London, 04 January 2007
Product name: **Keppra**
Procedure No. **EMEA/H/C/277/II/71**

SCIENTIFIC DISCUSSION

1. Introduction

Keppra (levetiracetam – LEV) is currently authorised in the treatment of partial onset seizures with or without secondary generalisation in patients with epilepsy. It is also authorised as adjunctive therapy in the treatment of partial onset seizures with or without secondary generalisation in adults and children from 4 years of age with epilepsy and in the treatment of myoclonic seizures in adults and adolescents from 12 years of age with juvenile myoclonic epilepsy (JME).

The MAH has applied for an extension of the indication for Keppra to include adjunctive therapy in the treatment of primary generalised tonic-clonic (PGTC) seizures in adults and children 4 years of age and older with idiopathic generalized epilepsy (IGE). The IGEs are those syndromes or diseases that are a primary epilepsy condition and are thought or known to have a genetic cause. The IGEs are estimated to constitute approximately one quarter of the incidence of epilepsy. IGE usually arises in childhood or adolescence, but a large number of patients continue to have seizures in adult life. There are a number of different epilepsy syndromes within the group of IGEs. The main types are childhood absence epilepsy (CAE), juvenile absence epilepsy (JAE), JME, and epilepsy with grand mal seizures on awakening. In these syndromes, primary generalized tonic-clonic (PGTC) seizures can occur as isolated events or in association with other generalized seizure types (e.g. myoclonic seizures, absence seizures). PGTC seizures have a usual onset during childhood or adolescence, but may appear later. They occur without warning or aura. The electroencephalogram pattern for PGTC seizures is generalised spike-and-wave or polyspike wave.

In addition to section 4.1 of the SPC, the MAH proposed to update section 4.8 to reflect the safety data generated by the pivotal study and to introduce minor grammatical changes to section 4.2. The Package Leaflet (PL) was revised accordingly.

2. Clinical aspects

GCP

The clinical trials were performed in accordance with GCP, as stated by the MAH. In addition, the MAH confirmed that the ethical requirements of the clinical trial directive 2001/20/EC were applied for clinical trials conducted outside the EU.

Clinical efficacy

The clinical programme was based on a pivotal double-blind, placebo-controlled, randomized study in patients with IGE with PGTC (N01057). A long-term follow-up study (N167), open to enrolment to patients who completed N01057 as well as patients from other studies with primary generalized seizures, was included to provide supportive long-term efficacy and safety in the proposed indication. Further supportive data from Study N166, the primary basis for the authorised indication in patients with myoclonic seizures, were provided (Table I).

Table I. Overview of clinical studies submitted

Study No.	No. Enrolled (Exposed to LEV)	Dates of Conduct (Countries)	Planned Patient Population	Overview of Design
N01057 [Main study]	164 (148)(a)	19 Sep 01 – 27 Jun 05 (Estonia, Poland, Russia, UK, US, Canada, Mexico, Australia, New Zealand)	N = 154 planned IGE with primary generalized tonic-clonic seizures (4 - 65 yrs)	Double-blind, placebo-controlled, randomized, 24-week treatment period (3000 mg/day or 60 mg/kg/day in children)
N166	50 (26)(b)	03 Sep 01 – 13 Dec 04 (EU, Canada, US, Mexico, Australia and New Zealand)	N = 116 IGE with myoclonic seizures (JME or JAE) (12 - 65 yrs)	Double-blind, placebo-controlled, randomized 16-week treatment period (3000 mg/day)
N167	135(c) (44 previously treated with PBO in N01057 and 17 previously treated with PBO in N166)	01 Nov 01 – ongoing (EU, Russia, US, Canada, Mexico, Australia, NewZealand) Data cut-off date: 31 Oct 05	N = N/A Primary generalized seizures	Open-label follow-up for N01057 (and 17 subjects previously treated with PBO in N166)

(a) 79 patients randomized and exposed to levetiracetam in N01057 and 69 patients randomized to placebo in N01057 who converted to open-label levetiracetam in N167.
(b) Subset of patients enrolled in N166 with PGTC seizure at baseline and/or on study (either in N166 and/or N167)
(c) Inclusive of the 95 patients who entered from N01057 and the subset of 40 patients from N166 who had PGTC seizures at baseline in N166 and/or in N167; N.B., the additional 10 patients in the N166 ITT (PGTC) population either did not enter N167 or had not yet returned for the first on-study visit (post Visit 1) at the time of the data cut-off date.

MAIN STUDY N01057: DOUBLE-BLIND, PLACEBO-CONTROLLED, RANDOMIZED, 24-WEEK TREATMENT PERIOD

METHODS

Objectives

The main objective of the study is to evaluate the efficacy and safety of LEV as adjunctive treatment (3000 mg/day, given b.i.d. or a target dose of 60 mg/kg/day in children, given b.i.d.) in adults and children (4 to 65 years) with IGE with PGTC seizures.

