyses for the safety and effectiveness. Categorical data in 2 x 2 tables were analyzed by Fisher's exact test, and those in larger than 2 x 2 tables were analyzed by Monte Carlo estimation. Ordered scale data were analyzed by Cochran-Armitage test. Tests were performed with two-sided significance level of 5%. Statistical measures were not used for other endpoints. Descriptive analyses were performed by calculating two-sided 95% confidence intervals.

Missing data were not imputed.

Results

Participant flow

Figure 1 Subject disposition chart



There were 93 patients with survey sheets collected in EP0081 who were 16 to <18 years of age. Of these 93 pediatric patients, 1 patient met the exclusion criteria for the safety analysis from EP0081.

Assessor's comment

It is noted that patients younger than 18 years old consisted only a small proportion (n=93) of all enrolled patients (n=3261).

Recruitment

EP0081 was conducted in Japan based on approved indications, dosage and administration, and included medical institutions where the Survey Drug had been delivered/adopted.

Baseline data

The mean age of pediatric patients was 16.49 years (range: 16.00 to <18.00 years of age), and the mean body weight was 49.61kg. The mean age at onset of epilepsy was 7.62 years, and the mean duration of epilepsy was 9.04 years.

The most common types of epilepsy reported by pediatric patients in the safety analysis set were complex partial seizures (64.13%) and secondarily generalized seizures (61.96%) (Table 5-2). The mean Baseline seizure frequency was 63.82 seizures per 4 weeks, and the most common Baseline seizure frequency was 1 to less than 4 seizures per 4 weeks (39.13%).

Overall, the use of prior medications for epilepsy in pediatric patients in the safety analysis set was high (97.83%) (Table 5-2). The most common complication/medical comorbidity reported was mental development retardation (56.52%).

Overall, demographic and Baseline characteristics for pediatric patients in the efficacy analysis set were similar to those for pediatric patients in the safety analysis set (Table 5-2).

Table 5-2: Pediatric patients' demographics and Baseline characteristics

Patients' Baseline characteristics	Category	Safety analysis set		Efficacy analysis set	
		N	Percentage (%)	N	Percentage (%)
Number of eligible patients	Analysis sets	92	—	84	—
Gender	Male	51	55.43	47	55.95
	Female	41	44.57	37	44.05
Age	<18 years	92	100.00	84	100.00
	N	92		84	
	Mean (SD)	16.49 (0.50)		16.49 (0.50)	
	Min, max	16.00, 17.00		16.00, 17.00	
Body weight	<40kg	16	17.39	16	19.05
	40 to <50kg	23	25.00	22	26.19
	50 to <60kg	17	18.48	12	14.29
	60 to <70kg	13	14.13	13	15.48
	≥70kg	5	5.43	3	3.57
	Not measured	18	19.57	18	21.43

Table 5-2: Pediatric patients' demographics and Baseline characteristics

Patients' Baseline characteristics	Category	Safety analysis set		Efficacy analysis set	
		N	Percentage (%)	N	Percentage (%)
	N	74		66	
	Mean (SD)	49.61 (14.41)		48.21 (14.08)	
	Min, max	17.00, 88.00		17.00, 82.90	
Age at onset of epilepsy	<10 years	52	56.52	49	58.33
	10 to <18 years	38	41.30	33	39.29
	Unknown	2	2.17	2	2.38
	N	90		82	
	Mean (SD)	7.62 (5.86)		7.26 (5.85)	
	Min, max	0.00, 17.00		0.00, 17.00	

