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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/P46/050

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	25-12-2023	25-12-2023	☐
☐	CHMP Rapporteur Assessment Report	29-01-2024	29-01-2024	☐
☐	CHMP members comments	12-02-2024	n/a	☐
☐	Updated CHMP Rapporteur Assessment Report	15-02-2024	n/a	☐
☒	CHMP adoption of conclusions	22-02-2024	22-02-2024	☐

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1. Introduction

On December 7, 2023, the MAH submitted a completed paediatric study EP0130 for lacosamide, 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 submitted the EP0130 study "Vimpat tablets 50mg, Vimpat tablets 100mg, Vimpat dry syrup 10% Specified drug use-results surveillance -Monotherapy for partial onset seizures in paediatric patients with epilepsy" is a stand-alone study.

2.2. Information on the pharmaceutical formulation used in the study

Lacosamide has been approved as monotherapy and adjunctive treatment in patients with partial onset seizures (POS) in the EU (2 years of age and older for tablets, oral solution [syrup], and intravenous [iv] infusion), US (1 month of age and older for tablets, oral solution [syrup], and iv infusion), and Japan (4 years of age 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 of age and older for tablets, oral solution [syrup], and iv infusion), US (4 years of age and older for tablets, oral solution [syrup], and iv infusion), and Japan (for patients 4 years of age and older with epilepsy who have not obtained sufficient response to other antiseizure medications for tablets, dry syrup, and iv infusion).

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted <a> final report(s) for:

- EP0130 study "Vimpat tablets 50mg, Vimpat tablets 100mg, Vimpat dry syrup 10% Specified drug use-results surveillance -Monotherapy for partial onset seizures in pediatric patients with epilepsy"

2.3.2. Clinical study

EP0130 study "Vimpat tablets 50mg, Vimpat tablets 100mg, Vimpat dry syrup 10% Specified drug use-results surveillance - Monotherapy for partial onset seizures in pediatric patients with epilepsy"

Description

EP0130 was a post-marketing surveillance study intended to detect the incidence of adverse drug reactions (ADRs), to evaluate effectiveness, and to evaluate factors that may have affected the safety and effectiveness during the actual post-marketing use of VIMPAT tablets 50mg, VIMPAT tablets 100mg, and VIMPAT dry syrup 10% (hereafter referred to as "the Survey Drug") as monotherapy.

This surveillance was conducted as a non-interventional study to confirm the safety and effectiveness of this drug under daily clinical practice based on the approved indications and dosage and administration.

EP0130 was conducted using a central registration system. Investigators registered patients, who newly initiated the administration of the Survey Drug, within 14 days, including the date initiating the administration for the first time. The observation period was 26 weeks. In case the administration period was less than 26 weeks (caused by discontinuation/no-show, etc), the observation period ended on the date of the discontinuation of the administration. Additionally, if patients had surgical operations or vagus nerve stimulation therapies, etc, aimed at treating epilepsy, the observation period ended on the previous date of the procedure. For those patients who discontinued the administration, as much as possible, a surveillance was conducted 2 weeks after discontinuation to check for possible withdrawal symptoms and rebound phenomenon.

Methods

Study participants

The surveillance population included patients with POS (including secondary generalized seizures), who were 4 years to <16 years of age on the start date of administration of the Survey Drug, and who had newly initiated treatment with the Survey Drug and received the Survey Drug as monotherapy.

Treatments

EP0130 was conducted in Japan based on approved indications, dosage, and administration and included medical institutions where the Survey Drug had been delivered/adopted.

Objective(s)

This surveillance is intended to detect the incidence of adverse reactions, to evaluate effectiveness, and to evaluate factors that may affect the safety and effectiveness during the actual post-marketing use of "Vimpat® Tablets 50mg, Vimpat® Tablets 100mg, Vimpat® Dry Syrup 10%.

Outcomes/endpoints

The prespecified time point for the evaluation of effectiveness under actual postmarketing use was Week 26 of the treatment with the Survey Drug (or upon discontinuation). Evaluable pediatric patients were those for whom global improvement rating was determined at the final evaluation time point. The acceptable time window for each evaluation time point was ±28 days.

Safety Specifications (serious and nonserious) for the safety analysis set included the following important identified risks: electrocardiogram PR prolongation-related events (eg, atrioventricular block, bradycardia, syncope); toxic epidermal necrolysis and mucocutaneous ocular (Stevens Johnson) syndrome; drug-induced hypersensitivity syndrome; and agranulocytosis.

