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Procedure Management and Committees Support 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/P46/024

Note

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

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Rapporteur's final assessment report for paediatric studies submitted in accordance with article 46 of regulation (EC) No 1901/2006, as amended

Vimpat

International non-proprietary name: Lacosamide

Procedure no.: EMA/H/C/863/P46 024

Marketing authorisation holder (MAH): UCB Pharma S.A.

Rapporteur:	Filip Josephson
Start of the procedure:	22 February 2015
Date of this report:	11 May 2015
Deadline for Rapporteur's AR:	11 May 2015
Date of the Rapporteur's final report:	11 May 2015

Administrative information

Invented name of the medicinal product:	Vimpat
INN (or common name) of the active substance(s):	Lacosamide
MAH:	UCB Pharma S.A.
Currently approved Indication(s)	Epilepsy
Pharmaco-therapeutic group (ATC Code):	N03AX18
Pharmaceutical form(s) and strength(s):	Film coated tablet (50 mg, 100 mg, 150 mg, 200 mg), Solution for infusion (10 mg) Syrup (10 mg)
Rapporteur: Rapporteur's contact person: Name of the Assessor:	**Name Filip Josephson** Email: filip.josephson@mpa.se **Name Carola Ryner** Email: carola.ryner@mpa.se **Name Dag Nilsson** Tel: +46 18 17 46 00 Email: dag.nilsson@mpa.se
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1. Introduction

On 2 February 2015, the MAH submitted a completed study for Vimpat, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

This procedure concerns the final report for the following study in accordance with Article 46 of Regulation (EC) No 1901/2006:

- EP0008 - A Multicenter , Double-blind , Randomized, Placebo-controlled , Parallel-group Study to Evaluate the Efficacy and Safety of Lacosamide as Adjunctive Therapy in Japanese and Chinese Adults with Uncontrolled Partial -onset Seizures with or without Secondary Generalization.

A subset of the subjects who were randomized to treatment were 16 or 17 years of age at the time of study entry. Therefore, this PAM submission is aimed at fulfilling the requirement of reporting pediatric data as outlined in Article 46, which requires MAH to submit information on studies conducted in children (<18 years of age) treated with lacosamide.

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that EP0008 – "A Multicenter , Double-blind , Randomized, Placebo-controlled , Parallel-group Study to Evaluate the Efficacy and Safety of Lacosamide as Adjunctive Therapy in Japanese and Chinese Adults with Uncontrolled Partial -onset Seizures with or without Secondary Generalization" is part of a clinical development program.

2.2. Information on the pharmaceutical formulation used in the study

The IMP (LCM) was supplied as immediate release, film-coated, tablets in strengths of 50mg and 100mg.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report(s) for:

- EP0008 - A Multicenter , Double-blind , Randomized, Placebo-controlled , Parallel-group Study to Evaluate the Efficacy and Safety of Lacosamide as Adjunctive Therapy in Japanese and Chinese Adults with Uncontrolled Partial -onset Seizures with or without Secondary Generalization.

Of the 548 total EP0008 subjects who were randomized to treatment, 35 were 16 or 17 years of age at the time of study entry.

2.3.2. Clinical study

Description

Methods

EP0008 was a Phase 3, multicenter, double-blind, randomized, placebo-controlled, parallel-group study to evaluate the efficacy and safety of orally administered LCM as adjunctive therapy in Japanese and Chinese adults with uncontrolled partial-onset seizures with or without secondary generalization. Subjects were required to be on a stable dose of at least 1 but no more than 3 concomitant antiepileptic drugs (AEDs).

The duration of the study per subject was up to 27 weeks, including an 8-week Baseline Period and a 16-week Treatment Period. Subjects who fulfilled eligibility criteria should have been enrolled and entered into a Baseline Period (8 weeks) to assess concomitant medications (including AED[s]), adverse events (AEs), and Baseline seizure frequency to ensure consistency with entry criteria before subjects were eligible to be randomized.

