17 March 2011
EMA/163062/2013
Committee for Medicinal Products for Human Use (CHMP)

Keppra

(levetiracetam)

Procedure No. EMEA/H/C/000277/P46 62

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

7 Westferry Circus ● Canary Wharf ● London E14 4HB ● United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7418 8416
E-mail info@ema.europa.eu **Website** www.ema.europa.eu
An agency of the European Union

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

AE	adverse event
AED	antiepileptic drug
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BID	bis in die (twice daily)
BMI	body mass index
BP	blood pressure
CDMS	clinical data management system
CFR	Code of Federal Regulation
CRF	case report form
CV(%)	coefficient of variation
DBP	diastolic blood pressure
ECG	electrocardiogram
EDV	Early Discontinuation Visit
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
HR	heart rate
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IGE	Idiopathic Generalized Epilepsy
ITT	intent-to-treat
IV	intravenous
JME	Juvenile Myoclonic Epilepsy
LEV	levetiracetam
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
PGTC	primary generalized tonic-clonic
PK	pharmacokinetic(s)
PK-ITT	pharmacokinetic intent-to-treat
Q1	25th percentile
Q3	75th percentile
SAE	serious adverse event
SBP	systolic blood pressure
SD	standard deviation
SDV	source data verification
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SOC	system organ class
TEAE	treatment-emergent adverse event
WHO	World Health Organization
XR	extended release

1. RECOMMENDATION

The CHMP endorsed the MAH's conclusions. No further action was required.

2. INTRODUCTION

Levetiracetam (LEV) is an antiepileptic consisting of the S-enantiomer of α-ethyl-2-oxo-1-pyrrolidine acetamide. The tablet formulation of the drug has been approved in Europe since 2000 and has since then been joined by oral solution, injection, and extended release (XR) tablet formulations.

Approved indications in the EU consist of:

Monotherapy in the treatment of partial onset seizures with or without secondary generalization in patients from 16 years of age with newly diagnosed epilepsy.

Adjunctive therapy in:

- treatment of partial onset seizures with or without secondary generalization in adults, children and infants from 1 month of age with epilepsy, except for the IV formulation which is limited to patients from 4 years of age and older.
- treatment of myoclonic seizures in adults and adolescents from 12 years of age with Juvenile Myoclonic Epilepsy.
- treatment of primary generalized tonic-clonic seizures in adults and adolescents from 12 years of age with Idiopathic Generalized Epilepsy.

Prior to US FDA approval of Keppra injection, UCB committed to conduct a post-approval study to assess the pharmacokinetics (PK), safety, and tolerability of the IV formulation of LEV in children aged 1 month to <4 years and in children aged 4 to 16 years. The study discussed here concerns the former.

3. STUDY DESIGN

This trial was a Phase 2, open-label, single-arm, multicenter study evaluating the safety, tolerability, and PK of the LEV IV 15-minute infusion in children (1 month to <4 years old) with epilepsy (except status epilepticus).

Subjects were hospitalized and had received LEV oral solution at a stable, twice-daily (bid) dose regimen for at least 5 days prior to the first LEV IV infusion and had presented with medical conditions that required temporary IV administration of LEV, or required LEV IV treatment for a short period of time prior to considering continuing AED treatment with LEV oral solution. A screening period of 1 to 7 days was used during which the subject's eligibility was confirmed.

The planned evaluation period for a subject consisted of a minimum of 1 complete set of PK sampling over a maximum of 4 days while the subject was inpatient and receiving a LEV IV 15-minute infusion every 12 hours. The first IV infusion was to be administered 12 hours after the final oral dose of LEV.

IV dosing, equivalent to oral dosing or calculated on age and weight, was as follows:

- ≥1 month to <6 months age: 7mg/kg bid to 21mg/kg bid
- ≥6 months to <4 years: 10mg/kg bid to 30mg/kg bid

The LEV IV dose had to be stable during the PK sampling period no wash out period was foreseen, and when necessary for the safety of the subject or when the investigator deemed it appropriate, the LEV IV dose could be modified once the PK samples were taken. In case an infant was preterm, the corrected gestational age had to be used when calculating the dose.

Plasma samples were taken for LEV determination on Day 1 (optionally on Day 2, Day 3, and Day 4) at the following time points around the morning infusion:

- 3 to 10 minutes after the start of infusion
- 15 minutes (at the end of the LEV IV infusion)
- Between 40 and 60 minutes post infusion

- Between 5 and 8 hours post infusion

A Final Visit was scheduled between 1 and 2 weeks following the final LEV IV infusion.