Effectiveness evaluations included:

Response rate based on global improvement rating

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

Seizure-free rate

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

Percent reduction in seizure frequency

Number of seizures noted within the past 4 weeks compared with Baseline seizure frequency.

Sample size

A total of 150 patients were planned in the surveillance. The following rational for the sample size was provided:

In the phase III study of lacosamide oral formulation in adults (all population including Japanese subjects), the incidence of adverse drug reactions related to cardiac disorder was 2.27%. Assuming that cardiac disorder occurred at similar rate (3%) in the study of pediatrics population, target sample size is set to 100 cases to estimate the incidence rate with a power of 95%.
On the other hand, for effectiveness, in a Phase III clinical study of monotherapy in adult patients (all population including Japanese subjects), the proportion of 6-month seizure-free subjects was approximately 70%. Assuming a true 6-month seizure-free rate of 70%, the sample size in the surveillance is set to 150 to detect the lower limit of 95% confidence interval for seizure-free rate in the surveillance exceeding the threshold of 56% (calculated as 20% lower than the assumed true rate) at a power of 90%.

Statistics

Descriptive analysis

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 Percent reduction in seizure frequency (%) = "Baseline seizure frequency"- "Seizure frequency at each evaluation time point" X 100 Baseline seizure frequency 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.

Results

Recruitment

There were 204 pediatric patients enrolled and 194 pediatric patients with surveillance sheets collected in EP0130. Of these 194 pediatric patients with surveillance sheets collected, 183 pediatric patients were included in the safety analysis set (after excluding patients who met exclusion criteria for the safety analysis). Of these 183 pediatric patients included in the safety analysis set, 151 pediatric patients were included in the effectiveness analysis set (after excluding patients who met exclusion criteria for the effectiveness analysis).

Table 1: Summary of pediatric patients' disposition and discontinuation reasons

Disposition	Pediatrics (<18 years) N
Pediatric patients enrolled	204
Surveillance sheets collected	194
Pediatric patients excluded from the safety analysis	11
Pediatric patients meeting the exclusion criteria for the safety analysis (including overlaps)	
Adjunctive administration of antiepileptic drugs (at Baseline)	10
No visits after the initial prescription	1
Unclear duration of administration	1
Safety analysis set	183
Pediatric patients excluded from the effectiveness analysis	32
Pediatric patients meeting the exclusion criteria for the effectiveness analysis (including overlaps)	
Effectiveness data at the evaluation time points were not available	13
Concomitant antiepileptic drugs at time of evaluation (26 weeks or discontinuation)	11
Response undeterminable	7
Seizure type discrepancy between Baseline and evaluation	2
Administration to pediatric patients <4 years of age and >16 years of age	1
Poor compliance to medication	1
Effectiveness analysis set (pediatric patients eligible for response rate calculation)	151
Pediatric patients with percent reduction in seizure frequency not calculable	13
Effectiveness analysis set (pediatric patients with percent reduction in seizure frequency calculable [a])	138

[a] Pediatric patients with seizure counts available both at Baseline and at the final evaluation time point.
Data source: EP0130 final report Section 10.1.2

Baseline data

In the safety analysis set, the proportion of males was higher compared with the proportion of females (58.47% vs 41.53%) (Table 2). The mean age of pediatric patients was 8.85 years, and the mean body weight was 30.09kg. The mean age at onset of epilepsy was 7.69 years, and the mean duration of epilepsy was 1.19 years.

The most common seizure types reported by pediatric patients in the safety analysis set were complex partial seizures (56.28%) and secondarily generalized seizures (38.25%) (Table 2). The mean Baseline seizure frequency was 4.26 seizures per 4 weeks, and the most common Baseline seizure frequency was 1 to less than 4 seizures per 4 weeks (65.03%). The most common complication/medical comorbidity reported was mental development retardation (22.40%).