At the end of the Baseline Period, subjects were randomized (1:1:1) in a double-blind fashion to 1 of the 3 treatment groups: placebo (twice a day), LCM 200mg/day (100mg twice a day), or LCM 400mg/day (200mg twice a day). The Treatment Period consisted of the following periods: a 4-week forced titration up to the respective randomized dose of LCM (200mg/day or 400mg/day) or placebo (referred to as the Titration Period) and a 12-week maintenance on the dose achieved during the Titration Period (referred to as the Maintenance Period). A single back-titration at the end of the Titration Period was allowed (LCM 200mg/day to LCM 100mg/day; LCM 400mg/day to LCM 300mg/day) if the subject was unable to tolerate the randomized target dose. Once the dose had been reduced, it could not be increased in the Maintenance Period. The Treatment Period was followed by a blinded 2-week Transition Period or a blinded 3-week Taper Period. In general, this study design was consistent with previous pivotal studies for the EU registration of LCM (SP667, SP754, and SP755).

Subjects who completed the Titration Period entered the 12-week Maintenance Period. Subjects were maintained on the dose achieved during the Titration Period. Subjects who required dose reduction during the Maintenance Period must have been withdrawn from the study.

After completion of the Maintenance Period, subjects had the option of enrolling in EP0009, an open-label extension study for continuation of LCM treatment and assessment of long-term safety and maintenance of efficacy; the blinded Transition Period was required for these subjects.

The blinded Taper Period was required for subjects who withdrew during the Titration or Maintenance Periods, and for those who completed the Maintenance Period and chose not to enroll in EP0009. Subjects who withdrew during the Titration or Maintenance Periods came back for the Final Visit 2 weeks after the final study medication intake.

Results

Efficacy results

The primary efficacy variable was the change in partial-onset seizure frequency per 28 days from Baseline to the Maintenance Period, as requested by Pharmaceuticals and Medical Devices Agency in Japan. Key secondary efficacy variables included the 50% response to treatment from Baseline to the

Maintenance Period and the percent change in seizure frequency per 28 days from Baseline to the Maintenance Period.

Consistent with previous studies (SP667, SP754, and SP755), LCM at doses of 200 and 400mg/day was efficacious in reducing partial-onset seizure frequency when used as adjunctive therapy with 1 to 3 approved concomitant AEDs in Chinese and Japanese subjects ≥16 years of age with uncontrolled epilepsy.

Efficacy data was not evaluated separately for the adolescent subjects 16 or 17 years of age.

Safety results

Of the 548 total subjects who were randomized to treatment, 35 were 16 or 17 years of age at the time of study entry.

The median age of the 35 adolescent subjects was 16.0. All subjects were of Asian descent. The gender distribution was similar between the placebo and LCM 200mg/day treatment groups with 6 of 12 and 6 of 11 subjects being male, respectively; however, the proportion of males was higher than females in the LCM 400mg/day group (10 of 12 subjects).

Median body mass index (BMI) was higher in the placebo group (21.32 kg/m2) than in either LCM group (19.05 and 18.92 kg/m2 for LCM 200mg/day and LCM 400mg/day, respectively).

When evaluated by BMI category, none of the subjects who received placebo had a BMI at study entry <18.5kg/m2, compared with 4 of 11 subjects and 5 of 12 subjects in the LCM 200mg/day and LCM 400mg/day groups, respectively.

All 35 adolescent subjects were taking at least 1 AED concomitantly per an inclusion criterion for the study. The most commonly used AEDs taken by ≥7 adolescent subjects overall (≥20%) were carbamazepine (19 of 35 subjects), valproate (18 of 35 subjects), levetiracetam (12 of 35 subjects), lamotrigine (8 of 35 subjects), and topiramate (7 of 35 subjects).

The median number of days of exposure to study drug among the adolescent subjects was identical across the 3 treatment groups for the Titration, Maintenance, and Treatment Periods with values of 29.0, 84.0, and 113.0 days, respectively.