A schematic representation of the schedule is given below:

Table 1: Study schedule of assessments

Study period	Screening	Baseline	Evaluation (inpatient)								End of Treatment/ EDV[a]	Final Visit
Day and time	D-7 to D-1	D0[b]	D1[b]		D2		D3		D4[c]			D11 to D18
			am	pm	am	pm	am	pm	am	pm		
Assessments												
Written informed consent	X											
Subject trial card dispensing	X											
Demographic data	X											
Verification of inclusion/exclusion criteria[d]	X	X										
Withdrawal criteria		X	X	X	X	X	X	X	X	X		
General medical/procedures history	X											
Epilepsy history/AED history	X											
Physical exam/neurological exam	X										X	X
Vital signs[e]	X	X	X	X	X	X	X	X	X	X	X	X
Body weight and height[f]	X										X	X
12-lead ECG[g]	X		X[h]								X	
Safety laboratory tests – blood[g,i]	X										X	X
LEV plasma concentrations – PK[j]			X		X		X		X			
Recording of concomitant medication (AEDs and non-AEDs) and concurrent procedures	X	X	X	X	X	X	X	X	X	X	X	X
Recording of adverse events		X	X	X	X	X	X	X	X	X	X	X
Hospitalization[k]		X	X	X	X	X	X	X	X	X	X	
LEV IV infusion[l]			X	X	X	X	X	X	X	X		
Investigational product accountability			X	X	X	X	X	X	X	X	X	
End of study status												X

AED=antiepileptic drug; D=day; ECG=electrocardiogram; EDV=Early Discontinuation Visit; IV=intravenous; LEV=levetiracetam; PK=pharmacokinetic(s)

[a] End of Treatment exams were performed in the morning of the last infusion day.

[b] When deemed necessary, Screening, Baseline (Day 0), and first IV infusion (Day 1) may have occurred on the same day. All Screening procedures and results of examinations must have been available to allow verification of subject's eligibility.

[c] D4 stands for Day 4 or last infusion day.

[d] Inclusion/exclusion criteria were assessed at Screening and re-assessed at Baseline to ensure that subjects met the required criteria before starting any LEV IV infusion.

[e] Vital signs included measurements of blood pressure and heart rate.

[f] Height was measured only at Screening.

[g] Results of the 12-lead ECG and the blood laboratory tests performed at Screening should have been available at Baseline to confirm that the subject met all required criteria before starting any LEV IV infusion.

[h] The ECG should have been performed on the day of the first infusion (Day 0 or Day 1 as applicable), prior to any procedure needed to set the infusion. If the ECG at Screening was performed less than 2 days prior to the first infusion and was normal, the ECG at Day 0 or Day1 should not be repeated.

[i] Safety blood laboratory tests included hematology and biochemistry.

[j] For subjects who need to start LEV IV infusion in the afternoon/evening of Day 0, collection of blood samples for PK assessments started the following morning with the second IV infusion (Day 1). The following blood samples for PK assessments were optional: those taken on Day 2, Day 3, and Day 4, with the following morning IV infusion.

[k] Subjects should have been hospitalized for the duration of the LEV IV treatment. Admission to the hospital should have taken place at least the day prior to the start of the first LEV IV infusion. However, when necessary for the wellbeing of the subject or when investigator deemed it appropriate, the hospitalization could have started on the same day as the first IV infusion. Discharge occurred as soon as the investigator deemed it appropriate (ie, the subject is in good medical condition).

[l] First LEV IV infusion preferably should have taken place in the morning. If needed, LEV IV infusions could have been started the afternoon of Day 0.

In total 6 protocol amendments were made of which the most important resulting changes were exclusion of subjects being treated with Vigabatrin in Germany, revision of the age categories to have more balanced age groups and the requirement that at least one third of the subjects should be in the high-dose range

4. OBJECTIVES

Primary

Evaluation of the safety and tolerability of the LEV IV 15-minute infusion administered every 12 hours, either as adjunctive treatment or monotherapy in children (1 month to <4 years old) with epilepsy (except status epilepticus), either after switching from the equivalent LEV oral dose administration or as a new antiepileptic treatment.

Secondary

Assessment of the pharmacokinetics (PK) of the LEV IV 15-minute infusion administered every 12 hours in children with epilepsy in the age range of 1 month to <4 years.

5. IN- & EXCLUSION CRITERIA

Inclusion

- Signed and dated informed consent
- Suffering from epilepsy
- Male or female between 1 month to <4 years of age
- Body weight at Screening was at least 3kg (amended to 8 at one site)
- Acute need of a short treatment with LEV IV
- If on LEV oral treatment: a stable dose regimen for at least 5 days prior the first LEV IV infusion.
- Inpatient
- Subject/legally acceptable representative considered reliable and capable of adhering to the protocol
- Concomitant enzyme inducing AEDs had to be stable over the 4 weeks prior to the first LEV IV infusion. A change of dose or new introduction was:
    - Acceptable at any time if a one single-dose administration
    - Accepted if repeated administration occurred ≤24 hours prior to the first LEV IV infusion
    - Not accepted if repeated administration occurred ≥72 hours prior to the first LEV IV infusion
    - Considered on a case-by-case basis (depending on the AED and its dosage) if repeated administration occurred between these 2 limits: >24 hours and <72 hours prior to the first LEV IV infusion

