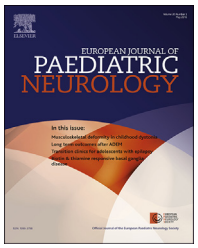
Official Journal of the European Paediatric Neurology Society



Original Article

Safety of levetiracetam among infants younger than 12 months – Results from a European multicenter observational study

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ARTICLE INFO

Article history:
Received 20 July 2015
Received in revised form
17 January 2016
Accepted 23 January 2016

Keywords:
Levetiracetam
Safety
Infants
Epilepsy
Children

ABSTRACT

Background: There are limited data on the use of the antiepileptic drug (AED) levetiracetam for the treatment of infants.
Aim: To prospectively evaluate the safety of levetiracetam oral solution and its impact on epilepsy severity in infants with different seizure types.
Methods: This noninterventional post-authorization safety study included patients 1–11 months of age. Patients' treatment – levetiracetam dose, and addition, withdrawal or changes in the doses of concomitant medications and AEDs – was at the discretion of the physician. The primary variable was treatment-emergent adverse events (TEAEs).
Results: Of 101 infants, 75 completed and 26 discontinued the study. Mean age was 6.0 months, 50 were male, most (80%) took 1 ≥ concomitant AED and had cryptogenic or symptomatic epilepsy that was focal (38.6%) or generalized (20.8%), particularly frontal lobe epilepsy (20.0%) or West syndrome/infantile spasms (20.0%). Among known aetiologies, congenital factors (22.8%) such as dysplastic lesions or perinatal events (17.8%) were predominant. Overall, 54.5% of patients had ≥1 TEAE. Five patients experienced drug-related TEAEs – convulsion, irritability, somnolence and hypotonia, all listed in the product label, with the exception of hypotonia, which was reported for one patient and resolved without any change in study medication. Seven patients discontinued due to TEAEs, mainly due to infantile spasms and respiratory disorders. At study end, 71.8% of patients showed improvement in epilepsy severity, 18.8% remained stable and 9.4% showed worsening. Levetiracetam did not appear to have a negative effect on growth parameters.
Conclusion: In this prospective study, which included the largest number of patients in this age range so far, levetiracetam was found to be well tolerated and efficacious for the treatment of infants with epilepsy.

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http://dx.doi.org/10.1016/j.ejpn.2016.01.006

1. Introduction

Treatment of infants and children with epilepsy presents with several important challenges. Childhood epilepsies are a heterogeneous group of conditions – they differ in their diagnostic criteria and management and are associated with markedly different outcomes.[1,2] Children present with seizure types and syndromes not seen in adults, and also frequently present with comorbid cognitive and behavioural conditions.[3] The substantial differences in pharmacokinetics between adults, children and infants must also be considered – age can affect drug bioavailability, half-life, time to steady state and elimination.[4]

Only few well-controlled studies have evaluated the safety and efficacy of antiepileptic drugs (AEDs) in paediatric populations, and children are often excluded from clinical trials of AEDs before their approval.[4–6] Indeed, despite the large number of AEDs that have become available in recent years, few have been approved for the treatment of children, especially those younger than 4 years. In Europe, levetiracetam is approved as adjunctive therapy for individuals with focal epilepsy from 1 month of age.[7] Data on the safety and efficacy of levetiracetam in children younger than 4 years are available from a double-blind, randomized, placebo-controlled trial, which included 12 children aged <12 months, 20 aged 12–24 months and 28 aged 24–48 months.[8] In this trial, using 48-h video electroencephalogram, treatment with levetiracetam resulted in a greater reduction from baseline in daily seizure frequency and a greater ≥50% responder rate compared with placebo. Levetiracetam appeared to be well tolerated; only two adverse events (AEs) – somnolence and irritability – occurred with a higher incidence in the levetiracetam group than in the placebo group. Both AEs were transient and were attributed to the rapid up-titration of levetiracetam. Pharmacokinetic data are also available for this age group.[9] As expected, the overall elimination half-life of levetiracetam administered as 10% oral solution was slightly shorter than that reported for children aged 6–12 years.[9]

While several open-label studies of levetiracetam in children have included infants,[10–12] overall knowledge on the safety profile of levetiracetam in this patient population remains limited. The objective of this prospective observational study therefore, was to evaluate the safety of levetiracetam oral solution and its impact on epilepsy severity in patients between the ages of 1 and 11 months with different seizure types in routine clinical practice.

