EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

23 April 2015
EMA/CHMP/382391/2015
Procedure Management and Committees Support Division

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

Keppra

LEVETIRACETAM

Procedure no: EMA/H/C/000277/P46/077

Note

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

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

KEPPRA

International non-proprietary name: Levetiracetam

Procedure no.: EMA/H/C/277/P46-077

Marketing authorisation holder (MAH):UCB Pharma SA

Rapporteur:	Daniel Brasseur
Start of the procedure:	22/02/2015
Date of this report:	23/03/2015
Deadline for Rapporteur's AR:	24/03/2015
Deadline for CHMP member's comments:	08/04/2015
Date of the Rapporteur's final report:	13/04/2015
Outcome	23/04/2015

Administrative information

Invented name of the medicinal product:	Keppra
INN (or common name) of the active substance(s):	Levetiracetam
MAH:	UCB Pharma S.A.
Currently approved Indication(s)	
Pharmaco-therapeutic group (ATC Code):	
Pharmaceutical form(s) and strength(s):	
Rapporteur: Rapporteur's contact person: Name of the Assessor:	**Name Daniel Brasseur** Tel: Email: daniel.brasseur@ext.emea.europa.eu **Name Charles sibilles** Tel: Email: charles.sibilles@afmps.be **Name Anne-Catherine Thomas** Email: anne-catherine.thomas@afmps.be
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1. Introduction

On January 30th 2015, the MAH submitted the final clinical study report for study NO1159, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical clinical overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that study NO1159 is a stand alone study.

2.2. Information on the pharmaceutical formulation used in the study

The study medication was provided as levetiracetam (LEV) 500mg tablets.

2.3. Clinical aspects

2.3.1. Description of the study

Title:

"A double-blind, multicenter, randomized, placebo-controlled study to evaluate the efficacy and safety of adjunctive treatment with oral levetiracetam (L059) in epilepsy patients aged ≥16 years with generalized tonic-clonic (GTC) seizures"

Methods

Objectives

The primary objective was to evaluate the efficacy of LEV treatment used as adjunctive therapy in Japanese and Chinese epilepsy patients aged ≥16 years with uncontrolled GTC seizures despite treatment with 1 or 2 AED(s). The secondary objective was to evaluate the safety and tolerability of LEV treatment.

Study design

N01159 was a double-blind, randomized, 2-arm (1:1), parallel-group, placebo-controlled, multicenter study in Japanese and Chinese subjects aged ≥16 years with uncontrolled GTC seizures, despite treatment with 1 or 2 concomitant AEDs. The study was conducted at 95 sites located in Japan and 20 sites located in China. Subjects were screened at 39 sites in Japan and 19 sites in China.

This study was conducted for 38 weeks and consisted of 4 periods, excluding the 4-week Retrospective Baseline. For those subjects without retrospective Baseline documentation, the

study duration was 42 weeks.

- Baseline Period (8 weeks: 4-week Retrospective Period and 4-week Prospective Period with single-blind placebo (PBO) treatment [or an 8-week Prospective Baseline Period for those subjects without retrospective Baseline documentation])
- Dose Adjustment Period (12 weeks)
- Evaluation Period (16 weeks)
- Conversion (4 weeks) or Withdrawal Period (6 weeks including the 2-week follow-up)

For a subject who completed the Evaluation Period, the investigator decided whether the subject would have benefited from continuing the treatment with open-label LEV at the end of the Evaluation Period. The treatment with open-label LEV was defined as LEV treatment in the long-term follow-up study N01361 in Japan or continuation of treatment with commercial Keppra® under the Named Patient Program in China.

In case the investigator decided to discontinue the subject from the study treatment, the subject went through the Withdrawal Period in order to stop the study medication.

Study population /Sample size

A required sample size of 116 subjects per treatment group (232 in total) was planned; the required number of Japanese subjects was 13 subjects per group (26 in total) and the required number of Chinese subjects was 103 subjects per group (206 in total).