Study Participants

Among the inclusion criteria were:

- Male/female aged 4-65 years.
- One or two concomitant anti-epileptic drugs (AEDs).
- Diagnosis of IGE with uncontrolled PGTC seizures and at least 3 documented PGTC seizures during the 8-week combined baseline period (at least 1 PGTC seizure in the 4-week historical baseline period and at least 1 PGTC seizure during the 4-week prospective baseline period).

Treatments

The study consisted of several periods:

- Combined baseline period: 4-week historical baseline followed by 4 weeks single-blind placebo (PBO) prospective baseline.
- Up-titration period (4 weeks): LEV 3000 mg/day (provided as 500-mg tablets) or matching PBO.
- Evaluation period (20 weeks): during the first week patients were allowed one dose reduction to 2000 mg/day (and were not allowed to subsequently increase the dose).
- Down-titration or conversion to open label LEV (long-term follow-up study N167).

The mean daily dose of levetiracetam during the evaluation period (exclusive of up- and down-titrations) was 2887.2 mg/day which is close to the target dose of 3000 mg/day.

Randomisation and sample size

Treatments were allocated to subjects by means of a centralised randomisation process. The randomisation was stratified by region and weight category [adults, children and adolescents < 16 years (> 40 kg, 31-40 kg and 20-30 kg)].
The ITT population consisted of 164 individuals (73 male and 91 female) ranging in age from 5 years to 62 years. Seventy of 84 patients randomised to PBO (82.56 %) and 69 of 79 patients randomised to LEV (86.3 %) completed the double-blind evaluation period. The most common reason for discontinuation in the active group was loss to follow-up (5 patients; 6.5 %) and withdrawal of consent (4 patients; 5.2 %). In the PBO group, adverse events (4 patients, 4.9 %) and lack of efficacy (3 patients; 3.8 %) were the most common reasons.

Endpoints

Primary efficacy variable

The primary efficacy variable was the percentage reduction from the combined baseline period in the PGTC seizure frequency over the treatment period.
The percentage reduction in the PGTC seizure frequency per week was also assessed over the evaluation period.

Secondary efficacy variables

- Absolute reduction in PGTC seizure frequency per week from the combined baseline period during the treatment period.
- Percent reduction in seizure days per week (all seizures) from the prospective baseline period during the treatment period.
- Responder rates in PGTC seizure frequency, and in seizure days (all seizures) per week. A responder was defined as a subject with a ≥ 50% reduction in the applicable measure from the baseline period to the treatment period. The baseline seizure frequency is calculated over the combined baseline period, and the baseline seizure days per week calculated over the prospective baseline period.
- Categorized response to treatment in PGTC seizures: Subjects were grouped into 4 categories (less than –25%, -25% to <25%, 25% to <75% and 75% to 100%) according to the percent reduction from the combined baseline period in PGTC seizures frequency during the treatment period. A similar grouping constructed on seizure days for all seizures used only the prospective baseline period.
- Percent of seizure-free subjects, with respect to all seizures, and with respect to PGTC seizures during the evaluation period and the entire treatment period.

Because the distributions of percent reductions in seizure frequency / seizure days from baseline were skewed with most values centering around the lower values and the extreme values tailing off to the right, the median difference in absolute and percent reduction between LEV and PBO was estimated with the Hodges-Lehmann method and statistically tested with the Wilcoxon-Mann-Whitney test in addition to the originally planned ANCOVA with rank transformation. Responder rates in PGTC seizure frequency per week were compared between treatment groups using a logistic regression analysis with treatment group as factor and the baseline PGTC seizure frequency as the covariate. The treatment difference in categorized responses has been tested with a Cochran-Mantel-Haenszel test based on ranks. Differences in seizure freedom were inferentially tested using Fisher's exact test.

RESULTS

Baseline data

The number of individuals in different age classes, the classification of epileptic syndromes for the ITT population and the types of seizures ever experienced by subjects as evaluated at screening visit are shown in tables II, III and IV respectively.

Table II. Age and age distribution of ITT population

Characteristics	Descriptive statistics	Placebo	Levetiracetam
Age (years)	N Mean (SD) Median	84 30.6 (12.1) 29.1	80 26.9 (11.2) 25.4
Age Class (years) <6 6-<12 12-<16 16-<65	 n (%) n (%) n (%) n (%)	 0 3 (3.6 %) 5 (6.0 %) 76 (90.5 %)	 1 (1.3 %) 5 (6.3 %) 3 (3.8 %) 71 (88.8 %)