2. Methods

This was a non-interventional sentinel sites post-authorization safety study (EudraCT number 2009-017333-21) conducted between January 2011 and November 2013 across 27 sites in Europe. The study protocol was reviewed by national, regional, or independent ethics committees, as required by local regulations for noninterventional studies. Before participation in the study, the patient's parent(s) or legal representative(s) provided informed, written consent.

2.1. Patients

One hundred patients aged 1–11 months (inclusive) with a diagnosis of epilepsy were planned for inclusion in the study; at least 30 patients were to be aged 1–6 months at the time of enrolment. Parents/guardians of the children were asked to enter their child to the study if the physician decided to initiate therapy with levetiracetam oral solution. Given the observational nature of the study, patients' treatment plan, including levetiracetam doses, was at the discretion of the treating physician, and determined according to standard practice. Physicians could also add, withdraw, or change doses of different medications, including concomitant antiepileptic drugs (AEDs). Recommended visits were a baseline visit followed by a maximum of 6 visits, once every 2 months during the treatment period, to the age of 13 months – if treatment ended before this, safety data were collected at the next scheduled visit.

2.2. Study outcomes

The primary variable was the incidence of treatment-emergent adverse events (TEAEs) as reported by parents/caregivers or observed by the physician. Other safety variables included observed values at each visit and changes from baseline in body weight, body length and head circumference. Raw values of body weight, body length and head circumference were converted to z-scores, according to the World Health Organization growth charts.

The study was not designed to evaluate efficacy per syndrome, and there was no primary efficacy variable. However, as part of routine clinical practice, at each visit the treating physician evaluated with the patient's parent(s) or guardian, the types and frequency of seizures experienced by the patient since Visit 1. With this information, physicians rated patients' change in epilepsy severity from start to study end using a 7-point global evaluation scale (GES), with 1 = marked worsening to 7 = marked improvement. The GES is a Likert-type scale often used in clinical trials; it can be adapted to provide answers to a variety of clinical and nonclinical questions. Respondents are asked to indicate their opinion on a given statement based on a continuum of response categories.

Psychomotor development was also evaluated using a similar GES during each visit. Physicians were asked to rate the change in psychomotor development from baseline at the end of the study (visit 7) with 1 = marked worsening to 7 = marked improvement.

A number of post hoc analyses were also conducted. Six safety variables, as well as epilepsy severity were analyzed according to the following subgroups: epilepsy aetiology (unknown, known); epilepsy aetiology differentiation (genetic, congenital, perinatal events); epileptic syndrome main categories (focal, generalized, undetermined, special); epileptic syndrome further categorization (focal [cryptogenic or symptomatic – frontal, temporal, parietal], generalized [Cryptogenic or symptomatic – West syndrome]); seizure type (International League Against Epilepsy seizure classification – focal, generalized, unclassified); age (<6 months, ≥6 months); number of concomitant AEDs at baseline (none, 1, ≥2) and the

combination of concomitant AEDs at baseline in addition to levetiracetam (benzodiazepines, phenobarbital, valproate, vigabatrin).

2.3. Statistical analysis

No formal sample size computations were performed for this study. However, based on the sample size of 100 patients, the probability of observing at least one TEAE within a category of interest (cardiovascular, psychiatric) was 63.4%, assuming an overall incidence rate of 1.0% for 1 group of TEAEs of interest. In addition, if zero events within a category of interest are observed out of 100 subjects, the upper 95% confidence limit for that event rate is slightly less than 3%. All statistical analyses were conducted using SAS® version 9.3.

Patient characteristics were based on the enrolled set (ES); safety and exposure data on the safety set (SS), defined as all patients in the ES who received at least one dose of study medication; and efficacy data on the full analysis set (FAS), defined as all patients in the ES who had at least one post-baseline efficacy assessment.

3. Results

3.1. Study disposition

Of 101 patients who started, 75 (74.3%) completed the study and 26 (25.7%) discontinued prematurely. Twelve patients (11.9%) discontinued due to lack of efficacy, seven (6.9%) due to AEs, three (3.0%) were lost to follow up, two (2.0%) discontinued due to 'other' reasons (one patient refused to swallow and another could not take glucose), one (1.0%) experienced disease remission, and one (1.0%) discontinued because the parent/guardian withdrew consent.