A total of 361 subjects were screened at 58 sites: 303 subjects screened at 19 sites in China and 58 subjects screened at 39 sites in Japan. A total of 251 subjects were randomized (125 to PBO and 126 to LEV). Of the 251 subjects randomized and included in the Randomized Set (RS), 141 subjects (56.2%) completed the study; a greater proportion of subjects randomized to LEV (64.3%) completed the study compared with subjects randomized to PBO (48.0%). The majority of subjects (82.9%) entered the open-label study N01361 (in Japan [81.4%]) or the Named Patient Program (in China [83.2%]).

A total of 15 subjects were <18 years old at study entry (10 subjects were 17 years old; 5 were 16 years old). Four of these subjects were female; 11 were male. See Table 4-1.

Main criteria for inclusion

Male or female subjects aged ≥16 years at Visit 1 must have had GTC seizures that were classifiable according to the International League Against Epilepsy (ILAE) classification of epileptic seizures (Commission on Classification and Terminology of the ILAE, 1981).

Subjects must have had at least 3 GTC seizures during the 8-week Combined Baseline Period (at least 1 GTC seizure during the 4-week Retrospective Baseline Period and at least 1 GTC seizure during the 4-week Prospective Baseline Period).

Historical seizure information (including type, frequency, and date) must have been prospectively recorded on a daily record card (DRC) in order to be acceptable. For subjects without retrospective Baseline documentation, an 8-week Prospective Baseline Period should

have been done. Subjects must have been on a stable dose of 1 or 2 AEDs for the last 4 weeks (potassium bromide and sodium bromide for the last 12 weeks) prior to the Combined Baseline Period and during the Combined Baseline Period.

Table 4–1: Subjects less than 18 years old at study entry in N01159

Subject ID	Age at Visit 1 (years)	Gender	Treatment	Subject disposition
002-00438	17	F	PBO	Discontinued due to lack of efficacy
005-00374	17	M	LEV	Completed
005-00560	17	M	LEV	Completed
010-00265	16	M	PBO	Completed
012-00287	17	F	LEV	Discontinued due to lack of efficacy
013-00362	16	M	LEV	Completed
013-00370	16	M	PBO	Completed
013-00412	16	M	PBO	Discontinued due to lack of efficacy
013-00523	17	M	LEV	Discontinued due to lack of efficacy
014-00499	17	M	PBO	Completed
015-00373	17	F	PBO	Discontinued due to lack of efficacy
019-00505	16	M	PBO	Discontinued due to AE
107-00325	17	F	PBO	Completed
117-00219	17	M	LEV	Completed
153-00352	17	M	LEV	Completed

AE=adverse event; F=female; LEV=levetiracetam; M=male; PBO=placebo
Data source: N01159 CSR Listing 1.3, N01159 CSR Listing 1.4, N01159 CSR Listing 2.1

Treatment

The study medication was provided as LEV 500mg tablets. The selected doses of this study were 1000mg/day and 3000mg/day (2000mg/day for fallback option due to an issue of tolerability).

Outcomes/endpoints

Efficacy: The primary efficacy variable was the percentage reduction from the Combined Baseline (a 4-week Retrospective Baseline + 4-week Prospective Baseline or 8-week Prospective Baseline) in the GTC seizure frequency per week over the 28-week Treatment Period (Dose Adjustment + Evaluation Periods).

The secondary efficacy variables included:

- The percentage reduction in GTC seizure frequency per week from the Combined Baseline over the Evaluation Period

- GTC seizures 50% responder rate (the proportion of subjects with 50% or more reduction from the Combined Baseline in the frequency of GTC seizures) during the Treatment Period
- GTC seizures 50% responder rate (the proportion of subjects with 50% or more reduction from the Combined Baseline in the frequency of GTC seizures) during the Evaluation Period
- GTC seizure freedom over the Evaluation Period

Pharmacokinetics (PK): Levetiracetam plasma concentrations were determined.