Table III. Classification of epileptic syndromes in the ITT population

Epileptic Syndrome Status[a]	PBO (N=84) [b] n (%)	LEV (N=80) n (%)	Overall (N=164) n (%)
Localization related – idiopathic [b]	1 (1.2%)	0	1 (0.6%)
Confirmed	1 (1.2%)	0	1 (0.6%)
Generalized - idiopathic - childhood absence epilepsy	4 (4.8%)	3 (3.8%)	7 (4.3%)
Confirmed	3 (3.6%)	2 (2.5%)	5 (3.0%)
Suspected	1 (1.2%)	1 (1.3%)	2 (1.2%)
Generalized - idiopathic - juvenile absence epilepsy	11 (13.1%)	8 (10.0%)	19 (11.6%)
Confirmed	10 (11.9%)	8 (10.0%)	18 (11.0%)
Suspected	1 (1.2%)	0	1 (0.6%)
Generalized - idiopathic - juvenile myoclonic epilepsy	30 (35.7%)	24 (30.0%)	54 (32.9%)
Confirmed	25 (29.8%)	20 (25.0%)	45 (27.4%)
Suspected	5 (6.0%)	4 (5.0%)	9 (5.5%)
Generalized - idiopathic - epilepsy with Grand Mal seizures on awakening	27 (32.1%)	22 (27.5%)	49 (29.9%)
Confirmed	22 (26.2%)	20 (25.0%)	42 (25.6%)
Suspected	5 (6.0%)	2 (2.5%)	7 (4.3%)
Generalized - idiopathic - other generalized idiopathic epilepsies not defined above [b]	10 (11.9%)	18 (22.5%)	28 (17.1%)
Confirmed	8 (9.5%)	14 (17.5%)	22 (13.4%)
Suspected	2 (2.4%)	4 (5.0%)	6 (3.7%)
Epileptic syndrome unknown	2 (2.4%)	5 (6.3%)	7 (4.3%)

[a] Subjects are counted once in each confirmed or suspected syndrome.
[b] 1subject (161/358) is counted twice, once under "localization related" and once under "Generalized idiopathic"

Table IV. Classification of epileptic seizures – ITT population

Seizure Type[a] Seizure Subtype	PBO (N=84) n (%)	LEV (N=80) n (%)	Overall (N=164) n (%)
Partial Seizures (I)	2 (2.4%)	3 (3.8%)	5 (3.0%)
Simple partial seizures (I A)	2 (2.4%)	3 (3.8%)	5 (3.0%)
Generalized Seizures (II)	84 (100.0%)	80 (100.0%)	164 (100.0%)
Absence seizures (II A1)	47 (56.0%)	31 (38.8%)	78 (47.6%)
Atypical absence seizures (II A2)	1 (1.2%)	1 (1.3%)	2 (1.2%)
Myoclonic seizures (II B)	35 (41.7%)	27 (33.8%)	62 (37.8%)
Clonic seizures (II C)	1 (1.2%)	0	1 (0.6%)
Tonic seizures (II D)	5 (6.0%)	1 (1.3%)	6 (3.7%)
Tonic-clonic seizures (II E)	84 (100.0%) [b]	80 (100.0%)	164 (100.0%)[c]

Classification of epileptic seizures represents the different seizure types ever experienced by the subject as evaluated at V1

[a] Subjects are counted once in each type/subtype of seizure ever experienced.

[b] 83 (98.8%)

[c] 163 (99.4%) . After database lock it was discovered that one subject (113/103) had a database data entry omission with respect to the historical presence of II E seizures.

Concomitant AED medication

The most commonly used AEDs during the treatment period were valproic acid (53,2 %) and lamotrigine (27 % of the patients). At baseline, 50 % of the patients took one concomitant AED and 44 % two AEDs. Of 11 patients who took more than two AEDs during the treatment period, use of lorazepam "as needed" accounted for all but three.

Outcomes and estimation

Primary efficacy variable:

During treatment, patients randomized to PBO had a mean 28.30% (median 44.57%) reduction in PGTC seizure frequency per week from a mean of 1.20 (median 0.62) PGTC seizure frequency per week at combined baseline. In the LEV group the mean percent reduction was 56.37% (median 77.58%) from a mean of 1.27 (median 0.62) PGTC seizure frequency per week at combined baseline. The difference between the treatment least-square means in percent reduction from baseline was statistically significant (p = 0.004).

A similar result was obtained when the primary efficacy hypothesis of no difference in mean percentage reduction in PGTC seizure frequency per week was tested using an ANCOVA model with treatment groups as factor and combined baseline PGTC seizure frequency as covariate (TableV).

Table V. ANCOVA on percent reduction in PGTC seizure frequency per week from combined baseline to treatment period – ITT

	PBO (N=84)	**LEV (N=78)**
Least Square mean (SE)	28.19 (6.79)	56.49 (7.05)
ΔLSmeans LEV-PBO (95% CI)	28.31 [8.97, 47.64]	
p-value	0.004	

ANCOVA model with percent reduction as response, treatment as factor and baseline seizure frequency per week as covariate.