3.2. Patient demographics and disease characteristics

In the safety set, the mean age of patients was 6.0 months (standard deviation [SD] 3 months, range 0–11), with 52 patients (52.5%) being younger than 6 months. Similar numbers of males (50, 49.5%) and females (51, 50.5%) were included in the study; their mean weight was 7.00 kg (SD 1.94, range 3.6–11.0 kg) and mean height was 64.16 cm (SD 8.04 cm, range 46.0–81.0).

The mean age at which patients experienced a first seizure was 4.153 months (range 0.03–11.34 months) and the mean duration of epilepsy at study entry was 2.161 months (range 0.03–10.28 months). Most patients had complex focal seizures (43, 42.6%) and focal evolving to secondary generalized (34, 33.7%) at any time prior to study entry. Simple focal seizures were reported for 25 patients (24.8%). In terms of syndrome, most patients had cryptogenic or symptomatic epilepsy that was focal (39, 38.6%) or generalized (21, 20.8%). Of these syndromes, most were frontal lobe epilepsy or West syndrome/infantile spasms (20 patients, 19.8% each). The epilepsy seizure types and syndromes are summarized in Table 1.

Over half the patients (59, 58.4%) had at least one general concomitant medical condition, the most common being gastro-oesophageal reflux disease (11 patients, 10.9%), hypotonia (10, 9.9%) and microcephaly (7, 6.9%). Epilepsy aetiology was unknown in approximately half of patients (53.5%; Table 2). Among those with a known aetiology, most had epilepsy attributed to a congenital factor (22.8%) or a perinatal event (17.8%).

The majority of patients had previously been treated with at least one AED (60.4%) before entering the study, with the most frequent being levetiracetam (34.7%), phenobarbital (30.7%) and vigabatrin (10.9%). Most patients (80.2%) were also on at least one concomitant AED during the study – the most frequently used were vigabatrin (33.7%), phenobarbital (25.7%), valproate sodium (22.8%) and diazepam (19.8%).

Mean study medication duration was 152.2 ± 86.8 days. The mean daily dose was 316.428 ± 134.767 mg/day (range 98.81–806.03 mg/day) and the mean daily dose per body

Table 1 – Disease characteristics (safety set).

Epileptic seizure profile/type,[a] n (%)	N = 101
Focal	**69 (68.3)**
• Simple	25 (24.8)
• Complex	43 (42.6)
• Partial evolving to secondary generalized	34 (33.7)
Generalized	**41 (40.6)**
• Absence	0
• Atypical absence	1 (1.0)
• Myoclonic	8 (7.9)
• Clonic	7 (6.9)
• Tonic	21 (20.8)
• Tonic clonic	17 (16.8)
• Atonic	1 (1.0)
Unclassified	**15 (14.9)**

Epileptic syndrome, n (%)	N = 101
Focal	
Idiopathic	**4 (4.0)**
Cryptogenic or symptomatic	**39 (38.6)**
• Temporal lobe epilepsy	12 (11.9)
• Frontal lobe epilepsy	20 (19.8)
• Occipital lobe epilepsy	5 (5.0)
• Parietal lobe epilepsy	11 (10.9)
Generalized	
Idiopathic	**7 (6.9)**
• Benign neonatal familial convulsions	2 (2.0)
• Benign neonatal convulsions	1 (1.0)
• Other generalized idiopathic epilepsies not defined above	4 (4.0)
• Epilepsy with myoclonic-astatic seizures	1 (1.0)
Cryptogenic or symptomatic	**21 (20.8)**
• West syndrome/infantile spasms	20 (19.8)
• Early infantile epileptic encephalopathy with suppression burst	1 (1.0)
Symptomatic	**8 (7.9)**
• Nonspecific aetiology	1 (1.0)
– Other symptomatic generalized epilepsies not defined above	3 (3.0)
• Specific syndromes	
Undetermined whether focal or generalized	
Generalized and focal features	**9 (8.9)**
• Neonatal seizures	6 (5.9)
Other indeterminate epilepsies	**15 (14.9)**
Special syndromes	
Situation-related seizures	6 (5.9)

[a] Patient could be included in more than one group.

Table 2 – Epilepsy aetiology (safety set).

