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Committee for Medicinal Products for Human Use (CHMP)

Assessment report for paediatric studies submitted in accordance with article 46 of regulation (EC) No 1901/2006, as amended

Vimpat

Lacosamide

Procedure no.: EMA/PAM/0000245458

Note

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

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1. Introduction

On 10 January 2025, the MAH submitted the results of EP0167, 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.

2. Scientific discussion

2.1. Information on the development program

Lacosamide was first approved in the European Union in 2008 for adjunctive therapy for partial onset seizures (including secondary generalized seizures) in adults and adolescents (16-18 years) with epilepsy. In Japan, adjunctive therapy for partial onset seizures in adult epilepsy patients was approved in 2016, and then monotherapy for partial onset seizures in epilepsy patients in 2017. Based on the results of Japanese and overseas clinical studies to obtain new indications for adjunctive therapy for primary generalized tonic-clonic seizures, the safety profile of lacosamide in patients with epilepsy with primary generalized tonic-clonic seizures was consistent with the known safety profile of lacosamide in patients with epilepsy with partial onset seizures. But the only available safety information on the surveillance study drug in Japanese pediatric patients with primary generalized tonic-clonic seizures is the limited investigation in Studies SP0982 and EP0012. In addition, unlike in clinical studies, the surveillance study drug is widely used in patients with various backgrounds in post-marketing use. Therefore, this study (EP0167) was planned as an additional pharmacovigilance activity for the purpose of confirming the safety of the surveillance study drug under the post-marketing use. The study (EP0167) is a stand-alone study.

2.2. Information on the pharmaceutical formulation used in the study

Vimpat Tablets 50 mg, Vimpat Tablets 100mg, Vimpat Dry Syrup 10%

2.3. Clinical aspects

2.3.1. Introduction

The only available safety data on Vimpat in Japanese pediatric patients with primary generalized tonic-clonic seizures is the limited information in Studies SP0982 and EP0012. Therefore, this study (EP0167) was planned as an additional pharmacovigilance activity for the purpose of confirming the safety of Vimpat under the post-marketing use.

This postmarketing surveillance study (EP0167) was conducted in Japanese pediatric patients with primary generalized tonic-clonic seizures, aged 4 or older and younger than 16 years treated with lacosamide. The objectives of the study, designed as a noninterventional prospective study, were to detect the incidence of selected ADRs, to evaluate effectiveness, and to evaluate factors that may have affected the safety and effectiveness of the Surveillance Study Drug (Vimpat) in the adjunctive treatment of pediatric epileptic patients with primary generalized tonic-clonic seizures (PGTCS) under routine clinical practice settings.

2.3.2. Clinical study

EP0167, Surveillance study on pediatric epileptic patients with primary generalized tonic-clonic seizures.

Description

Methods

Study participants

Japanese pediatric patients with primary generalized tonic-clonic seizures, aged 4 or older and younger than 16 years at the start of administration with Vimpat and with no experience of using Vimpat.

Inclusion criteria
Patients who meet all of the following conditions will be included:

Patients aged 4 years or older and younger than 16 years at the start of administration of the surveillance study drug

Patients with no experience of using any formulation of the surveillance study drug

Patients with primary generalized tonic-clonic seizures

Exclusion criteria
Patients with secondary generalized tonic-clonic seizures

Assessor's comment

Apart from age, diagnosis and previous use of Vimpat, there were no specific inclusion or exclusion criteria.

Treatment

Vimpat Tablets 50 mg, Vimpat Tablets 100mg or Vimpat Dry Syrup 10% as adjunctive treatment.

Objectives

This non-interventional prospective study is designed to assess the safety and effectiveness of Lacosamide in normal clinical practice according to the instructions for use in pediatric patients with primary generalized tonic-clonic seizures. The observation period of this surveillance study will be 24 weeks.

Primary objective

- To estimate the incidence of the selected ADRs among pediatric patients with primary generalized tonic-clonic seizures treated with the surveillance study drug in routine clinical practice in Japan
  - ECG PR prolongation-related events (atrioventricular block, bradycardia, syncope, etc.)

Secondary objectives

- To estimate the incidence of the selected ADRs among pediatric patients with primary generalized tonic-clonic seizures treated with the surveillance study drug in routine clinical practice in Japan

- Toxic epidermal necrolysis (TEN), oculomucocutaneous syndrome (Stevens-Johnson syndrome)
- Drug-induced hypersensitivity syndrome
- Agranulocytosis

- Estimate the incidence of ADRs (all events including the above) under routine use of the surveillance study drug
- Evaluate effectiveness of the surveillance study drug under the actual use

Outcomes/endpoints

Safety and effectiveness

Events evaluated for safety

Adverse drug reactions (ADRs) for which a causal relationship to this drug cannot be ruled out were evaluated.