Exclusion

- Difficult venous accessibility.
- History of status epilepticus during the 3 months prior to screening.
- Allergy to pyrrolidone derivatives or a history of multiple drug allergies.
- Clinically significant acute or chronic illness
- Any medical condition that might interfere with his/her study participation
- Terminal illness.
- Depressive symptoms and/or suicidal ideation and/or behavior.
- Clinically significant ECG abnormalities
- Clinically significant abnormal blood pressure and/or heart rate
- Clinically significant deviations from reference range values for laboratory parameters
- Subject received any investigational drug or device within the 30 days prior to screening.
- Use of felbamate with less than 18 months continuous exposure before screening.
- Ketogenic diet (currently or within 30 days prior to Screening).

- Previously allocation or received study treatment during this study.
- Investigator's, co-investigator's or any study collaborator's children were not to participate
- Included as subjects in the study.
- In Germany subjects currently on vigabatrin were excluded

6. POPULATION

As per the FDA request it was planned to include 18 subjects in the trial whom had to complete the PK assessments. They should have 4 post-dose PK samples over 1 infusion day available or alternatively at least 5 PK samples in case of LEV IV treatment lasted more than 1 day. The approximate distribution throughout the age brackets was planned as follows:

- 6 subjects: ≥1 month to <6 months
- 6 subjects: ≥6 months to <2 years
- 6 subjects: ≥2 years to <4 years

One half of the subjects were to be exposed to at least 3 consecutive IV doses and at least one third of the subjects had to receive a high-dose range (≥28mg/kg/day for subjects ≥1 month to <6 months and ≥40mg/kg/day for subjects ≥6 month to <4 years).

7. STATISTICAL METHODS

Categorical data were summarized using frequency tables, while descriptive statistics were used for continuous data. Plasma concentrations were described by way of calculation of both geometric mean and geometric coefficient of variation.

With regards to safety analysis the adverse events, physical abnormalities, the indication of the medications, medical history, and medical procedures were coded according to the latest version of the Medical Dictionary for Regulatory Activities (MedDRA). Unresolved

8. POPULATION RESULTS

In total 19 persons out of 23 volunteers were enrolled in the study. 6 in the ≥1 month to <6 months group, 6 in the ≥6 months to <2 years group, and 7 in the ≥2 years to <4 years group. Of these 19, sixteen completed the study. All subjects who completed the study received study drug according to the protocol

Subject disposition is given in table 2 below:

Table 2: Subject disposition

	Age			
	≥1 month to <6 months (N=7)	≥6 months to <2 years (N=8)	≥2 years to <4 years (N=8)	Overall (N=23)
	n (%)			
Screened	7 (100)	8 (100)	8 (100)	23 (100)
Enrolled	6 (85.7)	6 (75.0)	7 (87.5)	19 (82.6)
ITT population	6 (85.7)	6 (75.0)	7 (87.5)	19 (82.6)
Completed the study[a]	6 (100)	4 (66.7)	6 (87.5)	16 (84.2)
Discontinued from the study	0	2 (33.3)	1 (14.3)	3 (15.8)
Adverse event	0	1 (16.7)	0	1 (5.3)
Lost to follow-up	0	0	0	0
Withdrawal of consent for personal reasons not related to adverse event	0	0	0	0
Other	0	1 (16.7)	1 (14.3)	2 (10.5)
PK-ITT population	6 (85.7)	4 (50.0)	7 (87.5)	17 (73.9)

ITT=intent-to-treat; PK=pharmacokinetic
[a] All subjects received at least 1 IV infusion.

Overall, 17 subjects (90%) had at least 1 important protocol deviation: 5 (83%) in the ≥1 month to <6 months years group, 5 (83%) in the ≥6 months to <2 years group and 7 (100%) in the ≥2 years to <4 years group. The most frequent important protocol deviation was procedure noncompliance (16 subjects, 94% overall). Within this category, the most frequent deviations were deviation in timing of vital signs (12 subjects overall) and deviation in timing of PK sampling (6 subjects overall). None of these important deviations had an impact on the safety or PK results however.

Study population demographic breakdown is given in table 3. Differences among age groups in weight, height, and BMI were noted, but were also expected.