Aetiology,[a] n (%)	N = 101
Unknown	54 (53.5)
Known	47 (46.5)
Genetic	8 (7.9)
Congenital	23 (22.8)
• Cortical dysplasia/dysgenesis	15 (14.9)
• Vascular malformations	2 (2.0)
• Other	9 (8.9)
Perinatal events	18 (17.8)
• Asphyxia during birth	8 (7.9)
• Complication due to pregnancy	2 (2.0)
• Intrauterine viral infection	2 (2.0)
• Other	9 (8.9)
Cranial trauma	1 (1.0)
Cerebral neoplasm	0
Brain surgery	1 (1.0)
Primary degenerative lesion	0
Cerebrovascular accident	3 (3.0)
Cerebral infection	5 (5.0)
Toxic cause	0
Metabolic cause	3 (3.0)
Other	3 (3.0)

[a] Patient could be included in more than one group.

weight was 45.760 ± 15.950 mg/kg/day (range 16.06–87.61 mg/kg/day).

3.3. *Safety outcomes*

Overall, 54.5% of patients had at least one TEAE at any time during the study (Table 3). Five patients (5.0%) had at least one drug-related TEAE according to the investigator – two patients (2.0%) experienced irritability and convulsions, one patient experienced hypotonia (1.0%) and another experienced somnolence (1.0%). A summary of the most frequently reported TEAEs during the study is presented in Table 4.

Twelve patients (11.9%) had at least one severe TEAE, none of which were considered related to study medication by the physician. All other TEAEs were mild or moderate in intensity. Serious AEs were noted in 32 patients (31.7%), of which only two (both convulsion) were considered drug-related by the Investigator. Seven patients (6.9%) had at least one TEAE leading to study discontinuation – these TEAEs were respiratory disorder, respiratory distress and infantile spasms (two patients each), and irritability, lower respiratory tract infection, psychomotor retardation and respiratory failure (one patient each).

Table 3 – Overview of treatment-emergent adverse events (safety set).

AE category	N = 101 n (%)
Any TEAEs	55 (54.5)
Serious TEAEs	32 (31.7)
Discontinuation due to TEAEs	7 (6.9)
TEAEs requiring dose change	10 (9.9)
Drug-related TEAEs	5 (5.0)
Severe TEAEs	12 (11.9)
Deaths	6 (5.9)

Table 4 – Treatment-emergent adverse events reported for at least two patients (safety set).

Preferred term according to MedDRA version 16.1	N = 101 n (%)
Bronchitis	10 (9.9)
Convulsion	10 (9.9)
Pyrexia	8 (7.9)
Diarrhoea	6 (5.9)
Gastroenteritis	4 (4.0)
Irritability	4 (4.0)
Nasopharyngitis	4 (4.0)
Bronchiolitis	3 (3.0)
Ear infection	3 (3.0)
Constipation	3 (3.0)
Vomiting	3 (3.0)
Gastro-oesophageal reflux disease	3 (3.0)
Epilepsy	3 (3.0)
Infantile spasms	3 (3.0)
Hypotonia	2 (2.0)
Lower respiratory tract infection	2 (2.0)
Upper respiratory tract infection	2 (2.0)
Respiratory disorder	2 (2.0)
Respiratory distress	2 (2.0)
Urinary tract infection	2 (2.0)
Viral infection	2 (2.0)

Six deaths were reported during the study. The causes of death were epilepsy (1 patient), bronchitis and respiratory distress (1), respiratory distress (1), respiratory disorder (2) and lower respiratory tract infection and respiratory failure (1). None of the deaths were related to the study drug, as determined by the Investigator.

3.4. *Changes in body weight, body length and head circumference*

Mean z-scores (SD) at baseline (visit 1) were −0.480 (1.640), −0.586 (2.192) and −0.562 (2.171), respectively for body weight, body length and head circumference (safety set; Table 5). Measurements were not available for all patients at all visits; therefore, baseline values, as well as observed values and change from baseline for the specific cohort at each visit are provided (Table 5). Also, given the study design, no patients attended Visit 6; therefore, no data were attributed to Visit 6. While baseline and observed values at each visit were negative, the mean change in z-scores from baseline was positive, suggesting that these patients exhibited growth.