An analysis was also performed on the evaluation period only. The results are presented in Table VI.

Table VI. ANCOVA on percent reduction in PGTC seizure frequency per week from combined baseline to evaluation period – ITT

	PBO (N=79)	**LEV (N=74)**
Least Square mean (SE)	24.62 (8.75)	58.96 (9.04)
ΔLSmeans LEV-PBO (95% CI)	34.34 [9.48, 59.21]	
p-value	0.007	

ANCOVA model with percent reduction as response, treatment as factor and baseline seizure frequency per week as covariate.

Secondary efficacy endpoints

- Responder rate
  A subject was defined as a responder if the percent reduction in PGTC seizure frequency per week from combined baseline to treatment period was greater or equal to 50 %. The percentage of responders in the LEV group was 72.2 % vs. 45.2 % in the PBO group (p<0.001).

- Seizure freedom with respect to all seizures and PGTC seizures
  Seizure freedom was assessed over the evaluation period and the treatment period for both PGTC seizures and all seizure types. The results are presented in table VII.

Table VII. Seizure freedom over the evaluation period and the treatment period – ITT population

Analysis period Seizure-free	**PGTC seizures**			**Seizures (all types)**		
	PBO (N=84) n (%)	**LEV (N=79)** n (%)	**p-value**	**PBO (N=84)** n (%)	**LEV (N=79)** n (%)	**p-value**
Treatment period			0.004			0.072
Yes/Comp.*	6 (7.1)	19 (24.1)		5 (6.0)	12 (15.2)	
Yes/Disc.**	2 (2.4)	4 (5.1)		0	2 (2.5)	
No	76 (90.5)	56 (70.9)		79 (94.0)	65 (82.3)	
Evaluation period			<0.001			0.009
Yes/Comp.*	9 (10.7)	27 (34.2)		7 (8.3)	19 (24.1)	
Yes/Disc.**	0	2 (2.5) 50		0	1 (1.3)	
No	75 (89.3)	(63.3)		77 (91.7)	59 (74.7)	

p-value is from Fishers Exact test. Subjects who are seizure-free but who discontinued before completing a period are evaluated as not seizure-free for that period
*Yes/Comp: patients who completed the study and were seizure-free for the whole period considered
**Yes/Disc: patients who discontinued the study and were seizure-free for the period considered

- Efficacy within seizure type subgroups

50 % responder rate in PGTC seizure frequency per week over the treatment period by epileptic syndrome
The fifty percent responder rate in percent reduction in PGTC seizures was analysed from the combined baseline to treatment period in each of the five specified syndrome groupings. Table VIII summarizes the results.

Table VIII. 50 % responder rate in PGTC seizure frequency per week over the treatment period by epileptic syndrome – ITT population

Epileptic Syndrome	**PBO (N=84)** n (%)	**LEV (N=79)** n (%)
CAE + JAE	9/15 (60.0)	9/11 (81.8)
Grand Mal upon Awakening	13/27 (48.1)	15/21 (71.4)
JME	12/30 (40.0)	17/24 (70.8)
Other Idiopathic Generalized Epilepsies	3/10 (30.0)	12/18 (66.7)
Unknown or Localization Related	1/2 (50.0)	4/5 (80.0)

50 % responder rate over the treatment period in absence, myoclonic and PGTC exclusively subgroups
An analysis of responder rates within the subgroups of patients with exclusively PGTC seizures, those who experienced absence seizures during either the combined baseline or the treatment period, and those who experienced myoclonic seizures during the prospective baseline or the treatment period was performed. The results are presented in table IX.

Table IX. 50 % responder rate over the treatment period in absence, myoclonic and PGTC exclusively subgroups

	PBO n(%)	**LEV** n(%)
ITT with PGTC Seizures exclusively	34	27
PGTC Responders (Frequency/Week)	18 (52.9%)	22 (81.5%)
ITT with Absence Seizures	36	36
Absence Responders (Days/Week)	11 (30.6%)	11 (30.6%)
ITT with Myoclonic Seizures	32	26
Myoclonic Responders (Days/Week)	8 (25.0%)	9 (34.6%)

Patients being seizure-free during prospective baseline but with an absence/myoclonic seizure during the treatment period are considered non-responders.

- Newly occurring seizure types

Some subjects did not experience any episodes of a particular seizure during prospective baseline but presented episodes during the treatment period. Seven patients in the PBO group and 10 in the LEV group had no myoclonic seizures during prospective baseline but presented myoclonic seizures during the treatment period. Likewise, 7 patients in the PBO group and 13 in the LEV group had no absence seizures during prospective baseline but presented absence seizures during the treatment period.

