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Committee for Medicinal Products for Human Use (CHMP)

Vimpat

(Lacosamide)

Procedure No. EMEA/H/C/000863/P46/023

CHMP assessment report for paediatric use studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

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

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I. INTRODUCTION

On 24 March 2014, the Marketing Authorisation Holder (MAH) submitted the results of the study SP0962 (An open label extension study to assess the safety and seizure frequency associated with long-term oral lacosamide for uncontrolled primary generalised tonic-clonic (PGTC) seizures in subjects with idiopathic generalised epilepsy) for Vimpat in accordance with Article 46 of Regulation (EC) No1901/2006, as amended, on medicinal products for paediatric use.

A short critical clinical expert overview has also been provided.

The MAH stated that the submitted study does not influence the benefit risk balance for Vimpat in the paediatric population and that there is no consequential regulatory action.

II. SCIENTIFIC DISCUSSION

II.1 Information on the pharmaceutical formulation used in the study

Lacosamide (LCM) 50mg and 100mg oral tablets were used in the study.

II.2 Clinical aspects

1. Introduction

The MAH submitted a final report for:

- study SP0962, “An open label extension study to assess the safety and seizure frequency associated with long-term oral lacosamide for uncontrolled primary generalised tonic-clonic seizures in subjects with idiopathic generalised epilepsy”.

Lacosamide (LCM) tablets (50mg, 100mg, 150mg, and 200mg), solution for infusion (10mg/mL), and syrup (10mg/mL) have been approved in the European Union/European Economic Area via the centralised procedure as adjunctive therapy in the treatment of partial-onset seizures with or without secondary generalization in adult and adolescent (16 to 18 years) patients with epilepsy. UCB is developing LCM in a range of epilepsy indications including as a treatment of primary generalized tonic-clonic seizures in patients with idiopathic generalized epilepsy (IGE).

Subjects were eligible to participate in SP0962 if they had completed SP0961, without meeting withdrawal criteria or experiencing an ongoing serious adverse event (SAE), and were expected to benefit from participation in an open-label extension study with LCM, in the opinion of the Investigator.
SP0961 was a Phase 2, multicenter, open-label pilot study designed to assess the safety of LCM in subjects with uncontrolled PGTC seizures with IGE. The study was conducted in a total of 19 sites, all in the United States (US). Subjects aged between 16 and 65 years (inclusive) were eligible for enrolment. The study consisted of a 12-week Historical Baseline Phase, a 4-

week Baseline Phase (prospective baseline), a 3-week Titration Phase, a 6-week Maintenance Phase, and a 3-week End-of-Study Phase (for subjects not continuing into the open-label extension study [SP0962]). Subject had been maintained on a stable dose regimen of 1 to 3 marketed antiepileptic drugs (AEDs) for at least 28 days prior to Visit 1 and during the Baseline Phase with or without additional concurrent stable vagus nerve stimulation (VNS).

2. Clinical study

➢ Description

SP0962 was a multicenter, open-label extension study for subjects completing SP0961.

➢ Methods

- Objective(s) – The objectives of this study were to obtain data on the safety and seizure frequency associated with long-term oral LCM for uncontrolled PGTC seizures in subjects with IGE and to allow subjects who completed SP0961 to continue to receive LCM.

- Study design - SP0962 consisted of a 56-week Treatment Period and an End-of-Study Period lasting up to 5 weeks.

- Sample size - 39 subjects enrolled in SP0962 out of a total of 49 subjects who were enrolled in SP0961.

  A total of 3 subjects (6.1%) were <18 years old in SP0961 and 1 of the 3 subjects noted as <18 years old (based on the informed consent date of SP0961) turned 18 prior to signing informed consent in SP0962 (Subject 01126). Details regarding these 3 subjects during the parent study (SP0961) were provided in the CHMP Request for Supplemental Information submitted on 12 Mar 2013 (eCTD sequence LC0134).

