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Committee for Medicinal Products for Human Use (CHMP)

Keppra

(levetiracetam)

Procedure No. EMEA/H/C/000277/P46 60

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. Executive Summary

The MAH has submitted results from a paediatric study with the intravenous formulation of levetiracetam. A full description of this study as well as of the other published studies are given in this report.

II. Recommendation[1]

No major modification of the paediatric dosages is necessary. The safety of the recommended doses is confirmed by this new study.
Therefore, no changes to the Product Information are proposed.

III. INTRODUCTION

On August 2010, the Marketing Authorisation Holder (MAH) UCB Pharma submitted a completed paediatric study for Keppra, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended, on medicinal products for paediatric use.

A short critical expert overview has also been provided.

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

IV. SCIENTIFIC DISCUSSION

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

Levetiracetam injection was provided as 500mg/5mL vials (100mg/mL) to be diluted in a 50ml or 100mL polyvinyl chloride pouch for a 15-minute intrevenous (IV) infusion.

IV.2 Clinical aspects

1. Introduction

The Applicant has provided the final report for study N01274, in response to a post-approval commitment for Keppra injection issued by the US Food and Drug Administration (FDA).

2. Clinical study

N01274 Study title:
Open-label, single-arm, multi-center, pharmacokinetic, safety and tolerability study of levetiracetam intravenous infusion in children (4 - 16 years old) with epilepsy.

- **Description**

N01274 is a phase 2, open-label, single-arm, multicenter study evaluating the safety, tolerability and pharmacokinetics of the levetiracetam intravenous 15-minute infusion in children 4 to 16 year old with epilepsy.

- **Methods**

  - Objective(s)
    - **Primary objective :** To evaluate the safety and tolerability of the levetiracetam IV 15-minute infusion administered every 12 hours, either as adjunctive treatment or mono-therapy in children (4 to 16 years old) with epilepsy, either after switching from the equivalent levetiracetam oral dose administration or as a new antiepileptic treatment.

[1] *The recommendation from section V can be copied in this section*

- **Secondary objective:** To assess the pharmacokinetic of the levetiracetam IV 15 minute infusion administered every 12 hours in children (4 to 16 years old) with epilepsy.

- Study design
  This study was a phase 2, open-label, single-arm, multicenter, inpatient study who concerned subjects from 4 to 16 years old. These subjects were hospitalized either for reasons related to seizures which required levetiracetam IV for a short period of time due to uncontrolled seizures, either for temporarily inability to take oral Levetiracetam for medical reasons.

  - **Screening period**: Days 1 to 7 prior to hospitalization. During this period, clinical examinations and tests were performed to confirm the subject's eligibility.
  - **Evaluation period**: Duration of IV infusion treatment with levetiracetam. This period comprised a minimum of 1 complete set of pharmacokinetics sampling over a maximum of 4 days while the subject was inpatient and received a levetiracetam IV 15-minutes infusion every 12 hours. Saliva and plasma samples were taken at scheduled time points for Levetiracetam determination.
  - **Follow-up period**: A final visit was scheduled between 1 to 2 weeks following the final levetiracetam IV infusion.

- Study population /Sample size
  - **Study population:** Subject from 4 to 16 years old, suffering from epilepsy (except status epilepticus), not pregnant, with a body weight of at least 10 Kg.
  - **Sample size:** 11 subjects aged ≥4 to <8 years, 12 subjects aged ≥8 to <12 years and 10 subjects aged ≥ 12 to ≤ 16 years were enrolled.

- Treatments
  - **Description of investigational medicinal product:** Levetiracetam injection was provided as 500mg/5mL vials (100mg/mL) to be diluted in a 50ml or 100mL polyvinyl chloride pouch for a 15-minute IV infusion.
  - **Treatments to be administered (Dose):** Subjects who were already taking levetiracetam oral tablets/oral solution as an antiepileptic drug received an IV dose equivalent to their oral dose, always in bid regiment (levetiracetam 1500mg administered as a 15-minute IV infusion is bioequivalent to levetiracetam 3x500mg oral tablets after a single administration). The first IV infusion was administered 12 hours after the last oral dose of levetiracetam. Subjects who were not taking Levetiracetam oral tablets/oral solution as part of their antiepileptic drug treatment prior to entering the study received an IV dose corresponding to their weight:

Renal function	Weight (Kg)	Dose
Normal	< 50 Kg	20 mg/kg/day
	≥ 50 Kg	1000 mg/day
Moderate renal insufficiency (Creatinine clearance: 30 to 49mL/min)	< 50 Kg	10 mg/kg/day
	≥ 50 Kg	500 mg/day

  - **Method of assigning subjects to treatment:** All subjects received levetiracetam IV infusions. Approximately one half of the subjects were exposed to at least 3 consecutives IV doses. At least one third of the subjects received a high-dose range (≥40mg/Kg/day) of levetiracetam IV.

