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Committee for Medicinal Products for Human Use (CHMP)

Keppra

(levetiracetam)

Procedure No. EMEA/H/C/000277/P46 65

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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1. RECOMMENDATION

Two studies N01280 and N01281 were submitted in accordance with Article 46 of Regulation (EC) No1901/2006 (Paediatric Regulation), as amended,. After review of the study data, the CHMP considered that there is no impact on either the Product Information or on the benefit-risk balance of the EU authorised formulations.

2. INTRODUCTION

This assessment report concerns two study reports submitted under Article 46 of the Paediatric Regulation. Both studies focused on the extended release (XR) formulation of Keppra, which is licensed in the US but not in the EU.

Keppra XR comes in tablets with strengths of 500 and 750mg, and is indicated in the US as an adjunctive therapy in treatment of partial onset seizures in epileptic patients ≥ 16 years of age.

As this formulation is not authorised at this time in the EU, the Company only submits these studies in accordance with Article 46 of the Paediatric Regulation. No changes on the EU Product Information will result from the study outcomes, and thus there will be no influence on the benefit-risk balance for the approved Keppra formulations.

3. STUDIES

3.1. Study N01280

3.1.1. Introduction

Study N01280 was a Phase III double-blind, historically controlled multicentre trial investigating randomised conversion to monotherapy with Keppra XR for treatment of partial onset seizures.

A total of 60 investigators in 57 centres in the USA, Mexico, Poland and Russia participated.

The study took 29 weeks to complete, including an 8 week baseline period, and 18 week evaluation period, a 1 week down titration period and a 2 weeks treatment free period prior to the final visit.

3.1.2. Objectives

The primary objective of this study was assessment of the efficacy of Keppra XR compared to a historical control in conversion to monotherapy treatment of partial onset seizures.

The secondary objective entailed assessment of the safety and tolerability of 2 doses of Keppra XR is said conversion.

Direct medical resource use and indirect cost parameters were exploratory objectives.

3.1.3. Study Methodology

The study was double-blind, parallel, randomized, 2-arm, historical- controlled, multicenter design. A participating subject went through a number of periods during the study duration: Screening Visit, Baseline Period (8 weeks during which time subjects remained on a stable dose of maximally 2 of their existing antiepileptic drugs (AEDs) and maintained a seizure diary), Evaluation Period, Down-Titration Phase, and Follow-Up Visit.

Patients were randomized through a 3:1 scheme to either receive Keppra XR 2000mg/day or Keppra XR 1000mg/day.

The Evaluation Period consisted of 18 weeks of double-blind treatment, administered in 3 phases: Titration (2 weeks during which subjects were titrated to their targeted Keppra XR dose in a double-blind fashion), Concomitant AED Discontinuation Phase (6 weeks in which subjects were tapered and discontinued from their previous AEDs), and a Monotherapy Phase (10 weeks in which subjects remained on their assigned dosage of Keppra XR monotherapy until either study completion or occurrence of any 1 of 4 exit criteria).

Subjects who completed the study or met protocol-defined exit criteria after the 2-week titration phase, had their dosage down-titrated and received 1000mg/day open-label Keppra XR for 1 week. Final or follow-up visit assessments were required for all subjects who were randomized to treatment.

A total of 223 subjects needed to be randomised (167 in 2000mg/day group and 56 in 1000mg/day group), assuming a 10% drop-out rate, in order to ensure that 200 total subjects were included in the EFF (efficacy analysis) population with 3:1 ratio in 2 treatment arms.

3.1.4. Exclusion and Inclusion Criteria

Only subjects between 12 to 75 years of age with inadequately controlled partial onset epilepsy with observable partial seizures that may have been classified as simple, complex or partial seizures evolving to secondarily generalized seizures could participate. In addition, subjects had to have been experiencing 2 to 40 acute seizures (auras not included) per 4-week period while being maintained on at least 1, but no more than 2 standard AEDs. Subjects had to be on a stable dose for at least 4 weeks before screening (visit 1) of at least 1, but no more than 2 other concomitant AEDs. If taking 2 AEDs, 1 of the Baseline AEDs should have been taken at less than or equal to 50% of the minimum recommended dose.

A history of status epilepticus in the 6 months preceding randomization, seizures that were uncountable due to clustering during the 8-week period prior to screening (visit 1) and during the 8-week Baseline Period or taking neuroleptics and/or traditional herbal AEDs were grounds for exclusion from participation. Lactating or pregnant women were also barred from entry, as were patients suffering from problems which could impact absorption of Keppra XR.