- Treatments - Investigators were allowed to increase or decrease the dose of LCM within SP0962 to optimize tolerability and seizure reduction for each subject. Lacosamide doses may have been increased up to a maximum of LCM 800mg/day. The mean maximum daily dose was LCM 464.1mg/day, and the mean modal dose was 428.2mg/day.

- Outcomes/endpoints - The primary variables for assessing safety within SP0962 were:

  - Adverse events (AEs) as reported spontaneously by the subject and/or caregiver or observed by the Investigator

  - Subject withdrawals due to AEs

    Evaluations of seizure frequency were based on subject diaries where types, dates, and number of seizures were recorded.

- Statistical Methods
  The primary variables in this study evaluated safety. All presentations for safety parameters were based on the safety set (SS).

➢ Results

- Recruitment/ Number analysed

  A total of 39 subjects enrolled in this study; 29 subjects (74.4%) completed the study.

- Efficacy results/Safety results

  Ten (10) subjects (25.6%) discontinued the study. The reasons for discontinuation were withdrawal by subject (4 subjects [10.3%]), AE (2 subjects [5.1%]), other (2 subjects [5.1%], lack of efficacy (1 subject [2.6%]), and protocol violation (1 subject [2.6%]). According to the MAH the safety results from SP0962 were similar to what was observed in SP0961, with no major safety concerns arising after extended treatment (>12 months) with LCM in subjects with IGE.

  Two of the 3 subjects who were <18 years old when included in SP0961 completed study SP0962 and 1 discontinued due to "withdrawal by subject".

  Two subjects were 17 years of age at SP0962 study entry.
  One of these subjects had no generalized tonic-clonic (GTC), absence, or myoclonic seizures during SP0962. Treatment-emergent adverse events reported during the study were nausea, abdominal pain lower, headache, arthralgia, red blood cells urine, respiratory disorder, joint stiffness, musculoskeletal pain, feeling abnormal, mood swings, cystitis, bronchitis, upper respiratory tract infection, flank pain, anxiety, gastric pH decreased, abdominal pain, bronchospasm, panic attack, pain, joint sprain, herpes simplex, and blood calcium decreased. The majority of TEAEs reported were mild to moderate in intensity and none were serious. None of the TEAEs led to a dose reduction, and none of the TEAEs were considered related to study drug by the Investigator. Concomitant AEDs used by the subject during the study were ethosuximide, topiramate, and valproate semisodium. The subject discontinued the study prematurely (due to "withdrawal by subject") after 344 days of treatment with LCM in both SP0961 and SP0962 studies.
  The other subject had no GTC, absence, or myoclonic seizures during SP0962. Treatment-emergent adverse events (TEAEs) reported were blood alkaline phosphatise increased, tinea infection, stomach discomfort, gastroenteritis viral, gamma-glutamyltransferase increased, alinine aminotransferase increased, aspartate aminotransferase increased, and hepatitis A all of which were mild to moderate in intensity and none were serious. None of the TEAEs led to a dose reduction, and none of the TEAEs were considered related to study drug by the Investigator. Concomitant AEDs used by the subject during the study were levetiracetam and topiramate. The subject completed SP0962.

3. Discussion on clinical aspects

It is agreed with the MAH that since only 2 subjects were included in this study who were <18 years of age no meaningful conclusions or changes to the benefits and risks can be made from this study regarding the use of LCM in the paediatric population. It was especially noted

that none of the TEAEs reported in the two subjects who were <18 years old when included in SP0962 were serious. Furthermore, none of the TEAEs in these subjects led to a dose reduction, and none of the TEAEs were considered related to study drug by the Investigator. In addition, none of the two subjects had GTC, absence, or myoclonic seizures during SP0962.

III. OVERALL CONCLUSION AND RECOMMENDATION

- **Overall conclusion**

No meaningful conclusions or changes to the benefits and risks can be made from this study regarding the use of LCM in the paediatric population.
No changes to the approved EU Summary of Product Characteristics for VIMPAT are being proposed by the MAH, which is agreed by the CHMP.

- **Recommendation**

No further action required.

IV. ADDITIONAL CLARIFICATIONS REQUESTED

Not applicable