CLINICAL REVIEW

Application Type	NDA Efficacy Supplement
Application Number(s)	21872 (supplement 16)
Priority or Standard	Standard (plus 3 month extension)
Submit Date(s)	9/27/13
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Division / Office	DNP
Reviewer Name(s)	Norman Hershkowitz, MD, PhD
Review Completion Date	
Established Name	levetiracetam
(Proposed) Trade Name	Keppra
Therapeutic Class	Antiepileptic Drug
Applicant	UCB
Formulation(s)	Intravenous
Dosing Regimen	15 minute infusion, Twice Daily
Indication(s)	Epilepsy
Intended Population(s)	Pediatric patients 1 month – 16 years of age (depending on seizure subtypes)

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

The Sponsor has satisfactorily fulfilled their PREA PMR requirement for this formulation. This application provides adequate information for the pediatric labeling of intravenous Keppra down to one month.

1.2 Risk Benefit Assessment

The present studies are limited because of their small sample size and lack of control. A number of serious adverse events were identified. However, the population studied was at high risk for such events; when individually examined, these events could not be temporally or causally linked to drug infusion and were likely the result of the patients' underlying medical condition. No consistent drug related changes in blood pressure or heart rate were identified, nor were there obvious infusion site reactions. Other adverse reactions, already known associated the oral formulation were identified with this intravenous formulation. The absence of a definitive linkage of serious events or changes in cardiovascular function to the intravenous infusion, the demonstration of bioequivalence to the oral formulation in children, the acceptable safety/efficacy profile of such oral formulations in children, as well as an acceptable safety/efficacy profile in adults, indicates an acceptable risk/benefit for this formulation in pediatric patients down to 1 month of age.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

None.

1.4 Recommendations for Postmarket Requirements and Commitments

None.

2 Introduction and Regulatory Background

Keppra (levetiracetam), as an oral tablet formulation, was first approved for Partial Onset Seizures (POS) in adults in 1999. The oral solution formulation was later approved based upon bioequivalence bridging studies in 2003. Based upon additional adequately controlled efficacy/safety trials the oral formulations was subsequently shown to have a wide antiepileptic spectrum of activity and is presently labeled for patients: 1) 6 years and older with Primary Generalized Tonic-Clonic (PGTC) seizures, 2) 12 years and older with myoclonic seizures (MS) with Juvenile Myoclonic epilepsy, and 3) 1 month and older in patients with POS. In 2006 an intravenous formulation of Keppra was approved for use in adults when oral administration was not possible, based upon the demonstration of bioequivalence and acceptable safety profile. A 15 minute infusion at a dose equivalent to the adult labeled oral dose is recommended in the label. A PREA requirement, as part of this latter action, included a single study examining safety and pharmacokinetic is a pediatric population down to 4 years of age. The present application submitted fulfills this latter requirement, and provides studies in younger patients. It does so by providing completed reports on the following two studies:

- N01274: This was an open-label, single-arm, multicenter study to evaluate the safety, tolerability, and pharmacokinetics of the levetiracetam intravenous 15-minute infusion administered every 12 hours, either as adjunctive treatment or monotherapy in children (4 to 16 years old) with epilepsy.

- N01275: This was an open-label, single-arm, multi-center, pharmacokinetic, safety and tolerability study of levetiracetam intravenous infusion in children (1 month to 4 years old) with epilepsy.

Intravenous Keppra is approved in Europe in the indications and age ranges as listed above for the oral formulation, with the exception of adjunctive therapy in the treatment of partial onset seizures where it is approved only for patients 4 years and above.

(b) (4)

(b) (4)

2.2 Tables of Currently Available Treatments for Proposed Indications

The table includes anticonvulsants that are available in intravenous form. Note, the indications for the Keppra products are not necessarily the same as for those drugs listed. Moreover, phenobarbital is an unapproved, but marketed drug, used for seizures.

Drugs
diazepam
Fosphenytoin (phenytoin)
Lacosamide
Lorazepam
Phentobarbital
Phenytoin
Valproic acid

2.3 Availability of Proposed Active Ingredient in the United States

This product is presently available in the US but is note labeled for the pediatric population. The intravenous formulation, however, is used off label in the pediatric population.