In a further analysis, the set of ITT patients never having experienced myoclonic seizures at any time (in the subjects' life history including combined baseline) before randomization was identified. The numbers and percentages of these subjects experiencing myoclonic seizures for the first time during the treatment period were calculated. An analogous analysis was performed for absence seizures. The results are presented in table X.

Table X. Newly occurring myoclonic seizures and absence seizures during the treatment period

	PBO (N=84) n(%)	LEV (N=79) n(%)	p-value Fishers Exact Test
ITT with no history of myoclonic seizures	48	53	0.666
Newly occurring myoclonic seizure	3 (6.3%)	2 (3.8%)	
ITT with no history of absence seizures	35	47	0.289
Newly occurring absence seizure	2 (5.7%)	7 (14.9%)	

- Responder rates in children and adolescents

The fifty percent responder rates for PGTC seizure frequency per week was analysed in children and adolescents (Table XI).

Table XI. 50 % responder rates in PGTC seizure frequency per week over the treatment period in children and adolescents - ITT population

	PBO n(%)	**LEV** n(%)
0 - <12 Years	3	6
Responders	0	4 (66.7%)
12 - <16 Years	5	3
Responders	2 (40.0%)	2 (66.7%)

SUPPORTIVE RESULTS FROM STUDY N166 AND OPEN-LABEL FOLLOW-UP STUDY N167

Study N166

Study N166 was intended to evaluate the efficacy and safety of LEV as adjunctive treatment of myoclonic seizures at a dose of 3000 mg/day (given twice daily, *b.i.d.*) in adolescents (≥12 years) and adults (≤65 years) with IGE. It was a 16-week (inclusive of 4-week up-titration), multicenter, randomized, double-blind, placebo-controlled, add-on study performed in subjects with IGE experiencing myoclonic seizures (Type IIB) as their primary seizure type.

A subgroup analysis in N166 was conducted on the PGTC subgroup, defined as all subjects having at least 1 tonic-clonic seizure during the baseline and/or treatment period. A total of 42 subjects (20 subjects in the PBO group and 22 subjects in the LEV group) presented tonic-clonic seizures during baseline or treatment. The median percent reduction on tonic-clonic seizure frequency was 48% in the PBO group and 84% in the LEV group. These differences were not statistically significant (p=0.1228).

Study N167

Study N167 is an ongoing, open-label, long-term follow-up study. The main objective is to evaluate the safety and efficacy of LEV up to a maximum dose of 4000 mg/day (or 80 mg/kg/day bid for children and adolescents less than 50 kg). A total of 135 patients with IGE entered N167 from N1057 or N166. These patients who were included from N166 were restricted to those who received LEV and had PGTC seizures either at baseline, during the prior study of participation or in N167.

Mean LEV dose was 2948 mg/day (range 750-4000 mg/day). Most patients remained on the target dose from study N01057, 3000 mg/day, even though dose modification was allowed. The primary endpoint is the number and percentage of subjects having at least 6 months of seizure freedom.

All but 4 subjects in the ITT (PGTC) population remained on LEV for at least 6 months. For PGTC seizures, there were 64 subjects (47.4%) seizure free for 6 months at any time and 36 subjects (26.7%) seizure free for 6 months beginning from Visit 1.

The median percent reduction from baseline in PGTC seizure frequency per week during the N167 evaluation period was 82.0%. Overall, 97 subjects (71.9%) were categorized as responders as they had a 50% or greater reduction in PGTC seizure frequency during the evaluation period. When responder rates were evaluated over analysis interval and duration of exposure cohorts, the responder rates were maintained over time during N167. Eleven of 135 subjects (8.1%) had a period of LEV monotherapy of at least 91 days, and the majority remained seizure-free for 90% of their monotherapy periods.

Eight subjects had worsening of seizures (≥ 25 % increase in PGTC seizure frequency per week, or days per week with myoclonic or absence seizures). Four of these concerned worsening of myoclonic seizures, two worsening of absence seizures and three worsening of PGTC seizures (in one patients, there was worsening of both PGTC and myoclonic seizures).

CONCLUSIONS ON CLINICAL EFFICACY

The clinical efficacy programme was based on a pivotal double-blind, placebo-controlled, randomized study in patients with IGE with PGTC seizures.

The mean percent reduction in PGTC seizure frequency from the baseline to the treatment period (primary endpoint) was statistically significant in the LEV group (56.5 % in the LEV group vs. 28.2 % for PBO group). The responder rate was also significantly higher in the LEV group (72.2 % vs. 45.2 %). In addition, PGTC seizure freedom was achieved in 24.1 % in the LEV group compared to 7.1 % in the PBO group for the group of completers over the treatment period. The CHMP epilepsy guideline states that the analysis of efficacy should be based on the period when patients are stabilised on a fixed dose of the study drug (i.e. the evaluation period in this case) and not the treatment period (which includes up-titration + evaluation phases). However, the analyses performed showed similar results for both periods. Therefore, the efficacy of LEV as adjunctive therapy for PGTC seizures is considered to be sufficiently demonstrated.