3.1.5. Endpoints

The primary efficacy endpoint was the cumulative exit rate at 112 days after the beginning of concomitant AED discontinuation phase. Subjects who prematurely withdrew from the study for any reason other than the protocol-defined exit criteria were censored as of the last dose of study medication during the combined Concomitant AED Discontinuation and Monotherapy Phases.

These four protocol-defined exit-criteria were:

1. Two-fold increase in the average 28-day partial seizure frequency (PSF) in any 28-day period during the combined Concomitant AED Discontinuation and Monotherapy Phases compared to the average 28-day PSF over the Baseline Period
2. Two-fold increase in the highest consecutive 2-day PSF during the combined Concomitant AED Discontinuation and Monotherapy Phases compared to the highest 2-day PSF observed during the last 56 days of the Baseline Period
3. Occurrence of a generalized seizure if none had occurred in the 6 months prior to randomization
4. An episode of status epilepticus, a prolongation of seizure duration, a worsening of seizure frequency, or emergence of a new seizure type considered by the investigator to require intervention

The secondary efficacy analyses were conducted on the EFF population and were meant for descriptive purposes only:

- The cumulative rate of exit and its 95% CI for 1000mg/day group was calculated and descriptively compared to the historical control exit rate as the secondary efficacy analysis.
- The cumulative rate of exit events, which included meeting a protocol-defined exit criteria, discontinuation due to AE, and discontination due to lack of efficacy, at 112 days after entering the Concomitant AED Discontinuation Phase. For this endpoint, subjects who discontinued from the study during the combined AED D/C and Monotherapy Phases due to other reasons (not due to exit criteria, AE, or lack of efficacy) were censored as of the last dose of study medication during the combined periods
- The cumulative rate of exit or discontinuation events due to any reason at 112 days after entering the Concomitant AED Discontinuation Phase. For this endpoint, subjects who completed through the Final/Completion Visit (Week 26) and did not meet any pre- specified exit criterion of the study were censored at Day 112.

The exploratory endpoints were as follows:

- Average 7-day normalized PSF for the Baseline and Evaluation Periods
- Average 7-day normalized PSF by visit during the Evaluation Period
- Seizure-free days over the Evaluation Period
- The global evaluation of disease evolution using a GES assessed by the investigator at the end of the Evaluation Period
- Medical resources used over the Baseline and Evaluation Period, including healthcare provider consultations not foreseen by the protocol, emergency room visits, and hospitalizations
- Number of working or school days lost by the subject and the number of days with help from a caregiver
- Socio-professional data (driving status, employment status)

3.1.6. Subject Disposition

Out of a total of 303 subjects screened, 228 were randomized to treatment, 57 to the Keppra XR 1000mg group and 171 to the Keppra XR 2000mg group. A total of 191 (83.8%) completed the study, defined as either completed the Final Visit (Week 26) or withdrawn because they met an exit criterion. Thirty seven (16.2%) subjects withdrew from the study; the most common reason for discontinuation was protocol violation, followed by adverse event (AE), withdrawal of consent, other, lost to follow-up, and lack of efficacy.

3.1.7. Efficacy Results

The main efficacy results are summarized in table 1:

Table 1: Main Efficacy Results

	Descriptive Statistics	Keppra XR 2000mg (N=158)
Subjects meeting at least 1 exit criterion [a]	n (%)	56 (35.4)
Exit criterion 1	n (%)	34 (21.5)
Exit criterion 2	n (%)	23 (14.6)
Exit criterion 3	n (%)	12 (7.6)
Exit criterion 4	n (%)	11 (7.0)
Subjects meeting >1 exit criterion	n (%)	18 (11.4)
Time to exit [b]	Median	Undefined
	Q1 to Q3	55.0 to undefined
Estimate of exit rate at Day 112 [b]	Rate	0.375
	95% CI	(0.297, 0.453)*
Historical control exit rate	Rate	0.678
Number of subjects censored prior to Day 112	n (%)	19 (12.0)

*Keppra XR 2000mg/day predicted exit rate is significantly lower than historical control.
a. A subject may be counted under more than 1 exit criteria.
b. Exit rate and time to exit were estimated using Kaplan-Meier methods.