3.5. *Changes in psychomotor development*

Data were available from 85 patients at study end (visit 7; FAS) – relative to baseline, 52.9% of patients showed an improvement, 36.5% of patients remained stable and 10.6% of patients worsened. On the 7-point scale, 16 patients showed marked improvement in psychomotor development, while three patients showed marked worsening (Fig. 1).

3.6. *Changes in epilepsy severity*

Data were available from 85 patients at visit 7 (FAS) – relative to baseline, 71.8% showed improvement, 18.8% remained

Table 5 – z Scores for body weight, body length and head circumference based on observed values and baseline mean for cohorts at each visit and change from baseline (safety set).

Visit	Body weight z-scores				Body length z-scores				Head circumference z-scores			
	n	Mean observed value (SD)	Baseline mean	Mean change (SD)	n	Mean observed value (SD)	Baseline mean	Mean change (SD)	n	Mean observed value (SD)	Baseline mean	Mean change (SD)
Visit 1	100	−0.480 (1.640)	NA	NA	92	−0.586 (2.192)	NA	NA	99	−0.562 (2.171)	NA	NA
Visit 2	73	−0.324 (1.494)	−0.511	0.188 (0.721)	55	−0.257 (2.065)	−0.613	0.345 (1.214)	66	−0.514 (1.864)	−0.515	0 (1.131)
Visit 3	44	−0.075 (1.670)	−0.547	0.473 (1.097)	40	−0.406 (2.150)	−1.219	0.755 (1.770)	43	−0.680 (1.951)	−0.686	0.005 (1.536)
Visit 4	23	−0.101 (1.328)	−1.174	1.073 (1.497)	21	−0.720 (2.287)	−1.276	0.555 (1.502)	21	−1.244 (2.289)	−1.294	0.050 (1.090)
Visit 5	8	−0.300 (1.305)	−1.477	1.180 (1.729)	7	−1.044 (1.346)	−2.536	1.494 (1.352)	7	−2.404 (4.076)	−1.231	−1.173 (2.015)
Visit 7	80	0.063 (1.733)	−0.433	0.495 (1.195)	67	0.025 (2.082)	−0.605	0.624 (2.547)	72	−0.580 (1.864)	−0.593	0.071 (1.549)

NA = not applicable.

stable and 9.4% showed worsening. Twenty-eight patients showed a marked improvement on the 7-point scale; only three patients showed marked worsening (Fig. 2).

3.7. *Post hoc analyses*

Safety and epilepsy outcomes were also evaluated according to a total of 26 subgroups (see Section 2.2). Overall, no new safety concerns for levetiracetam oral solution were identified based on these subgroup analyses. However, the small numbers of patients in the subgroups preclude any firm conclusions. Given that levetiracetam was administered as adjunctive therapy, only the full results of the post hoc analyses based on the number of concomitant AEDs at baseline (none, 1, ≥2) and the combination of concomitant AEDs (those given at baseline in addition to levetiracetam, including benzodiazepines, phenobarbital, valproate, vigabatrin) are provided in the online supplement.

4. Discussion

In this prospective, noninterventional post-authorization safety study, 101 infants 1–11 months (inclusive) of age were treated with levetiracetam oral solution according to routine clinical practice. Safety analyses revealed no new concerns and the overall results were consistent with the known safety profile of levetiracetam. While efficacy was not evaluated formally, a reduction in the severity of epilepsy based on the physician's GES was reported for the majority of patients at study end.

The majority of infants in this study had focal seizures (68.3%). Complex focal and focal evolving to secondary generalized seizures were reported for 42.6% and 33.7% of patients, respectively, while simple focal seizures were

