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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/P46/049

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		☐
☐	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 07 December 2023, the MAH submitted a completed study EP0126 for lacosamide, which included paediatric patients 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 study "Vimpat IV 100mg, Vimpat IV 200mg General drug use results surveillance" (EP0125) report 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:

- EP0126 and "Vimpat IV 100mg, Vimpat IV 200mg General drug use results surveillance"

2.3.2. Clinical study

EP0126 "Vimpat IV 100mg, Vimpat IV 200mg General drug use results surveillance"

Description

EP0126 was a post-marketing surveillance study intended to grasp the incidence of echocardiogram PR prolongation-related events during the actual post-marketing use of VIMPAT iv (hereafter referred to as "the Survey Drug"), evaluate differences in such incidence between infusion formulation and oral formulation, and obtain effectiveness information of the Survey Drug.

EP0126 was conducted using a central registration system. Investigators registered patients, who newly initiated the administration/who were supposed to newly initiate the administration of the Survey Drug, during the period: 7 days before the initiation of the administration to the next day of the initiation of the administration. The observation period was from the date of the initiation of the administration to 2 weeks after the discontinuation of the Survey Drug. In case the administration of the Survey Drug was long, the maximum observation period was 1 month.

Methods

Study participants

The surveillance population included patients who were diagnosed with epilepsy, with POS (including secondary generalized seizures), who were 4 years or above on the start date of administration of the Survey Drug, and who had not used the Survey Drug in the past and received the Survey Drug as alternative to LCM oral formulations.

EP0126 was conducted in Japan based on approved indications, dosage, and administration and included medical institutions where the Survey Drug had been delivered/adopted. A total of 100 patients (including pediatric patients who were <18 years of age) were planned in the surveillance.

Treatments

Vimpat® IV 200 mg (hereinafter referred to as "the Survey Drug").

Objective(s)

This surveillance is intended to grasp the incidence of Echocardiogram PR prolongation–related events during the actual post-marketing use of "Vimpat® IV 200 mg (hereinafter referred to as "the Survey Drug")", evaluation of differences in such incidence between infusion formulation and oral formulation, obtaining effectiveness information of the Survey Drug.

Outcomes/endpoints

The safety specification and definition of data to be collected for this surveillance are summarized below.

➢ Electrocardiogram PR prolongation-related events (atrioventricular block, bradycardia, syncope, etc.)

Any events falling under the following MedDRA PTs:

Arrhythmia supraventricular, atrial tachycardia, wandering pacemaker, atrial parasystole, Adams-Stokes syndrome, atrioventricular block, atrioventricular block complete, atrioventricular block first degree, atrioventricular block second degree, conduction disorder, atrial conduction time prolongation, atrioventricular dissociation, inherited cardiac conduction disorder, anomalous atrioventricular excitation, arrhythmia, bradycardia, extrasystoles, nodal rhythm, parasystole, withdrawal arrhythmia, bradyarrhythmia, atrial septal defect, cardiac amyloidosis, cardiac sarcoidosis, dilatation atrial, myocardial fibrosis, atrial hypertrophy, left atrial hypertrophy, right atrial hypertrophy, right atrial dilatation, left atrial dilatation, cardiac steatosis (LLT: 10068130/ lipomatous hypertrophy of the interatrial septum), cardiomyopathy, cardiomyopathy alcoholic, ischaemic cardiomyopathy, stress cardiomyopathy and electrocardiogram PR prolongation.

Effectiveness evaluations included:

Status of epileptic seizure:

Presence/absence of seizures during the administration period of the Survey Drug

Effectiveness evaluation:

Evaluation was conducted at the time of discontinuation/1 month after the initiation of the administration of the Survey Drug by selecting “Effective” or “Ineffective”.

Sample size

A total of 100 patients (including pediatric patients who were <18 years of age) were planned in the surveillance.

Results

Baseline data

There were 2 pediatric patients recruited. The age of epilepsy onset ranged from 6 years to 16 years, and the duration of disease ranged from 0.0 years to 4.9 years. Concomitant medication use was reported for both pediatric patients (See Table below).

Table 1: Demographics and disposition for pediatric patients in the safety analysis

Age (years)/ Sex	Body weight (kg)	Age of epilepsy onset (years)	Duration of disease (years)	Concomitant medications	Complications	Completion status
		6	4.9	Topiramate	Mental development retardation (Intellectual disability)	Discontinued
				Lamotrigine		
				Maintenance medium		
				Ampicillin sodium/sulbactam sodium		
		16	0.0	Midazolam	Others (Cerebrovascular arteriovenous malformation)	Discontinued
				Dexmedetomidine hydrochloride		
				Concentrated glycerin/fructose		
				Omeprazole sodium		
				Carbazochrome sodium sulfonate hydrate		
				Tranexamic acid		
				Cefazolin sodium		
				Fentanyl citrate		

Efficacy results

There were 2 pediatric patients in the effectiveness analysis. The usefulness evaluation in both pediatric patients were judged to be effective (continued good seizure control), and there were no concerns regarding effectiveness, either by adjunctive therapy/monotherapy or by patient age.

Due to the small sample size (n=2) and exploratory nature of the evaluations, the limited effectiveness data of the Survey Drug in pediatric patients does not provide a basis for adding any significant information in the EU Summary of Product Information for VIMPAT.

Safety results

There were 2 pediatric patients in the safety analysis. The duration of treatment for pediatric patients ranged from 2 days to 3 days. One pediatric patient had a start, daily average, and maximum LCM dose of 100mg, and 1 pediatric patient had a start, daily average, and maximum LCM dose of 50mg. No Survey Drug-related AEs were reported in either pediatric patient.

An AE was reported for 1 of the 2 pediatric patients in the safety analysis. Details regarding the AE reported for the 1 pediatric patient are as follows:

The pediatric patient had an AE by preferred term of gastric haemorrhage starting on Day 1. Both the Investigator and the MAH considered the AE as nonserious and not related to the Survey Drug.

2.3.3. Discussion on clinical aspects

The MAH submitted the EP0126 study in accordance with Article 46 of Regulation (EC) No 1901/2006 (The Paediatric Regulation), since this surveillance study included also paediatric patients.

There were 2 paediatric patients included into the study. Both patients received concomitant antiseizure medications. The MAH claimed good effectiveness in those patients in terms of seizure control. However, treatment was discontinued after 2 and 3 days. No reasons for discontinuation were provided. The interpretation of observations on effectiveness, safety and tolerability reported in those 2 patients is limited by the small sample size. It appears that the observations did not differ substantially from the overall established safety profile of LCM. No new safety concerns were identified in these paediatric patients.

No changes to the approved EU Summary of Product Information for VIMPAT are being proposed by the MAH following the completion of EP0126. This is endorsed.

3. Rapporteur's overall conclusion and recommendation

The reported observations in 2 paediatric patients have not identified any new safety concerns and are of limited value. Based on these observations no changes in the SmPC of the product were proposed by the MAH what is endorsed. The benefit risk ratio remains unchanged.

☒ **Fulfilled:**

No regulatory action required.