Safety: The following safety information was collected during the study:

- Adverse events (AEs)
- Laboratory assessments, including blood biochemistry, hematology, and urinalysis
- Electrocardiograms (ECGs)
- Vital signs
- Body weight

Statistical Methods

In general, summaries were presented:

- By treatment group (LEV, PBO)
- For all subjects (ie, across treatment groups including PBO), with exception of exposure information and almost all safety presentations
- For LEV dose groups (LEV 1000mg/day, LEV 2000-3000mg/day): demography, epilepsy characteristics, and efficacy analyses

Unless otherwise specified, all efficacy analyses were performed for the FAS. The primary and secondary efficacy variables were also analyzed on the Per-Protocol Set (PPS) in order to verify the robustness of the results. Safety and exposure data were analyzed on the SS and PK data were analyzed on the Pharmacokinetic Per-Protocol Set (PK-PPS).

Comparisons were made between LEV (total) and PBO treatment groups. Comparisons between LEV 1000mg/day and PBO (pooled) and between LEV 2000-3000mg/day and PBO (pooled) were exploratory and planned for the primary and secondary efficacy variables.

Seizures, including seizure type, were documented in a DRC. This information was transferred into the Seizure Count electronic Case Report form (eCRF) at each visit retrospectively for the interval between the current and the previous visit. Seizure types for the Retrospective Baseline Period were documented in the Historical Seizure Count (and Historical Cluster Count) eCRF by the ILAE (1981) classification code. Seizures other than generalized seizures (IIA1, IIA2, IIB, IIC, IID, IIE, and IIF) were collectively reported as other seizures in the Seizure Count eCRF for

Visit 1.5 and later. For this reason, seizures classified into IA, IB, IC, and III during the Retrospective Baseline Period were pooled into other seizures in the listings. Generalized tonic clonic seizures were seizures with the ILAE seizure code IIE.

The primary efficacy variable was the percentage reduction from the Combined Baseline in the GTC seizure frequency per week over the 28-week Treatment Period. The percentage reduction was (B-T) / B*100 where B represented the Combined Baseline Period seizure frequency per week and T represented the Treatment Period seizure frequency per week.

The derivation of the number of GTC seizures during the Combined Baseline standardized to a 1-week period, also called GTC seizure frequency per week during Combined Baseline, depended on whether a subject had an "8-week Prospective Baseline" or a combined "4-week Retrospective + 4-week Prospective Baseline."

In general, seizures during Baseline were documented at Visit 1 in the Historical Seizure Count eCRF as well as in the Seizure Count eCRF at Visit 1.5 and Visit 2.

The number of GTC seizures standardized to a week period, also called GTC seizure frequency per week, was computed for a period (eg, Evaluation, Treatment Period) or time interval (eg, time interval from one to the next visit) as:

☐ GTC seizure frequency per week = [(Total number of GTC seizures documented in a certain period)/(Number of days within this period with nonmissing seizure information)] × 7

☐ GTC seizure frequency per week = [(Total number of GTC seizure documented in a certain period)/(End date of the period - Start date (or time interval) - number of days with missing seizure information)] × 7

where dates with missing seizure information, gaps in dates, days with nonmissing information, and days with zero seizure counts were derived as above for the subjects with an "8-week Prospective Baseline."

The confirmatory primary analysis was an analysis of covariance (ANCOVA) on the endpoint "percentage reduction from Combined Baseline of GTC seizures per week" using "treatment"; ie, LEV and PBO, and "country" as factors (categorical predictors) and "Combined Baseline GTC seizure frequency per week" as a covariate (a continuous predictor).

Least squares means for the treatment effects and their difference were provided together with 95% confidence intervals (CIs). The 2-sided p-value for the F-test for treatment effect was calculated. Inferences within ANCOVA were based on Type III sums of squares.