Evaluation method for effectiveness

The prespecified time point for evaluation was Week 24 of the treatment with surveillance study drug. The subjects rated as "improved" were considered as responders. The physicians in charge of the surveillance checked whether the subjects experienced seizures during the observation period by referring to the "Epilepsy Diary," etc. used in daily clinical practice. Seizure-free rate and percent reduction in seizure frequency were calculated.

Sample size

100 patients

Randomisation and blinding (masking)

N/A

Statistical Methods

Descriptive analysis and exploratory statistical tests were performed.

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%.

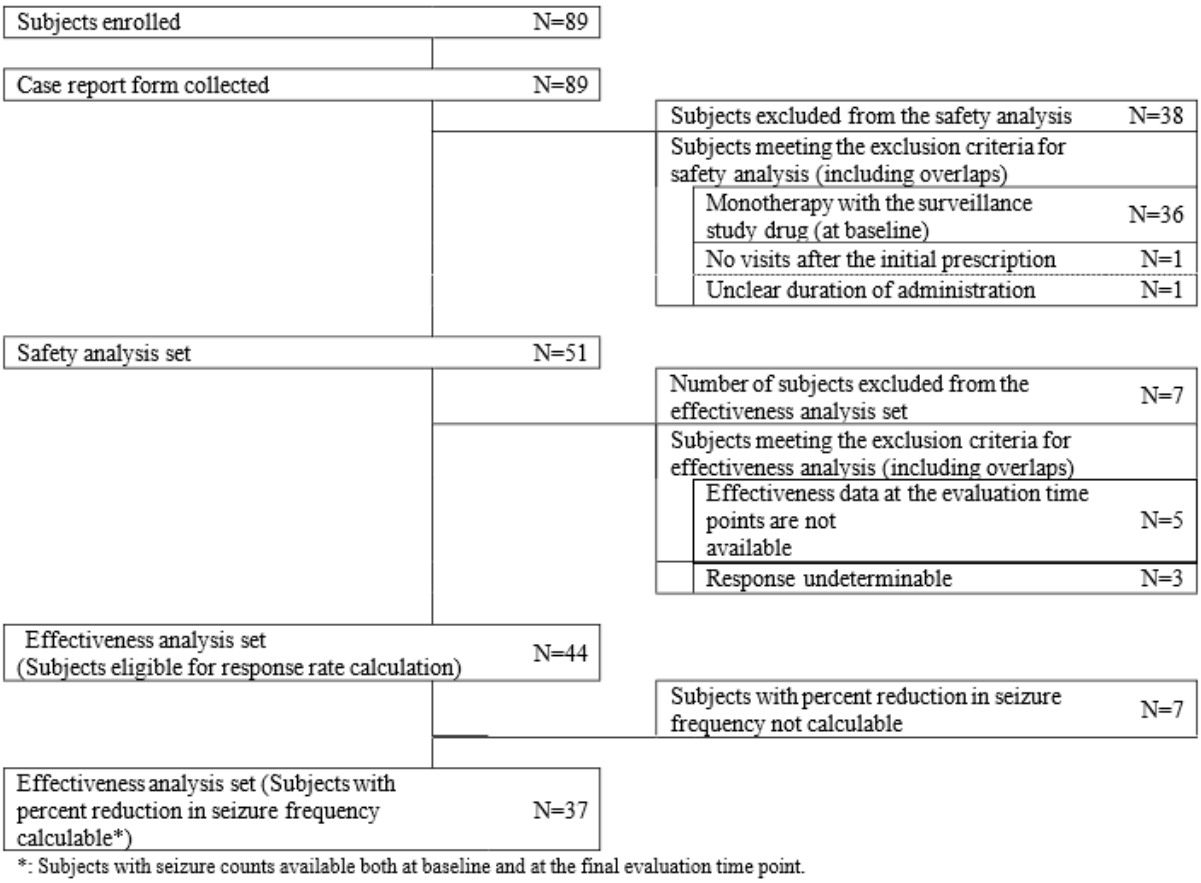
Statistical measures were not used for other endpoints. Descriptive analyses were performed by calculating two-sided 95% confidence intervals.

Results

Participant flow

Subject disposition is provided in Figure 1 below

Figure 1 Subject disposition



*: Subjects with seizure counts available both at baseline and at the final evaluation time point.

Rapporteur's comment

Vimpat is indicated as *adjunctive* treatment in *primary generalised tonic-clonic seizures*. Vimpat is also indicated as *monotherapy* in *secondary generalized tonic-clonic seizure*. Likely, a relatively large proportion of the enrolled patients were excluded due to these differential diagnostic difficulties. In the end 51 /89 patients were included in the safety analysis set and 44/89 subjects in the effectiveness analysis set.

Information regarding most common concomitant ASM had been of interest but is unfortunately not presented.