2.4 Important Safety Issues with Consideration to Related Drugs

This product is most notably known for its neuro-psychiatric effect, however other important adverse effects are described in the Precautions and Warnings section of the label including somnolence/fatigue, coordination difficulties, serious dermatologic effects, and suppression in red and white cell counts. Prior adult intravenous studies did not include a signal beyond that which already known for the oral solution. Nonetheless, because of observations made of adverse events associated with the intravenous administration of other anticonvulsants (e.g. phenytoin and phenobarbital), a special considerations is made in the evaluation local infusion as well as cardiac related event. Sponsor has been requested to provide detailed data on cardiac, vital signs, as well as EKG changes.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

Acceptable.

3.2 Compliance with Good Clinical Practices

Acceptable.

3.3 Financial Disclosures

See the Clinical Investigator Financial Disclosure Review Template submitted to DARRTS. The conclusion of which is that, while there was some degree of financial conflict for a few investigators, final results on safety and PK outcomes would not be affected

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

No CMC changes are being made. CMC recommends approval from their perspective.

4.2 Clinical Microbiology

No microbiology review, but as noted above this products has not changed.

4.3 Preclinical Pharmacology/Toxicology

No new data.

4.4 Clinical Pharmacology

Clinical Pharmacology concludes that the observed plasma concentrations in studies N01274 and N01275 when compared to those achieved after oral administration of Keppra oral tablets or solution (from a previous population PK study N01288, using data from previous studies) were overall in the same range at similar doses per kg. They

conclude bioequivalence to the oral formulation. Therefore, in pediatric patients, the dosing recommendations for Keppra IV should be the same as these for Keppra oral (IR or oral solution), and no dose adjustment is necessary when switching from one route of administration to the other.

4.4.1 Mechanism of Action

This has been discussed in other submissions. The mechanism for all antiepileptic drugs must be considered theoretical. But with that mind, this drug may have a unique mechanism in that it binds to synaptic vesicle protein (SV2A).

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

See the below listings.

6 Review of Efficacy

Efficacy Summary

The conclusion of efficacy is based upon the above noted conclusion of the bioequivalence. This allows the bridging of oral pediatric efficacy to that of the intravenous formulation.

7 Review of Safety

Safety Summary

The safety of this formulation is not only based upon safety data from the below described studies, but also upon the already demonstrated efficacy/safety considerations of the oral the formulation bridged by the PK analysis demonstrating bioequivalence between both oral and intravenous formulations.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

Two studies were performed:

Study 01275 (ages 1 month to <4 years): This was an open-label, single-arm, multi-center, pharmacokinetic, safety and tolerability study of levetiracetam intravenous infusion in children (1 month to 4 years old) with epilepsy. This study examined PK and safety in 18 patients (6 in each of 3 age groups: 1 month to < 6months, >6 months to < 2 years, and 2 years to <4 years). Patients were selected as those requiring a short intravenous treatment with levetiracetam, whether on this drug prior to the study or not. Treatment could be adjunctive or monotherapy. The dosage of Keppra IV varied from LEV 7mg/kg bid to LEV 30mg/kg bid (a dosage within too slightly above that recommended in the label). Infusions were performed over a 15 minute period, the time indicated in the package insert for adults. Subjects who were already receiving LEV orally were switched temporarily, for an Evaluation Period of a maximum of 4 days, to the IV infusion administration on the same bid dose regimen. For subjects who were not yet taking Keppra orally before this study, the dosing regimen was based on the recommendations following the development of a population PK model in children after oral administration. From a PK perspective, the observed plasma concentrations in this study were compared to those achieved after oral administration described in previous studies.