The statistical hypotheses, null hypothesis (H0) and alternate hypothesis (H1), are as follows:

H0: μ LEV = μ PBO vs H1: μ LEV $\neq$ μ PBO,

where μLEV and μPBO are adjusted means for LEV and PBO, respectively.

Results

Subject disposition

Overall, a total of 361 subjects were screened at 58 sites: 303 subjects screened at 19 sites in China and 58 subjects screened at 39 sites in Japan. A total of 251 subjects were randomized (125 to PBO and 126 to LEV). Of the 251 subjects randomized and included in the RS, 141 subjects (56.2%) completed the study; a greater proportion of subjects randomized to LEV (64.3%) completed the study compared with subjects randomized to PBO (48.0%). The majority of subjects (82.9%) intended to enter the Named Patient Program or the open-label study; 83.2% of subjects in China intended to enter the Named Patient Program and 81.4% of subjects in Japan intended to enter the open-label study N01361.

Overall, 110 subjects (43.8%) discontinued the study; there was a higher rate of discontinuation in the PBO group (52.0%) compared with the LEV group (35.7%). In both treatment groups, the most common reason for discontinuation was lack of efficacy (LEV: 21.4%; PBO: 32.0%) followed by AE (LEV: 3.2%; PBO: 6.4%) and protocol violation (LEV: 4.0%; PBO: 4.8%).

Paediatric subjects

A total of 15 subjects were <18 years old at study entry (10 subjects were 17 years old; 5 were 16 years old). Four of these subjects were female; 11 were male. Eight subjects were randomized to PBO and 7 to LEV.

Efficacy results

Levetiracetam was shown to be efficacious across a variety of endpoints when used as an adjunctive therapy with 1 or 2 other AEDs in Chinese and Japanese subjects aged ≥16 years of age. In N01159, subjects were first randomized to PBO or LEV 1000mg/day; subjects who reported no GTC seizures during the Dose Adjustment Period continued on the LEV dose of 1000mg/day (or PBO) and those who reported at least 1 GTC seizure during the same period increased the dose to LEV 3000mg/day or PBO (and could have decreased their dosage back to 2000mg/day as a fallback option if 3000mg/day was not tolerated).

Overall, subjects treated with LEV had an adjusted mean percentage reduction in the frequency of GTC seizures per week between the Combined Baseline Period and Treatment Period of 68.75%, which was a statistically significant improvement over PBO (12.62%, p<0.0001).

By LEV dose, the adjusted mean percentage reduction in the frequency of GTC seizures per week between the Combined Baseline Period and Treatment Period was 87.67% for subjects in the LEV 1000mg/day group and 54.76% for subjects in the LEV 2000 to 3000mg/day group; both dose groups showed statistically significant improvement over PBO (12.84%, p<0.0001). Subgroup analyses showed some descriptive differences in the median percentage reduction in GTC seizure frequency per week over the Treatment Period for Baseline GTC seizure frequency (subjects with <1 seizure per week at Baseline showed a greater reduction compared with subjects with ≥1 seizure per week). There did not appear to be any differences with regard to country, gender, weight, the number of concomitant AEDs, or whether the epilepsy was classified as idiopathic or symptomatic.

Generalized tonic-clonic seizure frequency also showed improvement from the Combined Baseline Period over the Evaluation Period; subjects treated with LEV had an adjusted mean percentage reduction in the frequency of GTC seizures per week between the Combined Baseline Period and Evaluation Period of 68.51%, which was an improvement over PBO (4.16%, p<0.0001).

The GTC 50% responder rates for the Treatment Period in the LEV group were higher compared with the PBO group (77.8% vs 28.4%, respectively). Subjects in the LEV group had higher odds of being a responder compared with subjects in the PBO group (OR: 9.222; p<0.0001). Similar results were observed for the Evaluation Period.