Table 2: Pediatric patients' demographics and Baseline characteristics

Pediatric patients' Baseline characteristics	Category	Safety analysis set		Effectiveness analysis set	
		N	Percentage (%)	N	Percentage (%)
Number of eligible pediatric patients		183	—	151	—
Gender	Male	107	58.47	90	59.60
	Female	76	41.53	61	40.40
Age at Baseline	4 years to <6 years	27	14.75	22	14.57
	6 years to <8 years	36	19.67	27	17.88
	8 years to <10 years	50	27.32	42	27.81
	10 years to <12 years	29	15.85	26	17.22
	12 years to <14 years	31	16.94	25	16.56
	14 years to <18 years	10	5.46	9	5.96
	N	183		151	
	Mean (SD)	8.85 (2.89)		8.92 (2.88)	
Body weight	<10kg	0	0.00	0	0.00
	10kg to <20kg	35	19.13	31	20.53
	20kg to <35kg	84	45.90	65	43.05
	35kg to <50kg	47	25.68	41	27.15
	≥50kg	12	6.56	10	6.62
	Not measured	5	2.73	4	2.65
	N	178		147	
	Mean (SD)	30.09 (11.70)		30.46 (11.84)	
Age at onset of epilepsy	<1 year	3	1.64	3	1.99
	1 year to <3 years	5	2.73	4	2.65
	3 years to <5 years	23	12.57	20	13.25

Table 2: Pediatric patients' demographics and Baseline characteristics

Pediatric patients' Baseline characteristics	Category	Safety analysis set		Effectiveness analysis set	
		N	Percentage (%)	N	Percentage (%)
	5 years to <10 years	95	51.91	74	49.01
	10 years to <18 years	55	30.05	48	31.79
	Unknown	2	1.09	2	1.32
	N	181		149	
	Mean (SD)	7.69 (3.18)		7.72 (3.23)	
Duration of epilepsy	<1 year	133	72.68	110	72.85
	1 year to <3 years	29	15.85	22	14.57
	3 years to <5 years	7	3.83	7	4.64
	5 years to <10 years	9	4.92	8	5.30
	10 years to <15 years	3	1.64	2	1.32
	≥15 years to <18 years	0	0.00	0	0.00
	Unknown	2	1.09	2	1.32
	N	181		149	
	Mean (SD)	1.19 (2.25)		1.24 (2.30)	
Seizure type [a]	Simple partial seizure	24	13.11	19	12.58
	Complex partial seizure	103	56.28	85	56.29
	Secondarily generalized seizure	70	38.25	59	39.07
	Others	1	0.55	0	0.00
Etiology of epilepsy [a]	Genetic disease	7	3.83	5	3.31
	Congenital	10	5.46	7	4.64
	Cortical dysplasia/ hypoplasia	3	30.00	2	28.57
	Cerebrovascular malformation	0	0.00	0	0.00
	Others	7	70.00	5	71.43
	Perinatal events	5	2.73	5	3.31
	Asphyxia	2	40.00	2	40.00
	Complications of pregnancy	0	0.00	0	0.00
	Intrauterine infection	0	0.00	0	0.00
	Others	4	80.00	4	80.00
	Head injury	0	0.00	0	0.00
	Brain surgery	1	0.55	0	0.00

Table 2: Pediatric patients' demographics and Baseline characteristics

Pediatric patients' Baseline characteristics	Category	Safety analysis set		Effectiveness analysis set	
		N	Percentage (%)	N	Percentage (%)
	Cerebral neoplasm	2	1.09	1	0.66
	Cerebrovascular disorder	2	1.09	1	0.66
	Degenerative disease	0	0.00	0	0.00
	Brain infection	1	0.55	1	0.66
	Toxic cause	0	0.00	0	0.00
	Metabolic cause	0	0.00	0	0.00
	Others	8	4.37	8	5.30
	Unknown	149	81.42	123	81.46
Estimated site of origin [a]	Frontal lobe epilepsy	49	26.78	39	25.83
	Temporal lobe epilepsy	58	31.69	50	33.11
	Parietal lobe epilepsy	28	15.30	24	15.89
	Occipital lobe epilepsy	24	13.11	22	14.57
	Multifocal epilepsy	6	3.28	5	3.31
	Others	3	1.64	3	1.99
	Unknown	42	22.95	31	20.53
Family history of epilepsy [b]	Absent	166	90.71	135	89.40
	Present	11	6.01	11	7.28
	Grandfather/mother	2	18.18	2	18.18
	Parent/child	2	18.18	2	18.18
	Sibling	5	45.45	5	45.45
	Others	3	27.27	3	27.27
	Unknown	6	3.28	5	3.31
Baseline seizure frequency	<1 seizure/4 weeks	18	9.84	16	10.60
	1 seizure to <4 seizures/ 4 weeks	119	65.03	96	63.58
	4 seizures to <28 seizures/ 4 weeks	23	12.57	19	12.58
	≥28 seizures/4 weeks	9	4.92	7	4.64
	Unknown	14	7.65	13	8.61
	N	169		138	
	Mean (SD)	4.26 (11.26)		3.60 (7.65)	
Complication	Absent	98	53.55	80	52.98
	Present	85	46.45	71	47.02
	Absent	181	98.91	149	98.68