Study N01274: This second study was an open-label, single-arm, multi-center, pharmacokinetic, safety and tolerability study of levetiracetam intravenous infusion in children (4 to < 16 years old) with epilepsy. This study examined PK safety, and tolerability in 33 patients (11 in the ≥4 to <8 years group, 12 in the ≥8 to <12 years group, and 10 in the ≥12 to <16 years group). Patients were selected as those requiring a short intravenous treatment with levetiracetam, whether on this drug prior to the study or not. Treatment could be adjunctive or monotherapy. The dosage of Keppra IV varied from Keppra 10mg/kg bid to Keppra 1500mg bid (similar to those recommended in the label). Infusions were performed over a 15 minute period, the time indicated in the package insert for adults. Subjects who were already receiving Keppra orally were switched temporarily, for an Evaluation Period of a maximum of 4 days, to the IV infusion administration on the same bid dose regimen. For subjects who were not yet taking Keppra orally before this study, the dosing regimen was based on the recommendations following the development of a population PK model in children after oral administration. From a PK perspective, the observed plasma concentrations in this study were compared to those achieved after oral administration described in previous studies.

7.1.2 Categorization of Adverse Events

Routine methodology was used.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

Because of the limited number in the study population no inter-study pooling was performed.

7.2 Adequacy of Safety Assessments

Analysis of the adequacy of the database has to be considered in the background of a number of issues:

- There is a large amount safety experience for the oral approved IR formulation at all doses and ages group that will be labeled for the intravenous formulation.
- OCP has concluded that there is bioquivalnce between the intravenous and oral formulations.

However, the additional safety data from the above described studies serves as crucial additional safety data.

There were a high number of deviations in study 01275 noted in 90 percent of patients, with the most common being the missing of exact required vital sign and PK measurement. This still represents a small number of the total data points obtained.

In all this reviewer believes that taken together the data is adequate for the characterization of safety,

7.3 Major Safety Results

Patient's Disposition and Demographics

Study 01275 (ages 1 month to <4 years)

Patient disposition is presented in the table below (transcribed from the Sponsor's review). Most patients enrolled, completed the study. All patients enrolled contributed to the ITT population

Table 7:1. 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	6 (100)	4 (66.7)	6 (87.5)	16 (84.2)
Discontinued from the	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	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.

Major demographic variables for this study are presented in the table below (transcribed form the Sponsor's review). The table reveals that there was relatively even distribution in the different age bins. It is noteworthy that there is a preponderance of males and "other race." The latter was principally Hispanic and Mestizo, (i.e. Hispanic/aboriginal American mix). Generally numbers were too small to allow for a meaningful comparison amongst different demographic groups. Comparisons of oral administration studies, however, were examined in prior NDA submissions. Conclusions should be deferred to those reviews.

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

Study 01274 (<4 years to < 16 years)

The table below (transcribed form the Sponsor's review) presents patient disposition in this study. All patients completed the study.

	Age (years)			
	≥4 to <8 (N=11)	≥8 to <12 (N=12)	≥12 to <16 (N=10)	Overall (N=33)
	n (%)			
Screened	11 (100)	12 (100)	10 (100)	33 (100)
Enrolled	11 (100)	12 (100)	10 (100)	33 (100)
ITT population	11 (100)	12 (100)	10 (100)	33 (100)
Completed the study	11 (100)	12 (100)	10 (100)	33 (100)
Discontinued from the study	0	0	0	0
PK-ITT population	11 (100)	12 (100)	9 (90.0)	32 (97.0)

ITT=intent-to-treat; PK=pharmacokinetic

Major demographic variables are presented in the table below (transcribed form the Sponsor's review). All age bins were equally represented. Both sexes were well, but not equally, represented. A majority of patients were classified as Caucasians although one-third were described as "other." Like above, "other" referred to Hispanic and Mestizo. Race was variably represented in the different age groups. Generally numbers were too small to allow for a meaningful comparison amongst different demographic groups. Data from oral administration studies, however, was examined in prior NDA submissions. Conclusions should be deferred to those reviews.