Table 3: Demographic and other Baseline characteristics

Characteristic	Descriptive Statistics	Age			
		≥1 month to <6 months (N=6)	≥6 months to <2 years (N=6)	≥2 years to <4 years (N=7)	Overall (N=19)
Age (years)	n	6	6	7	19
	Mean (SD)	0.22 (0.10)	1.50 (0.52)	2.86 (0.77)	1.59 (1.24)
	Median	0.25	1.70	2.40	1.70
	Min – Max	0.1 – 0.3	0.5 – 1.9	2.1 – 3.9	0.1 – 3.9
Gender	n	6	6	7	19
Male	n (%)	5 (83.3)	3 (50.0)	4 (57.1)	12 (63.2)
Female	n (%)	1 (16.7)	3 (50.0)	3 (42.9)	7 (36.8)
Race	n	6	6	7	19
Black	n (%)	0	0	2 (28.6)	2 (10.5)
Caucasian	n (%)	3 (50.0)	2 (33.3)	2 (28.6)	7 (36.8)
Other	n (%)	3 (50.0)	4 (66.7)	3 (42.9)	10 (52.6)
Weight (kg)	n	6	6	7	19
	Mean (SD)	5.32 (1.89)	10.72 (2.96)	13.74 (2.90)	10.13 (4.38)
	Median	5.00	12.00	14.00	10.70
	Min – Max	3.0 – 7.7	6.0 – 13.8	10.3 –17.4	3.0 – 17.4
Height (cm)	n	6	6	7	19
	Mean (SD)	54.33 (7.53)	75.67 (7.63)	89.29 (9.29)	73.95 (16.77)
	Median	54.00	72.50	87.00	74.00
	Min – Max	47.0 – 64.0	69.0 – 87.0	74.0 – 101.0	47.0 – 101.0
BMI (kg/m^2)	n	6	6	7	19
	Mean (SD)	17.50 (2.61)	18.77 (5.42)	17.80 (6.38)	18.01 (4.89)
	Median	17.15	17.30	15.00	16.70
	Min – Max	13.6 – 21.4	12.6 – 28.2	14.1 – 31.8	12.6 – 31.8

BMI=body mass index; ITT=intent-to-treat; max=maximum; min=minimum; SD=standard deviation

Baseline epilepsy etiology for the study population was as follows:

Confirmed or Suspected Etiology of Epilepsy	Descriptive Statistics	Age >=1m to <6m (N=6)	Age >=6m to <2yr (N=6)	Age >=2yr to <4yr (N=7)	Overall (N=19)
Epilepsy Duration (years) (a)	N	6	6	7	19
	Mean (SD)	0.145 (0.124)	0.752 (0.618)	1.226 (1.199)	0.735 (0.894)
	Median	0.105	0.670	1.160	0.300
	Q1 - Q3	0.040 - 0.250	0.150 - 1.470	0.230 - 2.070	0.110 - 1.290
	Min - Max	0.030 - 0.340	0.070 - 1.480	0.110 - 3.420	0.030 - 3.420
Etiology Unknown	n (%)	1 (16.7)	1 (16.7)	4 (57.1)	6 (31.6)
Etiology Known	n (%)	5 (83.3)	5 (83.3)	3 (42.9)	13 (68.4)
Genetic Origin Or Idiopathic	n (%)	0	0	0	0
Congenital Malformation	n (%)	1 (16.7)	2 (33.3)	1 (14.3)	4 (21.1)
Asphyxia During Birth	n (%)	1 (16.7)	1 (16.7)	0	2 (10.5)
Complications Due To Pregnancy	n (%)	0	1 (16.7)	0	1 (5.3)
Intra-Uterine Viral Infection	n (%)	0	0	0	0
Cranial Trauma	n (%)	0	0	0	0
Cerebral Neoplasm	n (%)	0	1 (16.7)	0	1 (5.3)
Brain Surgery	n (%)	0	0	0	0
Primary Degenerative Lesion	n (%)	0	0	0	0
Cerebrovascular Accident	n (%)	0	0	0	0
Cerebral Infection	n (%)	1 (16.7)	0	0	1 (5.3)
Others	n (%)	2 (33.3)	0	2 (28.6)	4 (21.1)

All subjects had at least 1 concomitant disease, which were most frequently reported in the nervous system disorders SOC (11 subjects; 58%), followed by the SOCs gastrointestinal disorders (9 subjects; 47%); congenital, familial, and genetic disorders (8 subjects; 42%); and surgical and medical procedures (8 subjects; 42%).

The majority of subjects (12 subjects; 63% overall) in the ITT population took at least 1 prior AED: 4 subjects (67%) in the ≥1 month to <6 months group, 4 subjects (67%) in the ≥6 months to <2 years group, and 4 subjects (57%) in the ≥2 years to <4 years group. The most frequently reported prior AED was valproic acid (4 subjects; 21% overall): no subjects (0%) in the ≥1 month to <6 months group, 2 subjects (33%) in the ≥6 months to <2 years group, and 2 subjects (29%) in the ≥2 years to <4 years group.