The CHMP noted, however, that the number of children in the main study was very limited as the majority of patients were older than 16 years whilst only one child was below 6 years of age, and 8 children were in the interval 6-12 years. Therefore, the MAH was requested to further justify how the data collected support the treatment of patients aged less than 16 years old in the claimed indication.

Considering the further data submitted, the CHMP concluded that, due to the very limited number of children in Study N01057, a reliable evaluation of safety and efficacy in subjects with PGTC seizures in this age group is not possible. The age limit of 4 years proposed by the MAH is therefore not acceptable to the CHMP. The Committee considered a lower age limit of 12 years, which would restrict the new indication to adults and adolescents, consistently with the same age groups as currently approved for Keppra in the treatment of myoclonic seizures. In summary, the CHMP considered the lower age limit for the applied new indication to be increased to 12 years, and recommended the corresponding amendment to the SPC and PL. The MAH agreed with the conclusions of the CHMP and provided updated Product Information accordingly.

In addition to the above point, the CHMP also noted that an analysis of efficacy within seizure type subgroups indicated no effect of LEV on absence seizures, and newly occurring absence seizure were more frequent in the LEV group (14.9 % vs. 5.7 %). Likewise, 7 patients in the PBO group and 13 in the LEV group had no absence seizures during prospective baseline but presented absence seizures during the treatment period. The MAH was therefore asked to further discuss this.

In their answer, the MAH performed an analysis of the efficacy within seizure type subgroups for the pivotal study N01057. Considering the further analysis performed by the MAH, the CHMP still concluded that, in the pivotal study N01057, the results showed that levetiracetam increased the proportion of responders in all seizure subtypes except for absence seizures, indicating that levetiracetam had no effect on the frequency of absence seizures. Therefore, a statement to be added to section 4.4 of the SPC to this end was provided by the CHMP. Changes to the proposed text for

section 5.1 were also recommended by the CHMP. The MAH agreed with the conclusions of the CHMP and provided updated Product Information accordingly.

Finally, the CHMP considered the analysis of responders showed a higher PBO response in study N01057 (45.2%) than has been reported for add-on studies in partial epilepsy. Factors such as regression to the mean, and the effects of participating in a clinical trial are likely to contribute to a high PBO response. The MAH was, however, asked to address this issue and discuss in more detail the reasons for the high PBO response.

In their answer, the applicant discussed several factors which are likely to have contributed to the high placebo response in study N01057. The CHMP considered the answer from the MAH satisfactory, and the issue resolved.

Clinical safety

PATIENT EXPOSURE

The safety populations included are based on subjects with PGTC seizures. This includes all subjects in N01057 and subsets of subjects in N166 and N167.

- For N01057, the population considered for the safety analysis is the ITT population.
- For N166, the population included corresponds to the subjects who had a PGTC seizure during N166 baseline and/or at any subsequent post-randomization time, either in N166 and/or N167 study participation.
- For N167, the population included is defined as "all subjects" from studies N01057 and N166 who took at least one dose of LEV in N167 prior to the clinical cut-off date, and who had a PGTC (IIE) seizure at N166 or N01057 Baseline.

This represents a total of 214 subjects, including 164 from N01057 and 50 from N166. Of these, 192 were exposed to LEV and provide on-treatment safety data.

ADVERSE EVENTS

In study N01057, 57 patients randomized to PBO (67.9%) and 57 patients randomized to LEV (72.2%) experienced one or more treatment emergent adverse events (AEs), considered related to treatment in about one-half of the cases (25 patients randomized to placebo (29.8%) and 31 patients randomized to LEV (39.2%). Most of the events were mild or moderate in intensity.
The most frequently reported treatment-emergent AEs (incidence of approximately 10%), were headache, nasopharyngitis, and fatigue. Nasopharyngitis was more common amongst patients randomized to LEV (13.9% as compared to 4.8%) but was judged treatment related in only one of the patients randomized to LEV. Irritability and mood swings were the only other AEs in N01057 more common amongst patients randomized to LEV than to PBO (difference $\geq$ 3%). Both tended to be judged treatment-related in patients randomized to LEV. The only treatment-related AE occurring more commonly in the PBO group than in the LEV one was nausea.

Somewhat greater proportions in the N166 ITT (PGTC) subset had treatment-emergent AEs (75.0% of patients randomized to PBO and 92.3% of patients randomized to LEV). Similarly, approximately one-half had one or more events that were treatment-related (10 patients randomized to PBO [41.7%] and 12 patients randomized to LEV [50.0%]). The majority of the events were mild or moderate in intensity. Headache and fatigue were the most commonly reported AEs. The most common AEs is given in Table XII.