Table 5-2: Pediatric patients' demographics and Baseline characteristics

Patients' Baseline characteristics	Category	Safety analysis set		Efficacy analysis set	
		N	Percentage (%)	N	Percentage (%)
Duration of epilepsy	<1 year	9	9.78	8	9.52
	1 to <5 years	22	23.91	18	21.43
	5 to <10 years	15	16.30	15	17.86
	10 to <18 years	44	47.83	41	48.81
	Unknown	2	2.17	2	2.38
	N	90		82	
	Mean (SD)	9.04 (6.09)		9.38 (6.10)	
	Min, max	0.00, 17.74		0.00, 17.74	
Seizure type[a]	Simple partial seizure	19	20.65	17	20.24
	Complex partial seizure	59	64.13	52	61.90
	Secondarily generalized seizure	57	61.96	52	61.90
	Others	5	5.43	5	5.95
Baseline seizure frequency	<1 seizure/4 weeks	12	13.04	10	11.90
	1 to <4 seizures/ 4 weeks	36	39.13	33	39.29
	4 to <28 seizures/ 4 weeks	23	25.00	21	25.00
	≥28 seizures/4 weeks	20	21.74	19	22.62
	Unknown	1	1.09	1	1.19
	N	91		83	
	Mean (SD)	63.82 (306.48)		69.36 (320.52)	
	Min, max	0.00, 2800.00		0.00, 2800.00	
Estimated site of origin[a]	Frontal lobe epilepsy	41	44.57	40	47.62
	Temporal lobe epilepsy	15	16.30	12	14.29
	Parietal lobe epilepsy	4	4.35	4	4.76
	Occipital lobe epilepsy	5	5.43	5	5.95
	Multifocal epilepsy	8	8.70	8	9.52
	Others	0	0.00	0	0.00
	Unknown	23	25.00	19	22.62
Complication (mental development retardation)	Absent	40	43.48	34	40.48
	Present	52	56.52	50	59.52

Table 5-2: Pediatric patients' demographics and Baseline characteristics

Patients' Baseline characteristics	Category	Safety analysis set		Efficacy analysis set	
		N	Percentage (%)	N	Percentage (%)
Degree of mental development retardation (Denominator: number of mental development retardation "Present")	Mild	14	26.92	14	28.00
	Moderate	5	9.62	5	10.00
	Severe	9	17.31	9	18.00
	Profound	24	46.15	22	44.00
Allergic predisposition	Absent	73	79.35	66	78.57
	Present	12	13.04	12	14.29
	Unknown	7	7.61	6	7.14
Previous medication (AED)	Absent	2	2.17	2	2.38
	Present	90	97.83	82	97.62
Number of concomitant AEDs (at Baseline)	0	0	0.00	0	0.00
	1	34	36.96	29	34.52
	2	33	35.87	31	36.90
	≥3	25	27.17	24	28.57
Concomitant medication other than AED	Absent	52	56.52	46	54.76
	Present	40	43.48	38	45.24
Other therapies for epilepsy than medication	Absent	90	97.83	82	97.62
	Present	2	2.17	2	2.38
Mean daily dose	<100mg	12	13.04	12	14.29
	100 to <200mg	43	46.74	38	45.24
	200 to <300mg	25	27.17	23	27.38
	300 to <400mg	12	13.04	11	13.10
	≥400mg	0	0.00	0	0.00
	N	92		84	
	Mean (SD)	195.39 (87.62)		194.82 (89.25)	
	Min, max	16.57, 385.27		16.57, 385.27	

AED=antiepileptic drug; max=maximum; min=minimum; N=number of pediatric patients; SD=standard deviation
[a] Figures include overlaps.
Figures of subcategories under "Present" include overlaps.
Data source: EP0081 Table 6.2

Assessor's comment

There were no patients younger than 16 years old included into the study. Thus, the information collected is not covering the whole patients' population included into the indication. Even though all patients were receiving from one to 3 concomitant anti-seizure medications, the most commonly used antiseizure medications are not listed in the report.

Number analysed

Out of a total of 93 pediatric patients with survey sheets collected, the efficacy analysis set consisted of 84 patients who were eligible for response rate calculation. Of these, 73 patients had a calculable percent reduction in seizure frequency.

Effectiveness results

The effectiveness results in paediatric patients are presented below.

The response rate based on global improvement rating was 57.14%. The seizure-free rate was 32.14%. The mean percent reduction in seizure frequency was 40.78%. The response rates for allergic predisposition (65.15% for absence, 25.00% for presence, and 33.33% for unknown) within pediatric patients were the only significant difference observed in the efficacy analysis set (Fisher's exact test p=0.012).