Use of concomitant AEDs was as follows:

Parameter Generic Drug name	Age >=1m to <6m N=6 n (%)	Age >=6m to <2yr N=6 n (%)	Age >=2yr to <4yr N=7 n (%)	Overall N=19 n (%)
Number of Subjects with At Least One Concomitant AED (a)	6 (100)	3 (50.0)	7 (100)	16 (84.2)
CARBAMAZEPINE	1 (16.7)	0	0	1 (5.3)
CLONAZEPAM	0	3 (50.0)	0	3 (15.8)
DIAZEPAM	0	0	2 (28.6)	2 (10.5)
LAMOTRIGINE	0	0	1 (14.3)	1 (5.3)
LEVETIRACETAM	1 (16.7)	1 (16.7)	1 (14.3)	3 (15.8)
LORAZEPAM	0	0	1 (14.3)	1 (5.3)
MIDAZOLAM	0	0	1 (14.3)	1 (5.3)
OXCARBAZEPINE	0	0	1 (14.3)	1 (5.3)
PENTOBARBITAL	0	0	1 (14.3)	1 (5.3)
PHENOBARBITAL	3 (50.0)	1 (16.7)	0	4 (21.1)
PHENYTOIN	2 (33.3)	0	0	2 (10.5)
TOPIRAMATE	0	1 (16.7)	1 (14.3)	2 (10.5)
VALPROIC ACID	2 (33.3)	1 (16.7)	1 (14.3)	4 (21.1)
VIGABATRIN	0	1 (16.7)	1 (14.3)	2 (10.5)

9. SAFETY RESULTS

ITT population analysis

During the trial 6 subjects (32%) received high-dose LEV IV: 1 subject (17%) in the ≥1 month to <6 months group, 3 subjects (50%) in the ≥6 months to <2 years group and 2 subjects (29%) in the ≥2 years to <4 years group. In general, the number of IV doses received ranged from 1 to 6, and the duration of exposure ranged from 1 to 4 days. Twelve subjects received 3 or more consecutive doses of LEV IV.

There was only one case of a pretreatment AE in the whole ITT population, which concerned a moderate, non-serious case of candidemia.

Table 4 below gives an overview of the treatment-emergent adverse events.

Table 4: Summary of Treatment-Emergent Events

	Age (years)			
	≥1 month to <6 months (N=6)	≥6 months to <2 years (N=6)	≥2 years to <4 years (N=7)	Overall (N=19)
	n (%)			
Total number of TEAEs	14	8	11	33
Subjects with at least 1 TEAE	3 (50.0)	3 (50.0)	6 (85.7)	12 (63.2)
Subjects with AEs that led to permanent study drug discontinuation	0	1 (16.7)	0	1 (5.3)
Subjects with drug-related TEAEs	0	2 (33.3)	1 (14.3)	3 (15.8)
Subjects with at least 1 severe TEAE	2 (33.3)	0	1 (14.3)	3 (15.8)
Subjects with psychiatric TEAEs	0	0	1 (14.3)	1 (5.3)
Subjects with nonserious TEAEs	2 (33.3)	3 (50.0)	5 (71.4)	10 (52.6)
Subjects with serious TEAEs	2 (33.3)	0	2 (28.6)	4 (21.1)
Subjects with drug-related serious TEAEs	0	0	1 (14.3)	1 (5.3)
Deaths	2 (33.3)	0	1 (14.3)	3 (15.8)

As can be seen, a higher percentage of subjects in the ≥6 months to <2 years group had drug-related TEAEs, but no severe TEAEs occurred in this group.

There was one SAE which was considered drug related and this occurred in the ≥2 years to <4 years group. Three deaths were reported: 2 subjects in the ≥1 month to <6 months group and 1 subject in the ≥2 years to <4 years group. The onset of these events in 2 of the subjects occurred within 30 days of the final IV infusion, and none of the 3 subjects were taking study drug at the time of death.

In total of 33 TEAEs were reported for 12 subjects (63%). Treatment-emergent adverse events were most frequently of the general disorders and administration site conditions (5 subjects; 26%) SOC, followed by cardiac disorders and nervous system disorders (each 4 subjects; 21%).

The most frequently reported TEAE was pyrexia (3 subjects; 16%), followed by bradycardia, pneumonia, metabolic acidosis, and hypotension (each 2 subjects; 11%). One TEAE was related to the IV infusion site (puncture site pain). No trend in the incidence of TEAEs by age group was identified.

The 33 TEAEs occurred in 5 high-dose category subjects (83%) and in 7 subjects (54%) in the low-dose category. In the former, the most frequently reported TEAE was pyrexia. In the latter category, the most frequently reported were bradycardia and pneumonia.

When stratified according to previous LEV (non-)use, 6 subjects with and 6 without prior use suffered from TEAEs. For the former the most common one was pyrexia, while bradycardia and pneumonia occurred the most frequent in the latter group.