- Statistical Methods
  - **Data analysis considerations:**
    Categorical data were summarized using frequency tables. Percentages were calculated using the number of subjects in the relevant population or subgroup, for whom data were available for that variable, as the denominator.
    Descriptive statistics for continuous variables included n (number of available observations), mean, median, standard deviation, 25th and 75th percentiles, minimum,

and maximum. For plasma and saliva concentrations, geometric mean and geometric coefficient of variation were calculated.

Adverse events, physical abnormalities, the indication of the medications, medical history, and medical procedures were coded according to the latest version (9.0) of the medical Dictionary for Regulatory Activities (MedDRA®). Medications were coded according to the latest version (2006/Q2) of the World Health Organization (WHO) Drug dictionary.

- **Statistical/analytical issues:** Analyses and summaries of demographic and safety variables were presented by age group categories (≥ 4 to < 8 years, ≥ 8 to < 12 years, ≥ 12 to ≤ 16 years)
- **Determination of sample size:**

Per FDA request:

- 30 subjects who completed the pharmacokinetics assessments were required.
- These subjects should have had a minimum of 4 post-dose pharmacokinetics samples over 1 infusion day.
- Approximately one half of the subjects should had been exposed to at least 3 consecutive IV doses.
- At least one third of the subjects should had received treatment in high-dose range (≥ 40mg/Kg/day) of levetiracetam.

Evaluable subjects were approximately distributed throughout the age categories.

- **Safety analyses:**

- Treatment-emergent adverse events (TEAE) are classified as: led to permanent discontinuation of the study drug, severe TEAE, drug-related TEAE, psychiatric TEAE, non-serious TEAE.
- The severity of adverse events was reported as mild, moderate or severe.
- The relation to study drug was reported as none, unlikely, possible, probable or highly probable.

- **Results**
  - Recruitment/ Number analysed

    Thirty-tree subjects were enrolled, included in the ITT (intent-to-treat) population, and treated (11 subjects aged ≥ 4 to < 8 years, 12 subjects aged ≥ 8 to < 12 years and 10 subjects aged ≥ 12 to ≤ 16 years). Thirty-two subjects were included in the PK-ITT population (11 subjects aged ≥ 4 to < 8 years, 12 subjects aged ≥ 8 to < 12 years and 9 subjects aged ≥ 12 to ≤ 16 years). All 33 subjects completed the study.
  - Baseline data
    - **Epilepsy characteristics:** The majority of the subjects had an unknown etiology for epilepsy, experienced partial onset seizures and were hospitalized for reasons related to seizures. The mean duration of epilepsy was 5.21 years.
    - **General medical and procedure history:** The majority of subjects had at least 1 general medical and procedure history. The most frequently reported system organ class (SOC) was surgical and medical procedures, followed by nervous system disorders.
    - **Prior and concomitant diseases:** The majority of the subjects had at least 1 concomitant disease. The most frequently reported SOC was the nervous system disorders, followed by congenital, familial, and genetic disorders and psychiatrics disorders.
    - **Prior antiepileptic drugs:** The majority of the subjects took at least 1 prior antiepileptic drug. The most frequently reported prior antiepileptic drug was valproic acid.
    - **Concomitant antiepileptic drugs:** All subjects took at least 1 prior or concomitant antiepileptic drug. The most frequently reported concomitant antiepileptic drug was Levetiracetam, followed by valproic acid, lamotrigine, clobazam, oxcarbazepine and topiramate.
    - **Prior and concomitant non antiepileptic drugs:** 52% of the subjects took at least 1 prior or concomitant non antiepileptic drug. The most frequently reported ATC were antiinfectives for systemic use and nervous system. The most frequently reported non antiepileptic drug by generic name was paracetamol.
    - **Treatment compliance:** All subjects who completed the study received study drug according to the protocol.

- Efficacy results
  Not applicable.