Recruitment

All sites were in Japan. The numbers of sites contracted, sites with subjects enrolled, sites with case report forms collected were 76, 37, and 37, respectively.

The enrollment period was from 01 April 2021 to 18 Oct 2023.

Baseline data

Baseline Characteristics

Pediatric patients' Baseline characteristics	Category	Safety analysis set		Effectiveness analysis set	
		N	Percentage (%)	N	Percentage (%)
Number of eligible pediatric patients	Analysis sets	51	–	44	–
Gender	Male	25	49.02	21	47.73
	Female	26	50.98	23	52.27
Age at Baseline	4 to <8 years	16	31.37	16	36.36
	8 to <12 years	18	35.29	12	27.27
	12 to <16 years	17	33.33	16	36.36
	≥16 years	0	0.00	0	0.00
	N	51		44	
	Mean (SD)	9.67 (3.60)		9.52 (3.82)	
Body weight	<10kg	0	0.00	0	0.00
	10 to <20kg	16	31.37	15	34.09
	20 to <35kg	14	27.45	13	29.55
	35 to <50kg	13	25.49	10	22.73
	50 to <65kg	2	3.92	2	4.55
	≥65kg	5	9.80	4	9.09
	Not measured	1	1.96	–	–
	N	50		44	
	Mean (SD)	32.74 (17.90)		31.87 (17.84)	

Pediatric patients' Baseline characteristics	Category	Safety analysis set		Effectiveness analysis set	
		N	Percentage (%)	N	Percentage (%)
Age at onset of epilepsy	<1 year	10	19.61	10	22.73
	1 to <3 years	8	15.69	7	15.91
	3 to <5 years	7	13.73	6	13.64
	5 to <10 years	12	23.53	9	20.45
	10 to <15 years	13	25.49	11	25.00
	≥15 years	0	0.00	0	0.00
	Unknown	1	1.96	1	2.27
	N	50		43	
	Mean (SD)	5.48 (4.81)		5.19 (4.91)	
Duration of epilepsy	<1 year	11	21.57	9	20.45
	1 to <3 years	13	25.49	10	22.73
	3 to <5 years	7	13.73	7	15.91
	5 to <10 years	15	29.41	13	29.55
	10 to <15 years	4	7.84	4	9.09
	≥15 years	0	0.00	0	0.00
	Unknown	1	1.96	1	2.27
	N	50		43	
	Mean (SD)	4.26 (3.56)		4.42 (3.66)	

Seizure type (ILAE-1981)[a]	Primary generalized tonic-clonic seizure	51	100.00	44	100.00
	Simple partial seizure	0	0.00	0	0.00
	Complex partial seizure	9	17.65	9	20.45
	Secondarily generalized seizure	2	3.92	2	4.55
	Absence seizure	3	5.88	2	4.55
	Atypical absence seizure	0	0.00	0	0.00
	Myoclonic seizure	11	21.57	8	18.18
	Clonic seizure	0	0.00	0	0.00
	Tonic seizure	6	11.76	4	9.09
	Atonic seizure	0	0.00	0	0.00
	Other	6	11.76	5	11.36

Baseline seizure frequency	<1 seizure/4 weeks	3	5.88	2	4.55
	1 to <4 seizures/4 weeks	30	58.82	27	61.36
	4 to <28 seizures/4 weeks	10	19.61	9	20.45
	≥28 seizures/4 weeks	8	15.69	6	13.64
	N	51		44	
	Mean (SD)	19.42 (42.37)		15.12 (32.51)	

Number analysed

Surveillance study period was from 01 April 2021 to 30 April 2024.

Although this survey has started with a target of 100 cases, the final number of case report forms collected remained at 89 cases. As a reason for not enrolling the cases, the investigators commented that, "Although there are pediatric patients with tonic-clonic seizures, we have not been able to differentiate whether they are primary generalized tonic-clonic seizures or secondary generalized tonic-clonic seizures, so we cannot conclude that they meet the criteria for enrollment." Therefore, we consider that the actual situation of seizure differentiation in actual clinical practice also affected the progress of case enrollment.

The safety analysis set consisted of 51 subjects, after excluding subjects meeting exclusion criteria for the safety analysis from subjects with case report forms collected.

The effectiveness analysis set consisted of 44 subjects, after excluding subjects meeting exclusion criteria for the effectiveness analysis from the safety analysis set.

Efficacy results

According to effectiveness data, the response rate based on the global improvement rating in this survey was 68.18%, the seizure-free rate was 27.27%, and the mean reduction in seizure frequency per 4 weeks was 41.88% (median 100.00%).

N	Global improvement rating			Response rate (%)
	Improved	Unchanged	Worsened	
44	30	13	1	68.18

Seizure-free rate (%) at the final evaluation			
N	Seizure-free	Not seizure-free	Seizure-free rate
44	12	32	27.27

In the analysis of factors affecting effectiveness, no items were observed to have a statistically significant difference.