Table 5-3: Response rate based on global improvement rating in pediatric patients

N	Global improvement rating			Improved response rate (%)	Two-sided 95% confidence interval of response rate
	Improved	Unchanged	Worsened		
84	48	31	5	57.14	45.88, 67.89

N=number of pediatric patients
Data source: EP0081 Table 7.1.1

Table 5-4: Seizure-free rate in pediatric patients

N	Seizure-free rate (%) at the final evaluation			Two-sided 95% confidence interval of seizure-free rate (%)
	Seizure-free	Not seizure-free	Seizure-free rate	
84	27	57	32.14	22.36, 43.22

N=number of pediatric patients
Data source: EP0081 Table 7.2.4

Table 5-5: Percent reduction in seizure frequency in pediatric patients

Percent reduction in seizure frequency (%) at the final evaluation							
N	Mean	Standard deviation	Min	Q1	Mid	Q3	Max
73	40.78	127.71	-900.00	7.70	73.30	100.00	100.00

max=maximum; mid=median; min=minimum; N=number of pediatric patients; Q1=first quartile; Q3=third quartile
Data source: EP0081 Table 7.2.1

Assessor's comment

No unexpected findings assessing effectiveness regarding response rate, seizure free rate or percent reduction in seizure frequency were reported in paediatric patients.

One of the goals of the study was to identify factors potentially affecting effectiveness. The MAH claimed that statistically significant difference was observed in response rates in paediatric patients with allergic predisposition. The clinical significance of the only statistically significant finding reported by the MAH is not clear. It was not discussed by the MAH and it is not possible to interpret the finding.

Safety results

Out of a total of 93 pediatric patients aged 16 to <18 years with survey sheets collected, the safety analysis set consisted of 92 patients, with 1 patient who met the exclusion criteria for the safety analysis. From the safety analysis set, 8 patients met the exclusion criteria for the efficacy analysis.

Table 5-6: Summary of pediatric patients' disposition and discontinuation reasons

Disposition	**Pediatrics (16 to <18 years) N**
Survey sheets collected	93
Week 16 survey sheets	93
Week 52 survey sheets	80
Patients excluded from the safety analysis	1
Patients meeting the exclusion criteria for the safety analysis	
Enrollment deadline exceeded	1
Safety analysis set	92
Week 16 survey sheets	92
Week 52 survey sheets	80
Patients excluded from the efficacy analysis	8
Patients meeting the exclusion criteria for the efficacy analysis	
Efficacy data at the evaluation time points are not available	6
Response undeterminable	1
Poor compliance to medication	1
Efficacy analysis set (patients eligible for response rate calculation)	84
Week 16 survey sheets	82
Week 52 survey sheets	74
Patients with percent reduction in seizure frequency not calculable	11
Efficacy analysis set (patients with percent reduction in seizure frequency calculable[a])	73
Week 16 survey sheets	72

Table 5-6: Summary of pediatric patients' disposition and discontinuation reasons

Disposition	Pediatrics (16 to <18 years) N
Week 52 survey sheets	64

Incidence of ADRs

The incidence rate of ADRs in the safety analysis set was 11.96% (11/92 pediatric patients). No infections were reported.

The most frequently reported ADRs in pediatric patients aged 16 to <18 years were within the system organ class (SOC) of Nervous system disorders (7 patients [7.61%]) and Gastrointestinal disorders (3 patients [3.26%]) (Table 5-3). The most commonly reported events were epilepsy and somnolence (3 patients [3.26%], each) and dizziness (2 patients [2.17%]) within the SOC of Nervous system disorders. All other ADRs were reported by 1 pediatric patient (1.09%), each.

Table 5-7: Incidence rate of ADRs by type (SOC and PT) in pediatric patients

Safety analysis set, N	92
Number of patients with ADRs, N	11
Proportion of patients with ADRs, %	11.96
Type[a] **SOC** **PT**	**Incidence rate (N, %)**
Metabolism and nutrition disorders	1 (1.09)
Increased appetite	1 (1.09)
Psychiatric disorders	1 (1.09)
Agitation	1 (1.09)
Nervous system disorders	7 (7.61)
Dizziness	2 (2.17)
Epilepsy	3 (3.26)
Hypertonia	1 (1.09)
Somnolence	3 (3.26)
Gastrointestinal disorders	3 (3.26)
Nausea	1 (1.09)
Salivary hypersecretion	1 (1.09)
Stomatitis	1 (1.09)
Investigations	2 (2.17)
Gamma-glutamyltransferase increased	1 (1.09)

Table 5-7: Incidence rate of ADRs by type (SOC and PT) in pediatric patients

Weight increased	1 (1.09)
Injury, poisoning and procedural complications	1 (1.09)
Toxicity to various agents	1 (1.09)

ADR=adverse drug reaction; MedDRA/J=Medical Dictionary for Regulatory Activities Japanese translation; N=number of pediatric patients; PT=preferred term; SOC=system organ class

[a] MedDRA/J Version 25.1

Data source: EP0081 Appendix Form 15

There were no ADRs related to the Safety Specification in the pediatric patient population EP0081.