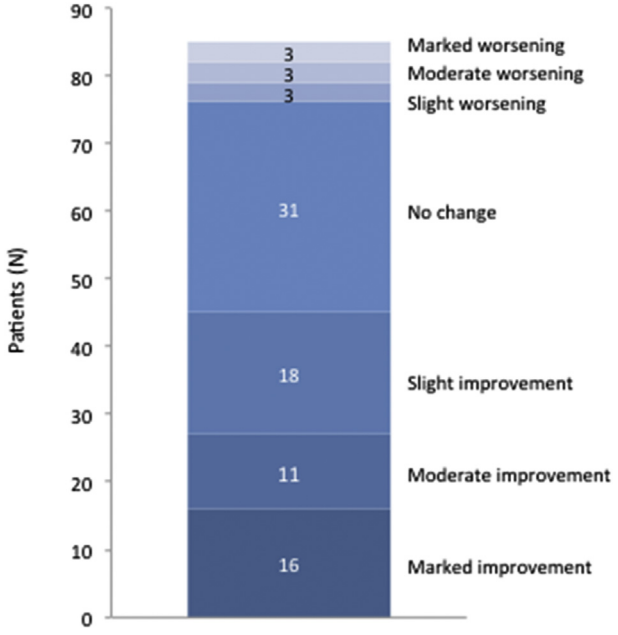

Fig. 1 – Change in psychomotor development of patients from baseline to study end (full analysis set).

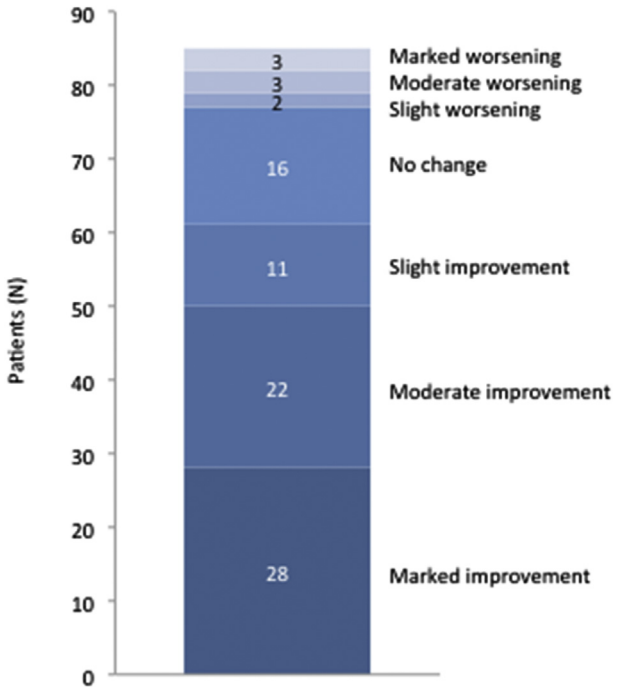

Fig. 2 – Change in epilepsy severity from baseline evaluated at the last visit (full analysis set).

reported for 24.8% of patients. Most infants had cryptogenic or symptomatic epilepsy that was focal (38.6%) or generalized (20.8%). In the focal group, most infants had frontal lobe epilepsy (20%), and correspondingly, in the generalized group, most had West syndrome/infantile spasms (20%). Syndromic diagnosis in the present study is in agreement with typical observations in children with severe epilepsies of very early onset.[13,14] Due to ongoing maturation, clinical expression of seizures is often difficult to characterize with certainty as focal or generalized, given rapid diffusion of the electrical discharges.[14]

The majority of patients (80.2%) were on at least one concomitant AED during the study, with vigabatrin being the most frequently used (33.7%). Adjunctive levetiracetam was well tolerated by the infants in this study – adverse events reported by the investigators were in line with those already listed in the product label. Approximately half (54.5%) of patients had at least one TEAE at any time during the study, with the most common being bronchitis, pyrexia and persistence of convulsions. Given that the majority of children in the study had very severe forms of epilepsy with frequent seizures, the TEAEs of "convulsion" was not unexpected. Most of the TEAEs were mild-to-moderate in intensity. Twelve patients (11.9%) experienced at least one severe TEAE. The most common severe TEAEs were persistence of convulsions and respiratory disorders, which are frequent at that age range. However, these were not were considered related to the study medication by the treating physician. Serious TEAEs were noted in 32 patients – with two exceptions, both convulsions, these were not considered related to study medication by the physician. Drug-related TEAEs – convulsion, irritability, hypotonia, somnolence – were experienced by five patients. With the exception of hypotonia, all are consistent with the known safety profile of levetiracetam and are listed in its product label. The event of hypotonia was reported for one patient – it was mild in intensity and resolved uneventfully without any changes in study medication. Seven patients discontinued the study due to TEAEs, which were infantile spasms and respiratory disorders. Six deaths were reported during the study; no pattern among these deaths was observed and none were deemed related to the study drug by the investigators.