Disposition for this small group of adolescent subjects was comparable to the overall population. Overall, 31 of the 35 adolescent subjects completed the study, and 4 of 35 discontinued the study due to an AE. Discontinuations from the study occurred in the LCM treatment groups with 1 of 11 subjects receiving LCM 200mg/day and 3 of 12 subjects receiving LCM 400mg/day.
Thirty-three of the 35 subjects completed the Titration Period, and 31 completed the Maintenance and Transition Periods. Three of 35 subjects reduced their dose prior to entering the Maintenance Period, and these subjects included 1 subject from each treatment group.
Subject disposition was summarized by treatment group, treatment period, and overall for the subjects who were randomized to treatment in EP0008 and were <18 years of age at study entry (Table 1).

Table 1: Disposition of subjects <18 years of age at study entry (SS)

Disposition	Placebo N=12 n (%)	LCM 200mg/day N=11 n (%)	LCM 400mg/day N=12 n (%)	All subjects N=35 n (%)
Completed study	12 (100)	10 (90.9)	9 (75.0)	31 (88.6)
Discontinued	0	1 (9.1)	3 (25.0)	4 (11.4)
Primary reason for discontinuation				
Adverse event	0	1 (9.1)	3 (25.0)	4 (11.4)
Started Titration Period	12 (100)	11 (100)	12 (100)	35 (100)
Completed Titration Period	12 (100)	10 (90.9)	11 (91.7)	33 (94.3)
Discontinued	0	1 (9.1)	1 (8.3)	2 (5.7)
Primary reason for discontinuation				
Adverse event	0	1 (9.1)	1 (8.3)	2 (5.7)
Started Maintenance Period	12 (100)	10 (90.9)	11 (91.7)	33 (94.3)
Reduced dose prior to entering	1 (8.3)	1 (9.1)	1 (8.3)	3 (8.6)
Completed Maintenance Period	12 (100)	10 (90.9)	9 (75.0)	31 (88.6)
Discontinued	0	0	2 (16.7)	2 (5.7)
Primary reason for discontinuation				
Adverse event	0	0	2 (16.7)	2 (5.7)
Started Transition Period	12 (100)	10 (90.9)	9 (75.0)	31 (88.6)
Completed Transition Period	12 (100)	10 (90.9)	9 (75.0)	31 (88.6)
Discontinued	0	0	0	0

LCM=lacosamide; SS=Safety Set

Note: Completed study was defined as the subject who completed both Visit 8 and the Transition/Taper Period.

AEs

Those TEAEs that occurred in >1 subject in any LCM treatment group are shown in Table 2.

Table 2: Incidence of TEAEs by PT occurring in >1 subject within any LCM treatment group and <18 years of age at study entry (EP0008, SS)

System Organ Class Preferred Term	Placebo N=12 n (%) [#]	LCM 200mg/day N=11 n (%) [#]	LCM 400mg/day N=12 n (%) [#]	LCM Total N=23 n (%) [#]
Any TEAE	11 (91.7) [20]	8 (72.7) [26]	9 (75.0) [36]	17 (73.9) [62]
Gastrointestinal disorders	2 (16.7) [2]	0	4 (33.3) [6]	4 (17.4) [6]
Vomiting	0	0	2 (16.7) [4]	2 (8.7) [4]
Infections and infestations	6 (50.0) [7]	2 (18.2) [3]	2 (16.7) [5]	4 (17.4) [8]
Upper respiratory tract infection	3 (25.0) [4]	0	2 (16.7) [2]	2 (8.7) [2]
Nervous system disorders	3 (25.0) [3]	5 (45.5) [13]	5 (41.7) [10]	10 (43.5) [23]
Dizziness	2 (16.7) [2]	4 (36.4) [12]	4 (33.3) [4]	8 (34.8) [16]
Headache	0	0	3 (25.0) [3]	3 (13.0) [3]

LCM=lacosamide; PT=preferred term; SS=Safety Set; TEAE=treatment-emergent adverse event

Note: [#] represents the number of individual occurrences of the TEAE.

Note: Terms were coded using the Medical Dictionary for Regulatory Activities, Version 16.1.

A total of 62 TEAEs were reported by 17 of 23 subjects across the LCM treatment groups, and 20 TEAEs were reported by 11 of 12 subjects in the placebo treatment group.