Table XII. Incidence (%) of drug-related treatment emergent AEs with an incidence ≥ 1% of patients in the LEV treatment arm during the treatment analysis period of N01057 and N166 (PGTC)

UCB SYSTEM ORGAN CLASS MedDRA Preferred Term	**N01057**		**N166 ITT (PGTC)**	
	PBO (N=84)	**LEV (N=79)**	**PBO (N=24)**	**LEV (N=26)**
	n (%)(a)	**n (%)**(a)	**n (%)**(a)	**n (%)**(a)
Ear and Labyrinth Disorders	**0**	**1 (1.3%)**	**1 (4.2%)**	**1 (3.8%)**
Vertigo	0	1 (1.3%)	1 (4.2%)	1 (3.8%)
Eye Disorders	**0**	**1 (1.3%)**	**0**	**2 (7.7%)**
Vision blurred	0	1 (1.3%)	0	2 (7.7%)
Gastrointestinal Disorders	**4 (4.8%)**	**4 (5.1%)**	**1 (4.2%)**	**2 (7.7%)**
Abdominal pain	0	1 (1.3%)	0	1 (3.8%)
Constipation	0	1 (1.3%)	0	0
Diarrhea	0	2 (2.5%)	0	0
Dyspepsia	0	1 (1.3%)	0	0
General Disorders And Administration Site Conditions	**5 (6.0%)**	**9 (11.4%)**	**3 (12.5%)**	**2 (7.7%)**
Asthenia	0	1 (1.3%)		
Fatigue	5 (6.0%)	8 (10.1%)	3 (12.5%)	2 (7.7%)
Infections And Infestations	**4 (4.8%)**	**3 (3.8%)**	**0**	**1 (3.8%)**
Nasopharyngitis	2 (2.4%)	1 (1.3%)	0	0
Sinusitis	0	1 (1.3%)	0	0
Vaginitis	0	1 (1.3%)	0	0
Injury, Poisoning And Procedural Complications	**4 (4.8%)**	**2 (2.5%)**	**0**	**0**
Anticonvulsant drug level above therapeutic	0	1 (1.3%)	0	0
Laceration	0	1 (1.3%)	0	0
Metabolism And Nutrition Disorders	**5 (6.0%)**	**3 (3.8%)**	**1 (4.2%)**	**1 (3.8%)**
Weight increased(b)	3 (3.6%)	3 (3.8%)	0	0
Nervous System Disorders	**8 (9.5%)**	**9 (11.4%)**	**4 (16.7%)**	**4 (15.4%)**
Dizziness	3 (3.6%)	3 (3.8%)	1 (4.2%)	1 (3.8%)
Gait abnormal	0	1 (1.3%)	0	0
Headache	3 (3.6%)	4 (5.1%)	1 (4.2%)	2 (7.7%)
Lethargy	0	1 (1.3%)	0	0
Paresthesia	0	2 (2.5%)	0	0
Somnolence	4 (4.8%)	4 (5.1%)	1 (4.2%)	2 (7.7%)
Syncope	0	1 (1.3%)	1 (4.2%)	0
Tremor	2 (2.4%)	1 (1.3%)	1 (4.2%)	0
Psychiatric Disorders	**12 (14.3%)**	**18 (22.8%)**	**4 (16.7%)**	**2 (7.7%)**
Abnormal behavior	1 (1.2%)	1 (1.3%)	0	0
Aggression	0	3 (3.8%)	0	0
Anger	1 (1.2%)	1 (1.3%)	0	0
Bradyphrenia	0	1 (1.3%)	1 (4.2%)	0
Conduction disorder	0	1 (1.3%)	0	0
Confusional state	0	1 (1.3%)	0	0
Delusional disorder, unspecified type	0	1 (1.3%)	0	0
Depression	1 (1.2%)	2 (2.5%)	0	0
Fear	0	1 (1.3%)	0	0

Insomnia	2 (2.4%)	3 (3.8%)	1 (4.2%)	1 (3.8%)
Irritability	1 (1.2%)	4 (5.1%)	0	0
Mood altered	0	2 (2.5%)	0	0
Mood swings	1 (1.2%)	3 (3.8%)	1 (4.2%)	1 (3.8%)
Negativism	0	1 (1.3%)	0	0
Reproductive System and Breast Disorders	**0**	**1 (1.3%)**	**0**	**0**
Dysmenorrhea	0	1 (1.3%)	0	0

(a) %: Denominator = number of patients participating in the analysis period. (b) The System Organ Class for this Preferred Term is different than the primary SOC assigned by MedDRA.