Generalized tonic-clonic seizure freedom over the Evaluation Period in subjects in the LEV group was higher compared with the PBO group (29.6% vs 3.1%; p<0.0001). In addition, subjects in the LEV group had higher odds of being seizure free compared with subjects in the PBO group (OR: 14.237; p<0.0001).

Overall, the time to first GTC seizure during the Evaluation Period for 50% of subjects (95% CI) was 54 days (23 to 82) in the LEV group compared with 9 days (6 to 13) in the PBO group. Similarly, the time to second GTC seizure during the Treatment Period for 50% of subjects (95% CI) was 55 days (41 to 117) for the LEV group compared with 19 days (15 to 24) in the PBO group.

Safety results

The following safety information was collected during the study:

- AEs
- Laboratory assessments, including blood biochemistry, hematology, and urinalysis

- Electrocardiograms (ECGs)
- Vital signs
- Body weight

Overall, the incidence of any treatment-emergent adverse events (TEAEs) was similar in the LEV and PBO groups (57.1% and 52.0% of subjects, respectively). Three subjects died during the study; all were in the PBO group and all were Chinese. A total of 5 subjects reported serious TEAEs during the Treatment Period; the incidence was lower in the LEV group (1 subject [0.8%]), compared with the PBO group (4 subjects [3.2%]). One subject in the LEV group (Subject 012-00329) experienced a serious AE during the Withdrawal Period. The incidences of discontinuations due to TEAEs, TEAEs requiring dose change, and severe TEAEs were similar in the LEV and PBO groups. The incidence of any TEAEs was slightly higher in the LEV group, compared with the PBO group during the Dose Adjustment Period (46.8% and 40.8%, respectively) and Evaluation Periods (37.7% and 31.4%, respectively); the incidence was higher during the Dose Adjustment Period, compared with the Evaluation Period.

Overall, for the system organ classes (SOCs) with most frequently reported TEAEs (≥4% of subjects in any treatment group in the overall population), the incidence was higher in the LEV group, compared with the PBO group, for the Investigations SOC; and the incidence was lower in the LEV group, compared with the PBO group, for the Nervous system disorders SOC. The incidence of most frequently reported TEAEs was higher in the LEV group, compared with the PBO group, for the preferred terms (PTs) of protein urine present, diarrhoea, constipation, neutrophil count decreased, and GGT increased. The incidence of the TEAE of dizziness was lower in the LEV group, compared with the PBO group. The most frequently reported TEAE PT during all study periods was nasopharyngitis. During the Dose Adjustment and Evaluation Periods, the incidence of nasopharyngitis was similar in the LEV and PBO groups. For the TEAEs with higher incidences during the study in the LEV group, compared with the PBO group, the incidences of the PTs of diarrhoea and constipation were higher during the Dose Adjustment Period, compared with the Evaluation Period; the incidences of the PTs of protein urine present, neutrophil count decreased, and GGT increased were similar during the Dose Adjustment and Evaluation Periods.

Overall, the incidence of any TEAEs was similar in male and female subjects in both the LEV and PBO groups. The incidence of TEAEs by SOC and PT was similar in male and female subjects, with the exception of nasopharyngitis (lower incidence in male subjects in both the

LEV and PBO groups), protein urine present (higher incidence in male subjects in the LEV group, and no gender difference in the PBO group), and pyrexia (lower incidence in male subjects in the LEV group and a higher incidence in male subjects in the PBO group).

Overall, a total of 3 subjects died during the study; all subjects were in the PBO group and all were Chinese (2 events of drowning were considered not related and 1 event of sudden unexplained death in epilepsy was considered related to study medication). In addition to the 3 fatal events, 1 Chinese subject reported a serious TEAE of epilepsy. In Japanese subjects, there were no deaths and 1 serious TEAE of pneumonia.