Three of the TEAEs which occurred could be categorized as severe. Pneumonia, abdominal sepsis, and metabolic acidosis occurred in 1 subject in the ≥1 month to <6 months group, respiratory failure in 1 subject in the ≥1 month to <6 months group and cardiac arrest and metabolic acidosis in 1 subject in the ≥2 years to <4 years group.

Four drug-related TEAEs manifested in three subjects. 2 subjects (33%) in the ≥6 months to <2 years group experienced EEG AE + hypotension and solomnolence. reported for 1 subject (14%) in the ≥2 years to <4 years group. ECG QT prolonged was reported for 1 subject (14%) in the ≥2 years to <4 years group.

During the study three deaths were reported: 2 subjects in the ≥1 month to <6 months group and 1 subject in the ≥2 years to <4 years group. In the former age group one subject died of pneumonia, abdominal sepsis, bradycardia, and metabolic acidosis, and the other due to respiratory failure. The subject in the ≥2 years to <4 years group died of cardiac arrest and metabolic acidosis. All three had significant co-morbidities. All these events were considered not related to study medication, as the onset of these events in 2 of the subjects occurred within 30 days of the final IV infusion, and none of the 3 subjects were taking study drug at the time of death.

There was one more incident of SAE in the ≥2 years to <4 years group, were a subject had an SAE of moderate QT interval prolonged. The event resolved and was considered possibly related to study drug.

One subject (17%) in the ≥6 months to <2 years group had a moderate AE of relative activation of the EEG (verbatim term) which led to discontinuation of study drug. The event was considered possibly related to study drug.

Laboratory Analysis

Mean values for all hematology and clinical chemistry parameters were within normal limits at each measured time point, and no AEs were linked to these laboratory findings.

The majority of subjects had normal ECG findings at Baseline; approximately half of the subjects (47%) had a normal ECG at End of Treatment/Early Discontinuation.

There were no clinically relevant findings other than those already mentioned in laboratory analyses, vital sign measurements, ECG measurements, or physical examinations

10. CLINICAL PHARMACOLOGY RESULTS

The applicant claims that observed LEV plasma concentrations were in the expected range, but that details of the PK analysis will be provided in a separate population PK report.

11. DISCUSSION AND OVERALL CONCLUSIONS

The primary objective of this study was to evaluate the safety and tolerability of the LEV IV 15-minute infusion administered every 12 hours, either as adjunctive treatment or monotherapy in children (1 month to <4 years) with epilepsy (except status epilepticus), either after switching from the equivalent LEV oral dose administration or as a new antiepileptic treatment.

This was an inpatient study, with majority of subjects being hospitalized for reasons related to seizures. Other subjects were temporarily unable to take oral LEV for medical reasons or hospitalized for surgery.

Overall, a total of 33 TEAEs were reported for 12 subjects. Treatment-emergent adverse events were most frequently reported general disorders and administration site conditions SOC, followed by cardiac disorders and nervous system disorders.

The most frequently reported preferred term was pyrexia, followed by bradycardia, pneumonia, metabolic acidosis, and hypotension (each 11% of subjects overall). One subject in the ≥2 years to <4 years group had puncture site pain.

No trend in the incidence of TEAEs by age group, dose category, or previous LEV could be identified.

Three deaths were reported. The onset of these events in 2 of the subjects occurred within 30 days of the final IV infusion, and none of the 3 subjects were taking study drug at the time of death and had severe co morbidities.

Apart from these three there was only one more subject with an STEAE. The patient resided in the ≥2 years to <4 years group and suffered an SAE of moderate QT interval prolonged. The event resolved and was considered by the investigator to be possibly related to study drug. Finally, one subject discontinued prematurely from the study due to an AE.

There were no clinically relevant findings in laboratory analyses, vital sign measurements, ECG measurements, or physical examinations.

The observed LEV plasma concentrations were in the expected range, but a full PK analysis report will follow later.

Conclusion

Overall, analysis of the data showed that the LEV IV 15-minute infusion administered every 12 hours is a safe alternative and was well tolerated as adjunctive therapy in the treatment of seizures in infants and children 1 month to <4 years with epilepsy when the oral administration is temporarily not feasible.

Nevertheless, even thought the data presented in the Clinical Study Report may be considered to support the use of Keppra IV in children aged 1 month to <4 years old. However, the CHMP considered that these results, whilst promising, report only safety experience in just 18 patients and are thus

insufficient to warrant an extension of Keppra IV into a younger patient population. Therefore, the CHMP did not request any change to the approved Product Information for Keppra.

12. COMMENTS RECEIVED FROM OTHER MEMBER STATES (MS)

One of the MS did not agree with the conclusion that: LEV IV 15-minute infusion administered every 12 hours is a safe alternative and was well tolerated as adjunctive therapy in the treatment of seizures in infants and children 1 month to <4 years with epilepsy when the oral administration is temporarily not feasible.