As can be seen, the exit rate at Day 112 for the Keppra XR 2000mg group was significantly lower than the historical control exit rate of 0.678. When comparing the KM (Kaplen-Meier) curves for time to exit, the Keppra XR 2000mg group had a longer time to exit when compared to the same KM curve for the historical control pseudo placebo population based on visual comparison of the slope of the curves.

In both the EFF and PP populations, the estimated rate of exit at Day 112 was significantly lower than that of the historical control. Sensitivity analyses demonstrated that the cumulative exit rate was significantly lower than that of the historical control under each of the conditions tested.

Based on the subgroup analyses, Mexico had a markedly higher proportion of subjects meeting an exit criterion compared to other countries. Subjects withdrawing from carbamazepine as a concomitant AED had a higher rate of exit.

Secondary analyses confirmed the results of the primary analyses.

3.1.8. Safety Results

A total of 177 subjects reported 575 TEAEs during the overall treatment period. Somnolence (21.9% of subjects) was the most commonly reported TEAE, followed by headache (19.7% of subjects). Most reported TEAEs were judged as mild or moderate in severity. Severe TEAEs were reported by 16 subjects overall (7.0%). There were no apparent differences between treatment groups in the incidence of TEAEs. The AE profile was similar to that reported in the US package insert.

There was no evidence for any effect of Keppra XR treatment on laboratory parameters, vital signs, weight, ECG evaluations, physical examinations, or neurological examinations.

3.1.9. Conclusions

In both the EFF and PP populations, the estimated rate of exit at Day 112 (primary efficacy endpoint) was significantly lower than that of the historical control based on the original exit rate of 67.8% and the revised exit rate of 65.3%.

Sensitivity analyses, conducted on the primary endpoint to evaluate the robustness of the effect of Keppra XR 2000mg, demonstrated that the cumulative exit rate was significantly lower than that of the historical control under each of the conditions tested.

Based on the subgroup analyses, Mexico had a markedly higher proportion of subjects (59.0%) meeting an exit criterion compared to other countries (US, 36.0%; Poland, 24.5%; Russia, 26.7%). Subjects withdrawing from carbamazepine as a concomitant AED had a higher rate of exit. Other subgroups did not appear to have an influence on the exit rate.

Secondary efficacy analyses confirmed the results of the primary analyses.

Keppra XR was safe and well-tolerated when administered as monotherapy to subjects with inadequately controlled partial onset epilepsy with observable partial seizures, with an AE profile similar to that reported in the package insert.

3.2. Study N01281

3.2.1. Introduction

Study N01281 was a Phase III open-label, long-term follow-up study with Keppra XR for treatment of partial-onset seizures. Forty-three investigators in 61 centres in the USA, Mexico, Poland and Russia enrolled subjects in the study.

The study took 6 months to 3 years to complete, depending on the time that a subject completed study N01280.

3.2.2. Objectives

The primary objective was was to provide continued treatment of Keppra XR for subjects who participated in the pivotal conversion to monotherapy study (N01280) and to assess the long-term safety of Keppra XR in patients with partial onset seizures.

There were no secondary or exploratory objectives planned.

3.2.3. Study Methodology

The study, an open-label multicentredesign, consisted of three distinct phases: Entry Visit, Treatment Period, and Final/Early Discontinuation Visit.

- The Entry Visit coincided with a subjects last study visit in study N01280.
- The Treatment Period consisted of all subjects receiving a daily dose of 2000mg or less, depending on the tolerability in a subject, open-label Keppra XR for at least 2 weeks. After the initial 2 weeks, the dose of Keppra XR could be adjusted if necessary. If possible Keppra XR monotherapy was mainained, but addition of other AEDs was allowed if needed.
- The Final/Early Discontinuation Visit was done approximately 2 weeks after the last dose of Keppra XR.

There were a total of 190 enrolled subjects in the ITT (Intent To Treat) Population. A total of 189 (99.5%) subjects received treatment and were included in the Safety Population. The same 189 (99.5%) subjects had at least 1 efficacy measurement reported, and were included in the EFF (Efficacy Analysis) population.

3.2.4. Exclusion and Inclusion Criteria

Subject wishing to participate had to have been randomised into the N01280 study and completed its 2-week Up-Titration Period.