- Safety results
  - **Extent of exposure**:

  Ten subjects (30%) received high-dose levetiracetam IV. The number of IV doses received ranged from 1 to 8, and the duration of exposure ranged from 1 to 4 days. Twenty-eight subjects received 3 or more doses of levetiracetam IV.
  - **Adverse events**:

Summary of TEAEs – ITT population

	Age (years)			
	≥4 to <8 N=11	**≥8 to <12** N=12	**≥ 12 to ≤ 16** N=10	**Overall** N=33
	n (%)			
Total number of TEAEs	16	28	21	65
Subjects with at least 1 TEAE	6 (54.5)	9 (75)	6 (60)	21 (63.6)
---Subject with AEs that led to permanent study drug discontinuation	0	0	0	0
---Subjects with drug-related TEAEs	3 (27.3)	3 (25)	2 (20)	8 (24.2)
---Subjects with at least 1 severe TEAE	0	1 (8.3)	0	1 (3)
---Subjects with psychiatric TEAEs	0	0	1 (10)	1 (3)
---Subjects with non serious TEAEs	5 (45.5)	9 (75)	6 (60)	20 (60.6)
Subjects with serious TEAEs	1 (9.1)	2 (16.7)	0	3 (9.1)
---Subjects with drug related serious TEAEs	0	0	0	0
Deaths	0	0	0	0

AE = adverse event; TEAE = Treatment-emergent adverse event; ITT = intent-to-treat; Orange = Percentage of the concerned group's population, Black = Percentage of the overall population.

TEAE were most frequently reported in the UCB SOC nervous system disorders (30% of subjects overall), followed by gastrointestinal disorders (24% of subjects overall).

- Convulsions: 12% of subjects overall
- Vomiting: 9% of subjects overall
- Nausea: 9% of subjects overall
- Dry mouth: 9% of subjects overall
- Hypotension: 9% of subjects overall

No trend in the incidence of TEAEs by aged group was identified.

Most frequently TEAEs occurring in at least 2 subjects in either dose category overall by UCB SOC and MedDRA preferred term – ITT population

	High-dose category (N=10)	**Low-dose category (N=23)**
	N (absolute number and %)	
Subjects with at least 1 TEAE	5 (50%)	16 (70%)
Dry mouth	2 (20%)	
Pyrexia	2 (20%)	
Convulsion		4 (17%)
Vomiting		3 (13%)
Nausea		3 (13%)
Hypotension		3 (13%)
Somnolence		2 (9%)

Most frequently TEAEs occurring in at least 2 subjects by previous levetiracetam use overall by UCB SOC and MedDRA preferred term – ITT population

	Previous use of Levetiracetam (N=21)	No previous use of Levetiracetam (N=12)
	N (absolute number and %)	
Subjects with at least1 TEAE	13 (62%)	8 (67%)
Vomiting	3 (14%)	
Hypotension	3 (14%)	
Nausea	2 (10%)	
Dry mouth	2 (10%)	
Pyrexia	2 (10%)	
Convulsions		3 (25%)
Somnolence		2 (17%)

TEAEs by maximum intensity – ITT population

	Mild TEAE	Moderate TEAE	Severe TEAE
Subjects with at least 1 TEAE (absolute number and %)	13 (39%)	7 (21%)	1 (3%)

The incidence of TEAEs by intensity was similar among the 3 age groups.

Drug-related TEAEs occurring in at least 5 % of subjects overall by UCB SOC and MedDRA preferred term – ITT population

Subjects with at least 1 drug-related TEAE	8 (24%)
Dry mouth	3 (9%)
Somnolence	2 (6%)
Hypotension	2 (6%)

The incidence of drug-related TEAEs was generally similar among the 3 age groups.

- **Death**: None
- **Serious adverse events (SAE)**:

	Group	
	≥4 to <8 years N=11	**≥8 to <12 years** N=12
Number of subjects with a SAE	1 (9%)	2 (17%)
Kind of SAE	Mild fever	Sever vomiting Moderate uncontrolled seizures
Evolution	Resolved	
Relation to study drug	None	None

- **Discontinuation due to adverse event**: None
- **Other significant adverse events:** An event of dermatillomania (psychiatric TEAE) was reported for a 15-year-old male. This event was considered mild and not related to the study drug. The event was ongoing.
- **Pregnancies**: Non
- **Clinical laboratory evaluation (hematology and biochemistry)**:
  Mean values for all hematology parameters and all clinical chemistry were within normal limits at each measured time point.

Individual subject change :

- **Hematology**

	Shifts from normal at Baseline to **low** at the last evaluation period assessment (% of subjects)	Shifts from normal at Baseline to **high** at the last evaluation period assessment (% of subjects)
Hemoglobin	12%	
Erythrocytes	9%	
Hematocrit	9%	
MCHC	6%	
Lymphocyte count	6%	
MCH	3%	
Leukocytes	3%	9%
Lymphocytes	3%	
Neutrophils	3%	9%
Platelets	3%	
Monocyte count		6%
Neutrophil count		6%

No trends by age were evident.