Table 2: Pediatric patients' demographics and Baseline characteristics

Pediatric patients' Baseline characteristics	Category	Safety analysis set		Effectiveness analysis set	
		N	Percentage (%)	N	Percentage (%)
Complication (cardiac disease)	Present	2	1.09	2	1.32
Degree of cardiac disease	Mild	1	50.00	1	50.00
	Moderate	1	50.00	1	50.00
	Severe	0	0.00	0	0.00
Complication (renal disease)	Absent	182	99.45	150	99.34
	Present	1	0.55	1	0.66
Degree of renal disease	Mild	1	100.00	1	100.00
	Moderate	0	0.00	0	0.00
	Severe	0	0.00	0	0.00
Complication (hepatic disease)	Absent	181	98.91	149	98.68
	Present	2	1.09	2	1.32
Degree of hepatic disease	Mild	2	100.00	2	100.00
	Moderate	0	0.00	0	0.00
	Severe	0	0.00	0	0.00
Complication (mental development retardation)	Absent	142	77.60	119	78.81
	Present	41	22.40	32	21.19
Degree of mental development retardation	Mild	11	26.83	10	31.25
	Moderate	11	26.83	7	21.88
	Severe	12	29.27	8	25.00
	Profound	7	17.07	7	21.88
Medical history	Absent	144	78.69	119	78.81
	Present	39	21.31	32	21.19
Allergic predisposition	Absent	137	74.86	115	76.16
	Present	27	14.75	23	15.23
	Unknown	19	10.38	13	8.61
Previous medication (AED)	Absent	157	85.79	132	87.42
	Present	26	14.21	19	12.58
Number of previous AEDs	0	162	88.52	135	89.40
	1	18	9.84	13	8.61
	2	2	1.09	2	1.32
	≥3	1	0.55	1	0.66

Table 2: Pediatric patients' demographics and Baseline characteristics

Pediatric patients' Baseline characteristics	Category	Safety analysis set		Effectiveness analysis set	
		N	Percentage (%)	N	Percentage (%)
Concomitant medication with non-AED	Absent	144	78.69	120	79.47
	Present	39	21.31	31	20.53
Therapies for epilepsy other than medication	Absent	183	100.00	151	100.00
	Present	0	0.00	0	0.00
Mean daily dose per body weight	<2mg/kg	22	12.02	16	10.60
	2mg/kg to <4mg/kg	87	47.54	77	50.99
	4mg/kg to <8mg/kg	68	37.16	53	35.10
	≥8mg/kg	1	0.55	1	0.66
	Unknown	5	2.73	4	2.65
	N	178		147	
	Mean (SD)	3.74 (1.48)		3.72 (1.46)	

AED=antiepileptic drug; SD=standard deviation

[a] Figures include overlaps.

[b] Figures of subcategories under "Present" include overlaps.

Data source: EP0130 final report Table 1

Efficacy results

The response rate based on global improvement rating was 85.43%. The seizure-free rate was 55.63%. The mean percent reduction in seizure frequency was 79.79%.

Table 3: Response rate based on global improvement rating

N	Global improvement rating			Improved response rate (%)	Two-sided 95% confidence interval of response rate
	Improved	Unchanged	Worsened		
151	129	19	3	85.43	78.78, 90.64

Data source: EP0130 final report Table 5

Table 4: Seizure-free rate

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	
151	84	67	55.63	47.33, 63.70

Data source: EP0130 final report Table 6

Table 5: Percent reduction in seizure frequency per 4 weeks

Percent reduction in seizure frequency (%) at the final evaluation					
N	**Mean**	**Standard deviation**	**Median**	**Minimum**	**Maximum**
138	79.79	48.74	100.00	-200.00	100.00

Data source: EP0130 final report Table 7

The MAH examined factors for potential impact on effectiveness by using the global improvement rating at the final evaluation (refer to the EP0130 final report [Module 5.3.5.4] for additional details). No statistically significant differences were observed for any factors.