Safety Specifications (serious and nonserious) for the safety analysis set included:

- Important identified risks: Electrocardiogram PR prolongation-related events (eg, atrioventricular block, bradycardia, syncope); toxic epidermal necrolysis and mucocutaneous ocular (Stevens-Johnson) syndrome; drug-induced hypersensitive syndrome; and agranulocytosis
- Important potential risk: Suicidal behavior; Suicidal ideation

The proportion of pediatric patients with ADRs in the safety analysis set by time of onset was the highest between 2 to <4 weeks of treatment (3 out of 91 pediatric patients [3.30%]) and the lowest between 28 to <40 weeks and ≥52 weeks (0 patient, each).

There were no statistically significant differences observed in the incidence rates of ADRs related to any pediatric patients' demographics and Baseline characteristics.

Assessor's comment

In general, the number of patients reporting the incidence of ADRs was low (11 out 93). Majority of patients (7 out of 11) reported ADRs within 8 weeks. No new unexpected safety findings were reported in the paediatric population of 16 - <18 years old. The MAH did not identify any specific factors related to appearance of ADRs in paediatric population.

2.3.3. Discussion on clinical aspects

The goal of the study EP0081 and the conducted survey was to confirm safety and effectiveness of lacosamide in real life use.

The four objectives of the study were related to identification of new unknown ADRs, appearance of known ADRs in real clinical practise and factors what could potentially affect safety and/or effectiveness.

A number of paediatric patients younger than 18 years old consisted only a small proportion (n=93) of all enrolled patients (n=3261). There were no patients younger than 16 years old included into the study. Thus, the information collected is not covering the whole patients' population included into the indication, but that was not the goal of the study. Even though all patients were receiving from one to 3 concomitant anti-seizure medications, the most common antiseizure medications are not listed in the report.

The MAH did not report any new/unexpected findings assessing effectiveness regarding response rate, seizure free rate or percent reduction in seizure frequency in paediatric patients.

One of the goals of the study was to identify factors potentially affecting effectiveness. The MAH claimed that statistically significant difference was observed in response rates in paediatric patients

with allergic predisposition. The clinical significance of the only statistically significant finding reported by the MAH is not clear. It was not discussed by the MAH and it is not possible to interpret the finding.

The safety analysis set consisted of 92 patients, with 1 patient who met the exclusion criteria for the safety analysis. In general, the reported incidence of ADRs was low (11.9%) and lower compared to incidence of ADRs reported for the whole study population (16.4%), or even phase III studies (59.4%). Majority of paediatric patients (7 out of 11) reported ADRs within 8 weeks of treatment.

No new/unexpected safety findings were reported in the paediatric population of 16 - <18 years old. The MAH did not identify any specific factors related to appearance of ADRs in paediatric population.

In conclusion, the results of this observational study evaluating safety and effectiveness of lacosamide reflects actual post-marketing use in paediatric patients. No new/unexpected concerns about the use of this drug were identified for safety or effectiveness.

3. Rapporteur's overall conclusion and recommendation

The safety and tolerability profile of LCM in the 92 patients who were 16 to <18 years of age with POS with or without secondary generalization under routine clinical practice of the Survey Drug was determined to be consistent with the overall established safety profile of LCM. No new safety concerns were identified in these paediatric patients. The benefit risk ratio remains unchanged.

The obligation to submit the paediatric data collected in study EP0081 in accordance with Article 46 of Regulation (EC) No 1901/2006 (The Paediatric Regulation) is fullfilled. No changes to the approved EU Summary of Product Information for VIMPAT are being proposed following the completion of EP0081.

☒ **Fulfilled:**

No regulatory action required.