- **Clinical chemistry**

	Shifts from normal at Baseline to **low** at the last evaluation period assessment (% of subjects)	Shifts from normal at Baseline to **high** at the last evaluation period assessment (% of subjects)
Alanine aminotransferase	3%	3%
Calcium	3%	3%
Potassium	3%	
Phosphate		6%
Chloride		6%
Gamma-glutamyl transferase		3%

- **Individual clinically relevant abnormalities**

2 subjects had an adverse event (AE) related to abnormal clinical chemistry findings:
- An AE of blood magnesium decreased: mild, not related to study medication, resolved
- An AE of blood alkaline phosphatise increased: mild, not related to study medication, resolved

No AE related to abnormal haematology findings.

- **Vital sign measurements and physical examination findings**:

Mean values for all vital sign parameters were within normal limits at each measured time point. Three subjects had an event of hypotension during the study.
Most subjects had normal ECG findings at Baseline that remained normal at the last evaluation period assessment. Overall, there was 1 subject (3%) who had a shift from normal at baseline to abnormal at the last evaluation period assessment.

- **Other observations related to safety**:

There were no significant clinical changes in the psychiatric and mental status of the subjects during the trial.

- **Safety conclusions**:

Review of safety data by an independent safety reviewer identified no issues of concern. Overall, analyses of safety data showed that the Levetiracetam 15-minute infusion administered every 12 hours was well tolerated in children and adolescents with epilepsy.

- Clinical pharmacology results

The observed Levetiracetam plasma and saliva concentrations were in the expected range, and the correlation between plasma and saliva concentrations was positive. The regression analysis of concentration data showed a statistically significant association between the levetiracetam saliva and plasma concentration.

3. Discussion on clinical aspects

In the two following tables, the major clinical studies in children found in the literature are summarised. In the first table, the administration of levetiracetam was intravenous, while it was taken orally in the studies of the second table.

Information found in the literature, about the safety of the utilization of levetiracetam **IV** in children with epilepsy.

	References				
	Goraya JS, Khurana DS. ***Intravenous Levetiracetam in children with epilepsy***. Pediatr Neurol 2008; 38(3):177-180.	Kirmani BF, Crisp ED. ***Role of intravenous Levetiracetam in acute seizure management of children***. Pediatr Neurol 2009; 41(1):37-39.	Abend NS, Monk HM. ***Intravenous Levetiracetam in critically ill children with status epilepticus or acute repetitive seizures***. Pediatr Crit Care Med 2009; 10(4):505-510.	Reiter PD, Huff AD. ***Intravenous Levetiracetam in the management of acute seizures in children***. Pediatric Neurol 2010; 43(2):117-121.	Ng YT, Hastriter EV. ***Intravenous Levetiracetam in children with seizures: a prospective safety study***. J Child Neurol 2010; 25(5):551-555.
Type of study	Retrospective	Retrospective	Retrospective	Retrospective	Prospective, open.
Number of patients	10	32	10	73 with 42 cases considered as valid for analysis.	30
Age	3 weeks to 19 years	2 months to 18 years	Mean age : 5 years Age range: 0.08 to 14 years (so cited in the publication).	Mean age : 5.59 years Age range : 1 day to 17.8 years	Mean age : 6.3 years 6 months to 14.8 years
Indication	Acute repetitive seizures/status epilepticus, temporarily replacement for oral Levetiracetam for medical reasons, seizure prophylaxis during brain biopsy, maintenance treatment after	Status epilepticus, acute exacerbation of seizures and increased intensity of infantile spasms.	Status epilepticus, including refractory or non-convulsive status, or acute repetitive seizures.	Acute seizure: Serial seizures, single seizure, status epilepticus.	

	acute seizures, substitute for sodium valproate.				
Dose	Mean dose : 50.5 mg/kg/day Maximum dose : 115mg/kg/day	Loading dose : 25-70 mg/kg Most patients received a bolus administration of 50mg/kg, followed by a maintenance dose of 25mg/kg every 12 hours	Loading dose range : 6.5-31 mg/kg	Mean dose : 29.4 mg/kg	50 mg/kg
Duration	Mean duration : 4.9 days Maximum duration : 16 days	24-48 hours	Information not found	Most patients were placed on levetiracetam as a maintenance regimen within 24 hours of the intravenous loading dose.	Single dose
Adverse events (AE)	No serious AE. Side effects might have been overlooked because most of the patients were very sick. All patients completed the treatment for the intended period. Most frequent AE: headache and fatigue.	No serious side effects were evident. No immediate side effects were evident during or after infusions. In one patient Levetiracetam was discontinued because of rash. One patient developed behavior issues, who responded to vitamin B6.	No acute AE. Long term AE were not assessed in this study.	Levetiracetam was well tolerated. 12 adverse drug effects were noted, with behavioral effects most common (aggression/irritability/mood swing), followed by gastrointestinal upset, ataxia and increased hunger.	No serious AE. Minor reactions included sleepiness, fatigue, and restlessness.