Infantile spasms are the seizure expression of a severe epileptic encephalopathy of early childhood, considered to be one of the most drug-resistant forms of seizures. Consequently, persistence of infantile spasms despite treatment with levetiracetam could be indicative of lack of efficacy in this extremely severe form of epilepsy rather than an AE. Twenty infants with West syndrome (cryptogenic and symptomatic) participated in this study and data from 15 were available from their last visit. Analysis of results revealed that none showed worsening in epilepsy severity; on the contrary, 13 showed an improvement in their condition, while in the other two patients it remained stable. Similarly, the majority (n = 12) of these patients showed an improvement in psychomotor development; three remained stable and none showed worsening.

In a retrospective study of 130 patients, which included 12 with infantile spasms, the discontinuation rate of levetiracetam was significantly higher in patients with infantile spasms than in those with Dravet or Lennox–Gastaut syndromes.[15] However, the patients were older in this study (mean age at start of levetiracetam adjunctive therapy was 7.7 years) compared with the current study. Furthermore, since the investigators noted a favourable response among the patients with infantile spasms, they attributed the discontinuation to the poor tolerability of levetiracetam by these patients. In another study[16] of five patients newly diagnosed with cryptogenic West syndrome, two became seizure free following treatment with levetiracetam, two experienced a 50% reduction in seizure frequency, and one had no improvement in seizure frequency. However, the investigators did not report the duration of the follow-up and seizure frequency was based on parental observation. The study being performed in children with newly diagnosed West syndrome, a 50% reduction in the frequency of infantile spasms cannot be considered as a clinically meaningful result. Positive results for patients with West syndrome treated with levetiracetam have also been shown in other open-label, uncontrolled studies.[10,11]

An overall favourable safety and tolerability profile of levetiracetam in children and infants has been reported in several open-label studies. Notably, in a retrospective study of 28 children younger than 2 years of age with various types of epilepsy, adverse effects occurred in two patients and were behavioural in nature.[17] Grosso and colleagues included 21 children younger than 4 years of age in one study and 81 in another.[10,11] In both studies, the children had a wide range of epileptic seizures and syndromes. Investigators noted that levetiracetam was well tolerated in both studies. In a study that included 12 children below the age of 4 years and six below the age of 1 year, very few AEs were reported.[12] The mean daily dose of levetiracetam was 46 mg/kg/day (range 16.0–87.6 mg/kg/day) in this study, which was somewhat

higher than that used in several other studies. Krief and colleagues reported 39 mg/kg/day and Grosso et al. reported 41 mg/kg/day (range 25–62 mg/kg per day).[17,11] The maximum recommended dose for infants from 1 month to less than 6 months is 42 mg/kg/day and for infants from 6 months of age it is 60 mg/kg/day in Europe.[7]

z-Scores for body weight, body length and head circumference of the infants obtained at baseline were all negative. A z-score of zero corresponds to the 50th percentile, the reference mean; therefore, negative values indicate that patients ranked low on WHO standard growth curves.[18,19] Deviations from normal milestones are reflective of the severity of the underlying neurological disorders. Very young children with severe neurological disorders, and seizures as one of the symptoms, typically present with deviations from standard body weight and height/or head circumference. The change in z-scores from baseline for body weight and body length were positive at each visit indicating that the infants grew and gained weight over time during the study. The change in head circumference was not as consistent across all visits. Overall, levetiracetam does not appear to have a negative effect on growth parameters.

At all visits, most patients had deviations from normal milestones of psychomotor development. Based on the GES of psychomotor development, 52.9% of patients showed improvement, while 36.5% of remained stable and 10.6% worsened by the end of the study. Physicians also used the GES to rate change in epilepsy severity. Results indicated that based on the reports of parents/guardians and physician observation, epilepsy became less severe in the majority of patients throughout the study. At study end, 71.8% of patients showed improvement in their condition, 18.8% remained stable and 9.4% showed worsening. Of 26 patients who discontinued the study, 12 withdrew due to lack or loss of efficacy.