It is accepted that the babies and infants were likely to have been seriously ill with multiple treatment; however a closer scrutiny of the safety data is warranted as follows:

It is not clear from the assessment report whether for example levetiracetam could have contributed to the 3 deaths:

- Were post-mortems performed?
- What were the findings?
- Was the levetiracetam well tolerated whilst they were on it?
- Were the ECGs of these infants/babies normal whilst on leviracetum?
- Were their LFTs normal?
- What events led to their demise?
- The QT prolongation does not appear to have been previously a problem with levetiracetum but there appears to be a positive challenge and dechallenge. Was this infant on any other medication that could have explained this? How many babies and infants had baseline and on treatment ECGs? What happened to their QT intervals?
- Generally how do the observed AEs relate to the AEs observed in adults and how to the AEs noted in children in studies with the oral formulations? Further data regarding this should be provided by the MAH.

Committee's view:

Please find below the narrative summaries of the three deaths that occurred:

- *One subject experienced serious adverse events (SAEs) of cardiac arrest and metabolic acidosis 8 days after study drug initiation, but no longer taking the study drug at time of SAE onset.*

  She had a previous medical history consisting of:

  - *Glycogen storage disease type I, 2006-ongoing*
  - *Sickle cell trait, 2006-ongoing*
  - *Gastrostomy tube insertion, 2007-ongoing*

  When the subject arrived at the hospital she was hypothermic, bradycardiac, hypotensive with shallow breathing, and she rapidly progressed into cardiopulmonary arrest with heart rate in the 30s. Chest X-ray revealed a bilateral airspace consolidation with air bronchograms consistent with pulmonary edema. Abdominal ultrasound showed mild ascites of unknown etiology and an abnormal thickened and collapsed gallbladder wall with pericholecystic fluid (gallstone-free). The spleen was fairly small. An infection or inflammatory etiology could however not be concluded.

  Laboratory culture tests indicated a moderate amount of white blood cells and rare Gram positive cocci. A respiratory culture grew normal colonizing flora of Corynebacterium, while a blood culture did not reveal any growth. Lab values denoted a severe lactic bicarbonate refractory acidosis, which worsened the complete heart block experienced by the subject.

  Video electroencephalograph was abnormal with little activity. No seizures were apparent and the subject was considered to have organ failure.

She received norephinephrine, potassium chloride, liothyronine, and levothyroxine sodium for cardiovascular support; sodium bicarbonate for the treatment of metabolic acidosis; calcium gluconate, dopamine, epinephrine, vasopressin, and atropine for resuscitation, morphine for the management of pain and hydrocortisone for the treatment of multiorgan failure. Despite the intervention the subject died due to the events of cardiac arrest and metabolic acidosis two days after onset of the SAE.

The subject's electrocardiogram evaluation at study entry and at the end of study treatment showed an abnormal profile, as at both times she showed signs of sinus tachycardia. She also discontinued from the study prematurely, but the reason for this is unknown.

At the time of SAE onset she was taking oral commercial levetiracetam 1400mg/day, midazolam 0.75mg (frequency not known) and allopurinol.

- *One subject experienced pyrexia, pneumonia and convulsions in the post-treatment period, 15 days after drug initiation. Twenty days later he experienced another episode of pneumonia, which was in turn followed 7 days later by an event of abdominal sepsis. A further five days later, at 47 days after study drug initiation, the patient experienced mild bradycardia followed by a metabolic acidosis one day later, for which he was administered cefotaxime, metronidazole, furosemide, buprenorphine, insulin, midazolam, and bicarbonate. The same day the subject the event led to cardioresperatory arrest and death.*

  This patient's prior medical history was as follows:

  - *Sepsis neonatal, Sep 2009-Oct 2009*
  - *Neurological infection, Sep 2009-Nov 2009*
  - *Quadriparesis, Sep 2009-ongoing*
  - *Anaemia, Oct 2009*
  - *Encephalitis, Oct 2009-Nov 2009*
  - *Cerebral atrophy (cortical cerebral atrophy), Oct 2009-ongoing*
  - *Gastrooesophageal reflux disease, Oct 2009-ongoing*
  - *Hypoxia, Unknown*

  The patient was taking phenobarbital 25mg/day, oral LEV 200mg/day, cefotaxime, iron, ranitidine and cispraside.

  He had been diagnosed with right ventricular hypertrophy at study screening, end of treatment and 8 days after EOT.

  The events of pneumonia (second event), abdominal sepsis, bradycardia and metabolic acidosis were considered fatal.