Brief summary of the information found in the literature, about the safety of the utilization of **oral** Levetiracetam in children with epilepsy.

	References		
	Grosso S, Cordelli DM. ***Efficacy and safety of Levetiracetam in infants and young children with refractory epilepsy***. Seizure 2007; 16(?):345-350.	Lee YJ, Kang H-C. ***Efficacy and safety of adjunctive Levetiracetam therapy in pediatric intractable epilepsy***. Pediatr Neurol 2010; 42(2):86-92.	Obeid M, Pong AW. **Efficacy and tolerability of high oral doses of Levetiracetam in children with epilepsy**. Epilepsy Res 2010 ;?(?)?-?
Dose	Two equal daily doses of 5-10 mg/kg. The dose was increased every week up to a maximum of 62mg/kg/day.	Mean maintenance dose: 47 mg/kg/day Target dose: 20-60 mg/kg/day	Median dose: 146 mg/kg/day Range dose: 70-275 mg/kg/day
Adverse events (AE)	AE were seen in 28 (34%) patients. The main side effects were drowsiness and nervousness. AE were either tolerable or resolved in time with dosage reduction or discontinuation of the drug.	None of the AE was life threatening. The most common complaint was irritability.	AE were observed in 4 patients (12%), and were behavioral (irritability, hyperactivity).

In study N01274, the number of paediatric subjects was equally balanced between the three groups, i.e. 4 to 8 years, 8 to 12 years, and 12 to 16 years. All 33 subjects of the ITT population completed the study. All subjects took at least 1 prior or concomitant antiepileptic drug. The normal dose of IV levetiracetam was 20 mg/kg/day. However, one third of the children received the high dose regimen (≥ 40 mg/kg/day). In the five clinical studies cited here above, the daily IV doses of levetiracetam were generally higher than these doses. In most studies the children received 30 to 50 mg/kg/day, with a maximum of 115 mg/kg/day. The duration of these studies was comprised between 1 to 5 days, thus fully in keeping with the duration of study N01274 (1 to 4 days).

The observation of the undesirable effects showed **no serious adverse reactions**, neither in the study reported here, nor in the 8 paediatric studies found in the literature (5 with IV administration – 3 with oral intake of levetiracetam). In study N01274, there were no more adverse reactions in the high dose regimen group (n = 10) than in the low dose group of levetiracetam (n = 23). Even with higher doses (50 to 70 mg/kg/day), few adverse effects were reported: irritability, headache, nausea and vomiting. No major changes of the haematological parameters and of the clinical chemistry were observed (in the studies from the literature).

In the **SmPC** of Keppra® IV the therapeutic initial dose in children aged 4 to 11 years and adolescents (12 to 17 years) weighing less than 50 kg is 10 mg/kg twice daily. The dose can be increased up to 30 mg/kg twice daily. The lowest effective dose should be used. These doses recommendations can be maintained as the safety of them has been confirmed in the clinical study reported here. Higher doses have been safely used in the literature studies. Moreover, younger children have been treated with the same doses or with higher ones, without showing any serious adverse effects.

The observed levetiracetam plasma and saliva **concentrations** were in the expected range, and the correlation between plasma and saliva concentrations was positive. The regression analysis of concentration data showed a statistically significant association between the levetiracetam saliva and plasma concentration.

References

- Abend NS, Monk HM. ***Intravenous Levetiracetam in critically ill children with status epilepticus or acute repetitive seizures***. Pediatr Crit Care Med 2009; 10(4):505-510.
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V. Overall Conclusion and Recommendation

➢ **Overall conclusion**

The CHMP concluded that the data analysed in this study and in studies available from the literature showed that the recommended doses of IV levetiracetam for children 4 to 12 years are safe and well tolerated.

➢ **Recommendation**

As the doses tested in study N01274 are in line with the already recommended doses in the SmPC of IV levetiracetam, the CHMP considered that no changes to the Product Information were required.