Screening failures of N01280 or subjects whom discontinued from N01280 prior to the end of the 2-week Up-Titration Period, or whom were taking neuroleptics and/or traditional herbal AEDs were not eligible for participation. Lactating or pregnant women were also barred from entry, as were patients suffering from problems which could impact absorption of Keppra XR.

3.2.5. Statistical Methods

Summary statistics consisted of frequency and percentage for categorical variables, and descriptive statistics.

3.2.6. Subject Disposition

A total of 190 subjects were enrolled in this study. Of these, 189 (99.5%) received medication. A total of 166 (87.4%) completed the study, defined as all subjects who did not discontinue.

Twenty four (12.6%) subjects withdrew from the study; the most common reason for discontinuation was withdrawal of consent and other reason, followed by AE and protocol violation.

3.2.7. Efficacy Results

Of the subjects who entered the study on Keppra XR monotherapy, 65.3% remained on Keppra XR monotherapy for at least 12 months and 47.1% remained on monotherapy at least 18 months. Two subjects even remained on Keppra XR monotherapy for at least 24 months.

Subjects who remained in the study had a reduction in seizure frequency at all study visits relative to Baseline of the N01280 study, as measured by the median 7-day PSF and the median 7-day seizure frequency based on all seizure types.

3.2.8. Safety Results

Keppra XR was well-tolerated when administered as long-term monotherapy or in combination with other AEDs in subjects with inadequately controlled partial onset seizures. A total of 126 subjects (66.7%) reported 588 TEAEs. Headache (13.8% of subjects) was the most commonly reported TEAE, followed by nasopharyngitis and somnolence (7.9% for each), influenza (5.3%) and dizziness (7.4%). Most reported TEAEs were judged as mild or moderate in severity.

A total of 5 subjects (2.6%) had a TEAE that led to discontinuation. This included 2 subjects (1.1%) who became pregnant. Twenty two subjects (11.6% of the overall population) had a SAE; Convulsion (4 subjects, 2.1%) was the most common treatment-emergent SAE. There was one death (drowning) in a subject aged 18 years. This death was judged to be unrelated to the study medication. A total of 26 subjects (13.8%) experienced at least one psychiatric TEAE during the overall treatment period. Insomnia (4.8%) was the most commonly reported psychiatric TEAE, followed by depression (2.6%) and anxiety (2.1%).

Table 2 on the next page gives a summary on the TEAEs.

There was no evidence for any effect of Keppra XR treatment on laboratory parameters, vital signs, weight, ECG evaluations, physical examinations, or neurological examinations.

Table 2: summary of Treatment-Emergent Adverse Events

	Keppra XR (N=189) n (%)
Total number of TEAEs	588
Subjects with at least 1 TEAE	126 (66.7)
TEAE led to permanent discontinuation	5 (2.6)
Drug-related TEAE	58 (30.7)
At least 1 severe TEAE	22 (11.6)
Psychiatric TEAEs	26 (13.8)
Non-serious TEAEs	123 (65.1)
Subjects with serious TEAEs	22 (11.6)
Drug-related serious TEAEs	4 (2.1)
Number of deaths	1 (0.5)
N=number of subjects in the safety population; n=number of subjects experiencing the event; TEAE=treatment-emergent adverse event; XR=extended release	

3.2.9. Conclusions

Keppra XR was safe and well-tolerated when administered as long-term treatment to subjects with inadequately controlled partial onset epilepsy, with an AE profile similar to that reported in the US package insert for Keppra XR.

Subjects in the study appeared to have maintenance of efficacy as evidenced by the percentage of subjects who remained on Keppra X R monotherapy for at least 12 months.

4. OVERALL CONCLUSIONS

The CHMP considered that the results of the two studies presented by the MAH showed that Keppra XR was effective and safe in long-term treatment of subjects with inadequately controlled partial onset epilepsy.

Nevertheless, Keppra XR is not a registered formulation in the EU, therefore no changes to the approved Product Information for Keppra were proposed following the completion of these studies. The MAH considered that the standard immediate release formulations of Keppra allows for appropriate use of levetiracetam in paediatric patients in the EU. These studies were solely submitted in accordance with Article 46 of the Paediatric Regulations.

However, in case the MAH should one day consider registering the XR formulation in the EU, the CHMP noted that the data as collected in both studies was nowhere near robust enough to support an extension of the approved monotherapy indication of the currently available formulations in the EU. For that to be possible, additional studies and more data were considered to be needed.