SERIOUS ADVERSE EVENTS (SAES) / DEATHS / OTHER SIGNIFICANT EVENTS

One death was reported in N01057, coded as a sudden death in epilepsy (SUDEP). The female patient was found dead in her home, 197 days after having been randomized to LEV. On autopsy, the death was attributed to "poorly controlled epilepsy with a grand mal seizure." The event was judged possibly treatment related by the investigator.
Across all studies (inclusive of the treatment-emergent SAEs in the PBO controlled studies), 26 LEV-exposed patients experienced at least one SAE. The most common pertained to seizure-related events (for the most part not treatment related) or were psychiatric in nature (treatment related). An overview of all SAEs is provided in Table XIII.

Table XIII. Serious adverse events – all levetiracetam-exposed subjects in N01057 ITT, N166 ITT (PHTC) and N167 ITT (PGTC)

UCB System Organ Class / MedDRA Preferred Term	**N=192 n (%)**
No. of Unique Subjects with SAE	**26**
Cardiac Disorders	
Myocardial Infarction	1 (0.5%)
General Disorders and Administration Site Conditions	
Multi-organ failure	1 (0.5%)
Pyrexia	1 (0.5%)
Sudden death	1 (0.5%)
Ulcer(a)	1 (0.5%)
Infections and Infestations	
Appendicitis	1 (0.5%)
Bronchitis bacterial	1 (0.5%)
Orchitis	1 (0.5%)
Injury, Poisoning and Procedural Complications	
Alcohol poisoning	1 (0.5%)
Concussion	1 (0.5%)
Eye injury	1 (0.5%)
Face injury	1 (0.5%)
Hand fracture	1 (0.5%)
Joint dislocation	1 (0.5%)
Mouth injury	1 (0.5%)

Scapula fracture	1 (0.5%)
Swelling face	1 (0.5%)
Musculoskeletal and Connective Tissue Disorders	
Neck pain	1 (0.5%)
Osteoarthritis	1 (0.5%)
Scoliosis	1 (0.5%)
Nervous System Disorders	
Coma	1 (0.5%)
Convulsion	4 (2.1%)
Grand mal convulsion	3 (1.6%)
Post-ictal state	1 (0.5%)
Status epilepticus	1 (0.5%)
Pregnancy, Puerperium and Perinatal Conditions	
Intra-uterine death	1 (0.5%)
Psychiatric Disorders	
Aggression	1 (0.5%)
Depression	2 (1.0%)
Psychotic disorder	1 (0.5%)
Schizophrenia	1 (0.5%)
Suicidal attempt	1 (0.5%)
Suicidal ideation	1 (0.5%)
Skin and Subcutaneous Tissue Disorders	
Rash erythematous	1 (0.5%)
Vascular Disorders	
Deep vein thrombosis	1 (0.5%)

Seizure-related SAEs
Eleven of the SAEs were seizure-related, occurring in 10 patients. Of these, one was considered possibly treatment related. One SAE occurred 2 days following the last dose; for the remaining, none resulted in discontinuation. In 1 patient with status epilepticus and significant sequelae (including coma, multi-organ failure, and deep venous thrombosis), LEV was temporarily discontinued. Two additional patients had SAEs that were sequelae of seizures, not treatment related.

Psychiatric SAEs
Five patients had SAEs that were psychiatric in nature. All were judged treatment related.
Two were mood disorders: depression followed by a suicide attempt in 1 patient and worsening of pre-existing depression that resulted in discontinuation. Two were psychotic disorders: one associated with suicidal ideation and resulted in discontinuation and one described as worsening schizophrenia. One was a behaviour disorder, violent episode, coded as a behaviour disorder.

Of the remaining SAEs, one patient suffered a myocardial infarction that was not treatment-related. One patient developed a diffuse erythematous rash that required hospitalization and treatment with intravenous corticosteroids and antihistamines, with temporary treatment interruption of LEV and, eventually, permanent discontinuation of valproic acid; the event resolved after 24 days. One woman was reported to be pregnant while down-titrating from LEV. An ultrasound indicated that fetal death occurred about 3 weeks after the last dose and was judged possibly related to treatment by the investigator. On follow-up, the final diagnosis of fetal tissues indicated a rare hydropic, degenerating "chronic" villi.

CONCLUSIONS ON CLINICAL SAFETY

The spectrum of AEs is similar to that reported previously in studies on partial seizures. A relatively high incidence of CNS-related adverse events and psychiatric adverse events was observed. No new or unexpected safety issues were reported. Section 4.8 of the SPC was updated to reflect the frequency of undesirable effects in the studies.

3. PHARMACOVIGILANCE

The CHMP did not require the MAH to submit a risk management plan because the safety profile of Keppra was considered unlikely to be different as adjunctive therapy in the treatment of primary generalised tonic-clonic seizures as compared to the approved epilepsy indications.

4. CONCLUSION

On 16 November 2006 the CHMP considered this Type II variation to be acceptable and agreed on the amendments to be introduced in the Summary of Product Characteristics and Package Leaflet.