Safety results

The incidence rate of ADRs in this survey was 11.76% (6 /51 patients), which did not exceed the incidence of 46.97% (124 /264 patients) in the clinical studies (Phase III clinical study SP0982 and Phase III long-term administration study EP0012) up to the time of approval. The types of ADRs that occurred were floating dizziness, epilepsy, somnolence, malaise, elevated transaminases, and sleeplessness in one case (1.96%) each. The most serious ADR was epilepsy in one case (1.96%).

None of the safety specifications were observed, and no action such as a change in risk category is considered necessary based on the results of this survey.

Analysis for ADR for timing of onset showed that the incidence rate of ADR was higher in the early phase of treatment (less than 2 weeks of treatment), but the events that occurred were epilepsy, somnolence and fatigue, which are frequently reported ADRs to this drug, and therefore, no safety concerns are identified.

In the analysis of factors affecting safety, a significant difference was observed in the mean daily dose per body weight, and although the incidence of ADRs was higher in the low-dose group (<2 mg/kg) and the difference was statistically significant, no dose-dependent trend was observed, and therefore, this is not considered to pose any issue.

Rapporteur's comment
No new safety or effectiveness concerns were identified.

2.3.3. Discussion on clinical aspects

In Japan, adjunctive therapy for partial onset seizures in adult epilepsy patients was approved in 2016, and then monotherapy for partial onset seizures in adult epilepsy patients in 2017. Based on the results of Japanese and overseas clinical studies to obtain new indications for adjunctive therapy for primary generalized tonic-clonic seizures, the safety profile of lacosamide in patients with primary generalized tonic-clonic seizures was consistent with the known safety profile of lacosamide in patients with partial onset seizures. But the only available safety information on the surveillance study drug in Japanese pediatric patients with primary generalized tonic-clonic seizures is the limited investigation in Studies SP0982 and EP0012. In addition, unlike in clinical studies, the surveillance study drug is widely used in patients with various backgrounds in post-marketing use. Therefore, this study was planned as an additional pharmacovigilance activity to confirm the safety of the surveillance study drug in pediatric epilepsy patients under post-marketing use.

This surveillance was conducted in Japan to confirm the safety and effectiveness of this drug under actual condition of use in pediatric patients with primary generalized tonic-clonic seizure of epilepsy.

Although this survey has started with a target of 100 cases, the final number of case report forms collected remained at 89 cases.

In conclusion, no safety or effectiveness concerns for this drug were identified in the adjunctive treatment of pediatric patients with primary generalized tonic-clonic seizures of epilepsy.

3. Rapporteur's overall conclusion and recommendation

The only available safety information on Vimpat in Japanese pediatric patients with primary generalized tonic-clonic seizures is phase III clinical study SP0982 and phase III long-term administration study EP0012. Therefore, this study was planned as an additional pharmacovigilance activity to confirm the safety of Vimpat as adjunctive therapy in pediatric patients (≥4 to <16 years) with primary generalized tonic-clonic seizures under post-marketing use. The observation period of this non-interventional prospective surveillance study was 24 weeks. The sample size was determined to be 100 patients. However, due to difficulty in achieving patients the enrolment period was extended and finally 89 patients were enrolled. However, 36 of them had Vimpat in monotherapy and were excluded. Finally, 51 patients were included in the safety analysis set. The primary objective was to estimate the incidence of the selected ADR ECG PR prolongation-related events. The secondary objectives were to estimate the incidence of the selected ADRs (drug induced hypersensitivity syndrome, Toxic epidermal necrolysis, Stevens-Johnson syndrome and agranulocytosis), estimate the incidence of all ADRs and evaluate effectiveness of Vimpat under the actual use.

The incidence rate of ADRs was 11.76% (6 /51 patients), which did not exceed the incidence of 46.97% (124 /264 patients) in the clinical phase III studies. The types of ADRs that occurred were floating dizziness, epilepsy, somnolence, malaise, elevated transaminases, and sleeplessness in one case (1.96%) each. The most serious ADR was epilepsy in one case (1.96%). None of the safety specifications were observed.

According to effectiveness data, Finally, 44 patients were included in the effectiveness analysis set. The response rate based on the global improvement rating in this survey was 68.18%, the seizure-free rate was 27.27%, and the mean reduction in seizure frequency per 4 weeks was 41.88% (median 100.00%).

Conclusion

No safety or effectiveness concerns for Vimpat were identified in the adjunctive treatment of pediatric patients with primary generalized tonic-clonic seizures of epilepsy.

Recommendation

No action such as a change in risk category is considered necessary based on the results of this survey.

Regulatory action

☒ **Fulfilled:**

No regulatory action required