Safety results

A total of 183 pediatric patients were included in the safety analysis set.

The incidence of ADRs was 12.02% (22/183 pediatric patients); ADRs were most frequently reported in the system organ class (SOC) of Nervous system disorders (7.65%). The most commonly reported ADRs by preferred term (PT) were somnolence (7 pediatric patients [3.83%]) and dizziness (5 pediatric patients [2.73%]), which were within the SOC of Nervous system disorders. The incidence of serious ADRs was 1.09% (2/183 pediatric patients); serious ADRs by PT were epilepsy and leukopenia (1 pediatric patient each). No infections were reported.

Of the pediatric patients excluded from the safety analysis set, 2 pediatric patients experienced ADRs (by PT of anxiety, crying, and epilepsy [1 pediatric patient] and dizziness and headache [1 pediatric patient]). Of these ADRs by PT, epilepsy was considered serious in 1 pediatric patient.

None of the Safety Specifications were observed.

Table 6: Incidence of ADRs by time of onset and by SOC

	Duration of treatment before the onset (weeks)						
	<2	**2 to <4**	**4 to <8**	**8 to <16**	**16 to <26**	**≥26**	**Unknown/ undocumented**
Number of pediatric patients surveyed, N	183	179	176	171	168	92	183
Number of pediatric patients with ADRs, N	7	3	2	7	1	1	2
Number of ADRs, N	10	4	4	9	1	1	2
Proportion of pediatric patients with ADRs, %	3.83	1.68	1.14	4.09	0.60	1.09	1.09
Type of ADRs by SOC [a]	**Number (proportion %) of pediatric patients with ADRs**						
Blood and lymphatic system disorders	0	0	0	0	0	0	1 (0.55)
Psychiatric disorders	0	1 (0.56)	0	1 (0.58)	0	0	0
Nervous system disorders	4 (2.19)	1 (0.56)	2 (1.14)	6 (3.51)	1 (0.60)	0	1 (0.55)
Eye disorders	0	1 (0.56)	0	0	0	0	0
Respiratory, thoracic and mediastinal disorders	0	0	0	1 (0.58)	0	0	0
Gastrointestinal disorders	1 (0.55)	0	0	0	0	0	0
Skin and subcutaneous tissue disorders	2 (1.09)	1 (0.56)	0	0	0	0	0
General disorders and administration site conditions	1 (0.55)	0	0	0	0	0	0
Investigations	0	0	0	0	0	1 (1.09)	0

Table 6: Incidence of ADRs by time of onset and by SOC

	Duration of treatment before the onset (weeks)						
	<2	2 to <4	4 to <8	8 to <16	16 to <26	≥26	Unknown/ undocumented

ADR=adverse drug reaction; MedDRA/J=Medical Dictionary for Regulatory Activities Japanese translation; SOC=system organ class

Note: The values in parentheses are the percentages, calculated using the number of pediatric patients in the safety analysis set falling under each category as denominator.

[a] MedDRA/J Version 25.1

Data source: EP0130 final report Table 2

The MAH examined factors for potential impact on the incidence rates of ADRs (refer to the EP0130 final report [Module 5.3.5.4] for additional details).

There were statistically significant differences by age at Baseline (see Section 5.1.3.1 for additional details regarding the incidence rates of ADRs by age at Baseline). The incidence rate of ADRs tended to be higher in the older age groups. The incidence rate of pediatric patients with ADRs in the 12 years to <16 years age group was 27.50%. The incidence rate of ADRs in the SOC of Nervous system disorders, including neurological events, which are the main, commonly observed ADRs for antiepileptic drugs, including this Survey Drug, tended to be higher in the older age groups.