Overall, the incidence of any adverse drug reaction (ADR) was higher in the LEV group (23.8%), compared with the PBO group (13.6%). There were higher incidences in the LEV group, compared with the PBO group, for the most frequently reported ADR PTs of protein urine present, platelet count decreased, neutrophil count decreased, and somnolence. Almost all ADRs were mild or moderate in intensity; only 1 Chinese subject in the PBO group had a severe ADR.

The incidence of any ADR was higher during the Dose Adjustment Period, compared with the Evaluation Period, in both the LEV and PBO groups. The incidence of any ADR was higher in the LEV group, compared with the PBO group, during both the Dose Adjustment and the Evaluation Periods. During the Dose Adjustment Period, there were higher incidences in the LEV group, compared with the PBO group, of the most frequently reported ADR PTs of protein urine present, neutrophil count decreased, and somnolence; the incidence of platelet count decreased was similar in the LEV and PBO groups. During the Evaluation Period, there were higher incidences in the LEV group, compared with the PBO group, of the most frequently reported ADR PTs of protein urine present, platelet count decreased, and neutrophil count decreased. The ADR of somnolence was not reported by any subjects during the Evaluation Period.

Overall, mean and median changes from Baseline in hematology and blood chemistry values were similar in the LEV and PBO groups, and did not show any trends. Few subjects in the LEV and PBO groups had hematology or blood chemistry parameter values that shifted from not possibly clinically significant (PCS) at Baseline to PCS during the study. There were few TEAEs related to abnormal hematology, blood chemistry, or urinalysis parameter results. The most frequently reported TEAE related to abnormal clinical laboratory parameter results was the PT of protein urine present.

Overall, the changes from Baseline in mean and median vital signs were similar in the LEV and PBO groups, and did not show any trends. Few PCS abnormalities in vital sign results were

reported. Few TEAEs related to vital signs were reported.

Overall, no clinically significant abnormal 12-lead ECG findings were reported during the study and there were no shifts from normal or abnormal not clinically significant at Baseline to abnormal clinically significant post-Baseline.

Paediatric subjects

Thirteen of the 15 subjects <18 years old (7 subjects in the PBO group and 6 subjects in the LEV group) had TEAEs. Most TEAEs were mild or moderate in intensity, not related to study medication, and resolved.

One subject in the PBO group (Subject #019-00505) had a fatal TEAE of sudden unexplained death in epilepsy and 1 subject in the LEV group (Subject #117-00219) had a serious TEAE of pneumonia (N01159 CSR Listing 7.4).

Conclusion

Based on the study results, the following conclusions were made:

- LEV at doses of 1000mg/day or 3000mg/day was effective in reducing GTC seizure frequency when used as an adjunctive therapy with 1 or 2 other AEDs in Chinese and Japanese epilepsy subjects with uncontrolled GTC seizures aged ≥16 years of age.
- The evaluation of the safety data demonstrated that LEV was well tolerated. No new safety concerns were identified in this study.

3. Rapporteur's overall conclusion and recommendation

Overall conclusion

Results from study N01159 show that LEV at doses of 1000mg/day or 3000mg/day was effective in reducing GTC seizure frequency when used as adjunctive therapy with 1 or 2 other AEDs in Japanese or Chinese subjects aged ≥16 years.

The evaluation of the safety data demonstrated that LEV was well tolerated. No new safety concerns were identified in this study.

The MAH considers that no changes to the approved EU Product Information for Keppra are proposed following the completion of this study.

At this time, the MAH considers that the standard immediate-release formulations of Keppra allow for appropriate use of LEV in paediatric patients in the EU. This study was solely submitted in accordance with Article 46 of the Paediatric Regulation.

Recommendation

The Rapporteur endorses the submission of this study in accordance with Article 46 of the Paediatric Regulation and confirms that there is no impact on either the Product Information or on the benefit-risk balance of the EU authorized formulations.

☒ **Fulfilled:**

No regulatory action required

Additional clarifications requested

Not applicable