- *One subject was a patient with an extensive medical history at the time of death:*
  - *Premature labour, Aug 2009*
  - *Respiratory failure, Aug 2009-Sep 2009*
  - *Aspiration bronchial (bronchoaspiration), Sep 2009*
  - *Atelectasis, Sep 2009*
  - *Cardiac arrest, Sep 2009*
  - *Inhalation therapy, Sep 2009-ongoing*
  - *Parenteral nutrition, Sep 2009-ongoing*
  - *Cardiac arrest, Oct 2009*
  - *Cardiac arrest, Oct 2009*
  - *Pneumonia, Oct 2009*
  - *Upper gastrointestinal haemorrhage, Oct 2009*
  - *Whole blood transfusion, Oct 2009*

- *Whole blood transfusion, Oct 2009*
- *Cerebral atrophy, Oct 2009-ongoing*
- *Gastro esophageal reflux disease, Oct 2009-ongoing*
- *Hypotonia, Oct 2009-ongoing*
- *Nervous system disorder (mesencefalic necrosis), Oct 2009-ongoing*
- *Pyramidal tract syndrome, Oct 2009-ongoing*
- *Thalamic infarction, Oct 2009-ongoing*
- *Sepsis, Nov 2009*
- *Aspiration bronchial (intermitent bronchoaspiration), Nov 2009-ongoing*
- *Dysphagia, Nov 2009-ongoing*
- *Visual disturbance, Nov 2009-ongoing*
- *Asphyxia, Unknown*

He experienced a mild event of pneumonia in the post-treatment period, 16 days after study drug administration. Thirteen days later he had a respiratory failure with fatal outcome.

At the time of the pneumonia event the subject was admitted to the ER due to acute respiratory failure caused by bronchoaspiration with a consolidation in the apical region of the right lung. The patient was given vancomycin, ciprofloxacin, amikacin, ceftriaxone, and dicloxacillin as treatment. He took LEV via gastrostomy for 11 days (9 days 100 mg/day, 2 days 64 mg/day). The subject was discharged with an aspirator device 10 days after this admittal.

Two days later he was admitted to the ER with respiratory failure and tonic seizures, where he received diazepam 2mg/day, midazolam 2µg/day, and phenytoin (dose unknown). In the afternoon his condition worsened and he developed cardiorespiratory arrest and died. The cause of death was respiratory failure.

Like the previous subject he had been diagnosed with right ventricular hypertrophy at study screening and at end of treatment.

Concomitant drugs at the time of the SAEs of pneumonia and respiratory failure included valproic acid 45mg/day and chloramphenicol.

Based on the data there was no causal effect to be found between study drug and pneumonia/respiratory failure.

Thus, based on the data provided, the MAH's view that the deaths that occurred are likely not causally connected to the administration of IV LEV, is not endorsed.

The data on concomitant medical conditions and drug use at the time of death is too confounded to properly investigate the role of IV LEV in the subjects' demise. But, based on the timing of the events it seems unlikely that IV LEV contributed to their fatal condition. Furthermore, the patients' extensive comorbidities seem to indicate that it is far more likely that their deaths are affiliated to their poor prior health conditions than to a specific problem with IV LEV itself.

Concerning the ECG readings, there was only one subject which exhibited a shift from a normal ECG reading at baseline to an abnormal one at end of treatment. This subject exhibited a prolongation of the QT interval approximately 1 hour post IV LEV administration. The child was in sinus rhythm at 95bpm. An ECG performed 3 days later showed the QT interval had returned to the Baseline value. His prior medical history consisted of Reflux oesophagitis (Jan 2006-Aug 2006), Phimosis (Aug 2006), Food allergy (2006-ongoing), Neurodermatitis (2006-ongoing) and Gastrointestinal infection (Feb 2009). The only concomitant drug he took at the time of SAE onset was oxcarbazepine 480mg/day.

It was considered possible that the QT prolongation was causally linked to the study drug. It is agreed that there might perhaps be a causal connection given the temporal association of study drug administration and the SAE onset. Also, there is no indication in the data available that this event would probably have been caused by another medicinal product.

Nevertheless, given that this was the only subject to display a worsening of their ECG reading during the study window and combined with the fact that cardiologic issues are known already to have rarely occurred during LEV treatment, this single event is not believed to be a cause for alarm.

There is no necessity of a comparison of the observed AEs to the AEs observed in adults and in children noted in studies with the oral formulations. Given the extremely small patient population in this study, this would likely only lead to nice-to-know but clinically not very meaningful results.

Conclusion

Overall, the CHMP agree with the MAH's conclusions. None of the data suggested that the use of LEV IV in epileptic infants and children aged 1 month to <4 years, to temporarily offset unfeasibility of the oral administration, was a cause for concern.

Although three deaths occurred, the timing and presence of existing serious co-morbidities were considerd by the Committee to make it seem doubtful that the mortalities were due to LEV IV use. One more SAE and one discontinuation also occurred, and these were assessed to be possibly drug related.

However, the CHMP was of the opinion that the fact that this study only included 18 patients makes it difficult to draw any definitive conclusions from the data presented. Therefore the outcomes can only be seen as informative rather than conclusive. This is also fully recognised by the MAH and no changes to the SmPC are proposed.