Table 7: Incidence rates of ADRs by age at Baseline (grouped by 4 years of age) and by SOC

	Age at Baseline (years)			
	4 to <8	8 to <12	12 to <18	
Number of pediatric patients surveyed, N	63	79	41	
Number of pediatric patients with ADRs, N	5	6	11	
Proportion of pediatric patients with ADRs, %	7.94	7.59	26.83	
Type of ADRs by SOC [a]	**Number (incidence rate %) of ADRs**			
Blood and lymphatic system disorders	0	0	1 (2.44)	
Psychiatric disorders	1 (1.59)	0	1 (2.44)	
Nervous system disorders	1 (1.59)	4 (5.06)	9 (21.95)	
Eye disorders	1 (1.59)	0	0	
Respiratory, thoracic and mediastinal disorders	0	0	1 (2.44)	
Gastrointestinal disorders	0	1 (1.27)	0	
Skin and subcutaneous tissue disorders	2 (3.17)	1 (1.27)	0	
General disorders and administration site conditions	0	0	1 (2.44)	
Investigations	1 (1.59)	0	0	

ADR=adverse drug reaction; MedDRA/J=Medical Dictionary for Regulatory Activities Japanese translation; SOC=system organ class

[a] MedDRA/J Version 25.1

Data source: EP0130 final report Table 4-2

The Survey Drug was administered to 1 pediatric patient with renal impairment. The Survey Drug was administered to 2 pediatric patients with hepatic impairment. No ADRs were observed in the pediatric patient with renal impairment or in the pediatric patients with hepatic impairment.

2.3.3. Discussion on clinical aspects

The MAH submitted a completed paediatric study EP0130 for lacosamide, in accordance with Article 46 of Regulation (EC) No1901/2006. The study EP0130 was a post-marketing surveillance study intended to detect the incidence of adverse drug reactions (ADRs), to evaluate effectiveness, and to evaluate factors that may have affected the safety and effectiveness during the actual post-marketing use of lacosamide as monotherapy.

This surveillance was conducted as a non-interventional study to confirm the safety and effectiveness of this drug under daily clinical practice based on the approved indications and dosage and administration.

The surveillance population included patients with POS (including secondary generalized seizures), who were 4 years to <16 years of age on the start date of administration of LCM, and who had newly initiated treatment with the LCM and received it as monotherapy.

There were 204 pediatric patients enrolled and 183 pediatric patients included in the safety analysis set, and 151 pediatric patients were included in the effectiveness analysis set. The observation period was 26 weeks.

The mean age of pediatric patients was 8.85 years, and the mean body weight was 30.09kg. The mean duration of epilepsy was 1.19 years with the majority (73%) having a duration of less than 1 year. The most common seizure types reported by pediatric patients in the safety analysis set were complex partial seizures (56.28%) and secondarily generalized seizures (38.25%). The seizure frequency was relatively low with the mean Baseline seizure frequency of 4.26 seizures per 4 weeks. Approximately 88.5% have not been previously treated with any ASM. Thus, it could be considered that patients included into this survey were rather mild and early in their disease development.

The most common mean daily doses per body weight were between 2mg/kg and 4mg/kg (47,52%), and 4mg/kg and 8mg/kg (37.16%) for safety analysis set.

The effectiveness assessed as response rate based on global improvement rating, seizure-free rate and the mean percent reduction in seizure frequency was 85.43%, 55.63% and 79.79%, respectively. These exploratory data do not indicate any potential issues/differences of effectiveness of LCM treatment from the known effect in the population studied in real world setting.

The safety analyses set included 183 patients. The incidence of ADRs was 12.02%. The most common reported ADRs by preferred term were somnolence and dizziness in line with the information provided in the SmPC. The incidence of serious ADRs was 1.09% and included epilepsy and leukopenia (1 pediatric patient each). No infections were reported.

The MAH reported that the incidence rate of ADRs tended to be higher in the older age groups. The incidence rate of paediatric patients with ADRs in the 12 years to <18 years age group was 26.86%. This observation that there were statistically significant differences in age at baseline in reporting the ADRs is difficult to interpret having in mind study design.

In summary, no new information regarding effectiveness of LCM when used as monotherapy according to approved indication and dosing was reported. Also, safety and tolerability of LCM in patients included into the study did not reveal any new safety concerns and can be considered to be consistent with the known safety profile. Thus, the MAH proposal not to update the SmPC could be endorsed.

The benefit risk ratio of LCM treatment in paediatric patients when treated according to approved indications and dosage remains unchanged.

3. Rapporteur's overall conclusion and recommendation

The safety and tolerability of LCM in paediatric patients with POS included into the study EP0130 did not reveal any new safety concerns. Thus, based on the results of the EP0130 study the MAH proposal not to update the SmPC of lacosamide could be endorsed.

The benefit risk ratio of LCM treatment remains unchanged.

☒ **Fulfilled:**

No regulatory action required.