The most common SOCs for TEAEs reported among the adolescent subjects receiving LCM were consistent with those observed in the adult population and included nervous system disorders (10 of 23 subjects) and gastrointestinal disorders, infections and infestations, and investigations (4 of 23 subjects each). The most commonly reported TEAEs among subjects who received LCM were dizziness (8 of 23 subjects), headache (3 of 23 subjects), and vomiting (2 of 23 subjects). Headache and vomiting were only reported in the LCM 400mg/day group.

Upper respiratory tract infection was experienced by 3 of 12 subjects in the placebo group and 2 of 23 subjects in the LCM total group. Weight decreased was experienced by 2 of 12 subjects in the placebo group and 1 of 23 subjects in the LCM total group.

All other PTs were experienced by ≤1 subject within any treatment group.

Two subjects experienced an AE that was either an AE of special interest (syncope) for the LCM program or a partial-onset seizure related term (convulsion). One of 12 subjects in the LCM 400mg/day group experienced mild syncope that was considered related to study drug by the investigator. One of 11 subjects in the LCM 200 mg/day experienced mild, intermittent convulsion that was considered not related to study drug by the investigator.

Treatment-related AEs considered related to study drug by the investigator that occurred in >1 subject in any LCM treatment group are shown in Table 3.

Table 3: Incidence of related TEAEs by PT, according to the investigator, occurring in >1 subject within any LCM treatment group and <18 years of age at study entry (EP0008, SS)

System Organ Class Preferred Term	Placebo N=12 n (%) [#]	LCM 200mg/day N=11 n (%) [#]	LCM 400mg/day N=12 n (%) [#]	LCM Total N=23 n (%) [#]
Any TEAE	2 (16.7) [6]	5 (45.5) [17]	9 (75.0) [24]	14 (60.9) [41]
Gastrointestinal Disorders	1 (8.3) [1]	0	4 (33.3) [6]	4 (17.4) [6]
Vomiting	0	0	2 (16.7) [4]	2 (8.7) [4]
Nervous system disorders	2 (16.7) [2]	4 (36.4) [12]	4 (33.3) [7]	8 (34.8) [19]
Dizziness	2 (16.7) [2]	4 (36.4) [12]	3 (25.0) [3]	7 (30.4) [15]
Headache	0	0	2 (16.7) [2]	2 (8.7) [2]

LCM=lacosamide; PT=preferred term; SS=Safety Set; TEAE=treatment-emergent adverse event

Note: [#] represents the number of individual occurrences of the TEAE.

Note: A subject may be counted more than once according to the relationship of the TEAEs.

Note: Terms were coded using the Medical Dictionary for Regulatory Activities, Version 16.1.

Overall, the proportion of subjects with at least 1 related TEAE was higher in the LCM treatment groups than in the placebo group and increased with the higher daily LCM dose (2 of 12, 5 of 11, and 9 of 12 subjects for the placebo, LCM 200mg/day, and LCM 400mg/day groups, respectively).

The most commonly reported related TEAE among subjects who received LCM was dizziness (7 of 23 subjects), and this incidence of related dizziness among subjects receiving LCM was higher than in the placebo group (2 of 12 subjects). Related events of headache and vomiting were only reported in the LCM 400mg/day group (2 of 12 subjects each).

Deaths

None of the 35 adolescent subjects who received study medication died during the clinical study.

Serious adverse events

One adolescent subject of 12 from the placebo treatment group experienced a serious TEAE of pneumonia that was considered unrelated to study drug. No serious TEAEs were reported in either LCM treatment group within this adolescent population.

Treatment-emergent adverse events that led to discontinuation

Four adolescent subjects discontinued the study due to at least 1 TEAE, and these subjects included 1 of 11 subjects in the LCM 200mg/day group and 3 of 12 subjects in the LCM 400mg/day group. None of the adolescent subjects who received placebo discontinued the study due to a TEAE.