Given that levetiracetam was administered as adjunctive therapy in this study, and that the majority (80.2%) were also on at least one concomitant AED, a post hoc analysis was conducted to evaluate the safety of levetiracetam based on the number and specific combination of concomitant AEDs. No differences emerged in the safety profile of levetiracetam and AE patterns were similar regardless of the number of concomitant AEDs and whether levetiracetam was administered concomitantly with vigabatrin, phenobarbital, valproate or diazepam. Furthermore, a pharmacokinetic study of 187 children with epilepsy ranging from 3 to 17 years of age showed that levetiracetam does not affect the plasma concentrations of carbamazepine, valproic acid, topiramate or lamotrigine.[20] Overall, no clear trend or safety concern was identified when reviewing study outcomes by concomitant AEDs, or the other subgroups listed in section 2.2. However, as noted, the strength of conclusions drawn from the post hoc analyses is limited by the small numbers of patients in the subgroups.

This was an open-label study, and therefore presents with the methodological limitations associated with studies that are not randomized and blinded. However, given the difficulties inherent in conducting randomized controlled trials in this patient population, results from prospective observational studies such as the current study can be of value for healthcare professionals working with infants with epilepsy. There are few studies evaluating the use of levetiracetam in infants; to our knowledge, the current study included the largest number of patients in this age range so far. Since patients were treated according to local, routine clinical practice, the results provide an overview of how levetiracetam is used for the treatment of infants with different epileptic seizures and syndromes. Based on the findings of this study, levetiracetam can be considered an effective and well-tolerated option for the treatment of infants with epilepsy.

Conflict of interest

This study was sponsored by UCB Pharma. CL, JB and PG are employees of UCB Pharma. AA has received grants from the European Commission and consulting fees from Eisai, GSK, Shire and UCB Pharma.

Acknowledgements

The authors express their profound gratitude to the parents/guardians who allowed their child to take part in this study. They also acknowledge the contribution of the following to the study: Drs Helena Alarcón Martínez, Hospital Universitario Virgen de la Arrixaca, Murcia, Spain; Richard Appleton, Alder Hey Children's Hospital, Liverpool, UK; Stéphane Auvin, Hopital Robert Debre, Paris, France; Thomas Bast, Klinikum Kehl-Kork, Germany; Patrick Berquin, Centre Hospitalier Universitaire d'Amiens, France; Helen Cross, Great Ormond Street Hospital for Children, London, UK; Bernardo Dalla Bernardina, Borgo Roma, AOU Integrata di Verona, Italy; Giuseppe Gobbi, Ospedale Maggiore, AUSL di Bologna, Italy; Renzo Guerrini, AOU Ospedale Pediatrico Meyer, Bologna, Italy; Rajat Gupta, Birmingham Children's Hospital, Birmingham, UK; Joseph Kaleyias, University Hospital of Patras, Greece; Iwona Kochanowska, NZOZ EuroMedis, Szczecin, Poland; Elisabeth Korn-Merker, Epilepsiekliniken Mara, Bielefeld, Germany; Gerhard Kurlemann, Westfälische Wilhelms-Universität, Münster, Germany; Antonio Martinez Bermejo, Hospital Universitario Infantil La Paz, Madrid, Spain; Maria Mazurkiewicz-Beldzinska, Uniwersyteckie Centrum Kliniczne, Gdansk, Poland; Eleni Panagiotakaki, Hôpital Femme Mère Enfant, Lyon, France; Antigoni Papavasiliou, General Children's Hospital Pedeli, Athens, Greece; Miquel Raspall Chaure, HU Vall d'Hebron, Barcelona, Spain; Antonino Romeo, Ospedale Pediatrico Fatebenefratelli, Milano, Italy; Maria Luz Ruiz-Falcó Rojas, Hospital Universitario Niño Jesús, Madrid, Spain; Susanne Schubert-Bast, Universitätsklinikum, Heidelberg, Germany; Ulrich Stephani, Universitätsklinikum, Kiel Schleswig-Holstein, Germany; Jolanta Strzelecka, SPZOZ Szpital Dzieciecy, Warsaw, Poland; Federico Vigevano, Ospedale Pediatrico Bambino Gesù, Rome, Italy; Dorothée Ville, Hôpital Femme Mère Enfant, Lyon, France; Janusz Wendorff, Instytut Centrum Zdrowia Matki Polki, Lodz, Poland; Bernhard Weschke, Virchow-Klinikum, Berlin, Germany. The authors thank Barbara Pelgrims, UCB Pharma, for coordinating

development of the manuscript. Writing support was provided by Azita Tofighy, funded by UCB.

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.ejpn.2016.01.006.

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