Further details of the TEAEs that led to discontinuation are provided in Table 4

Table 4: Treatment-emergent adverse events leading to discontinuation in subjects who were <18 of age at study entry (EP0008, SS)

Dose level of LCM	Subject number	Preferred term	Severityt	Relationship	Continuous/ intermittent	Resolution
200mg/day		Dizziness	Mild	Related	Intermittent	Resolved
400mg/day		Vomiting	Mild	Related	Intermittent	Resolved
		Dizziness	Mild	Related	Intermittent	Resolved
		Headache	Mild	Related	Intermittent	Resolved
		Agitation	Mild	Related	Intermittent	Resolved
		Transaminases Increased	Moderated	Related	Continuous	Resolved
		Aspartate Aminotransferase increased	Mild	Related	Continuous	Resolved
		Blurred vision	Moderated	Related	Intermittent	Resolved
		Nausea	Moderated	Related	Intermittent	Resolved
		Dizziness	Moderated	Related	Intermittent	Resolved

SS=Safety Set

None of the events were deemed serious by the investigator. All the events were considered related to study drug and resolved. Dizziness was experienced by 3 of the 4 subjects who discontinued the study. All other PTs occurred in 1 subject each.

2.3.3. Discussion on clinical aspects

Efficacy data was not evaluated separately for the included 35 adolescent subjects 16 or 17 years of age.

The safety profile among this adolescent Chinese and Japanese population was generally consistent with the established profile of LCM in subjects with partial-onset seizures. The most frequently reported adverse reactions with LCM treatment are dizziness, headache and nausea according to the current SmPC. Other AEs reported in the adolescent in this study are included in the AE profile described in the current SmPC, or AEs frequently reported in young adults (i.e. upper respiratory tract infections). Due to small sample sizes, it is difficult to interpret any small differences between treatment groups. To conclude, no new safety concerns were identified.

3. Rapporteur's overall conclusion and recommendation

The safety profile of the 35 adolescent Chinese and Japanese subjects in EP0008 was consistent with what has been observed with adjunctive LCM treatment in subjects with partial-onse seizures in the pivotal studies. No new or major safety concerns were observed; therefore, the benefit/risk ratio remains favourable.

Overall conclusion

This study is being submitted in accordance with Article 46 of Regulation (EC) No 1901/2006 (The Paediatric Regulation). No changes to the approved EU Summary of Product Information for VIMPAT are being proposed.

Recommendation

X Fulfilled:

Additional clarifications requested

One member state (MS) commented:

The MS agrees with the rapporteur that no new safety concerns were identified in this procedure. However, it is noted that no efficacy results for the subgroup of adolescents were submitted by the MAH. This would be useful as a confirmation that efficacy outcomes in the paediatric subset are consistent with the favourable efficacy outcomes of the overall population studied.

MAH response in summary

Considering that VIMPAT is already approved for use from 16 years of age in this indication in the EU and considering the low number of patients in this age group in the EP0008 study, UCB is of the opinion that a separate analysis of efficacy in this age group will not inform further on the benefit/risk profile of VIMPAT.

In principle and from scientific standpoint, while it is acknowledged that one single severe adverse event may potentially impact the product information, inconsistent efficacy results in one or very few subjects are not expected to trigger any revision of a medicinal product for which the efficacy has been demonstrated through large scale well-controlled clinical studies.

For the sake of transparency, individual patient listings on EP0008 subjects aged from 16 to 17 years are provided in Appendix 1 of this submission in Module 5.3.5.1.

Rapporteur's overall conclusion and recommendation

The rapporteur agrees with the MAH that a separate analysis of efficacy in the 16 or 17 years of age group will not inform further on the benefit/risk profile of VIMPAT considering the low number of patients in this age group in the EP0008 study. For the sake of transparency, individual patient listings on EP0008 subjects aged from 16 to 17 years are provided by the MAH in Appendix 1 of this submission in Module 5.3.5.1. The rapporteur considers therefore the request outlined above by the MS is fulfilled.

This study is being submitted in accordance with Article 46 of Regulation (EC) No 1901/2006 (The Paediatric Regulation). No changes to the approved EU Summary of Product Information for VIMPAT are being proposed.

No regulatory action required.