Characteristic	Descriptive Statistics	Age (years)			
		≥4 to <8 (N=11)	≥8 to <12 (N=12)	≥12 to <16 (N=10)	Overall (N=33)
Age (years)	n	11	12	10	33
	Mean (SD)	5.86 (1.10)	9.87 (1.13)	13.74 (1.29)	9.71 (3.38)
	Median	5.90	9.80	13.50	9.60
	Min – Max	4.1 – 7.5	8.0 – 11.7	12.0 – 15.5	4.1 – 15.5
Gender	n	11	12	10	33
Male	n (%)	7 (63.6)	5 (41.7)	7 (70.0)	19 (57.6)
Female	n (%)	4 (36.4)	7 (58.3)	3 (30.0)	14 (42.4)
Race	n	11	12	10	33
Black	n (%)	0	2 (16.7)	0	2 (6.1)
Caucasian	n (%)	11 (100)	5 (41.7)	5 (50.0)	21 (63.6)
Other	n (%)	0	5 (41.7)	5 (50.0)	10 (30.3)
Weight (kg)	n	11	12	10	33
	Mean (SD)	21.96 (7.23)	30.24 (7.99)	50.79 (14.11)	33.71 (15.41)
	Median	21.00	32.40	47.25	32.50
	Min – Max	12.0 – 37.6	16.0 – 39.5	35.5 – 78.7	12.0 – 78.7

Deaths

Study 01275 (ages 1 month to <4 years)

Three deaths were noted in the 18 patients that were randomized. While this appears to be a substantial signal it must be remembered that drug was principally used in a young seizure population requiring intravenous administration, a population that appeared to be relatively ill. Thus, examination of individual narratives is important to evaluate. A brief description of the narratives, with this reviewer's discussion follows:

- Subject N01275/[redacted] (b) (6): This patient is noted to have died as a result of "cardiac arrest and metabolic acidosis." The patient was a 3.6 year old black female with a diagnosis of glycogen storage disease (type I) and sickle cell trait. The immediate cause of death appears to be "cardiac arrest and metabolic acidosis." This patient received a single intravenous dose of (350 mg). The patient was admitted from home, 8 days after intravenous drug administration. Concomitant medication on that day included oral levetiracetam (1400 mg/day) and midazolam. The mother brought the patient to the hospital because she noted the child was not acting normal. On arrival, the subject was hypothermic, bradycardia, hypotensive with shallow breathing; she rapidly progressed into cardiopulmonary arrest with heart rate in the 30s. A chest x-ray showed bilateral diffuse airway opacity with air bronchograms, probably representing pulmonary edema in the setting. A severe lactic acidosis was noted. During this hospitalization the patient received fentanyl, insulin, glucose/sodium chloride/potassium chloride, glucose, sodium chloride, vancomycin, cefotaxime, ketorolac, oseltamivir, and ranitidine. The fact that this event appears to be a potential pneumonia with sepsis occurring 8 days following drug administration and that the patient received only one dose, following which she was discharged, makes the association to drug infusion very unlikely. Moreover the lactic acidosis may be exacerbated by the underlying storage disease
- Subject N01275/[redacted] (b) (6): This patient is noted to have died as a result of "abdominal sepsis", bradycardia, metabolic acidosis and pneumonia. The patient is described as a 0.1 year old Hispanic male who received 2 days of dosing of about 30 mg Keppra. According to the provided narrative, before receiving intravenous Keppra, this patient had a neonatal history of neonatal sepsis, cerebral infection, quadriparesis, anemia, encephalitis, cerebral atrophy (cortical cerebral atrophy), and gastrooesophageal reflux disease. Prior to the study entry, the subject had been admitted to the hospital due to neonatal sepsis, cerebral infection and seizures. It appears that the patient received intravenous Keppra during this period. The patient was discharged on both oral Keppra and phenobarbital. Fifteen days after treatment, the patient was admitted for pneumonia. "Abdominal sepsis" and seizures were also diagnosed. Patient was started on antibiotics and antacids. There appeared to be some resolution of these symptoms, but latter exacerbation so that the patient died as a result of

"abdominal sepsis", bradycardia, metabolic acidosis and pneumonia died 35 days after receiving the test product. Again, in this case, death occurred many days after receiving intravenous levetiracetam. The patient had many confounders that may have led to these serious events including his undermined neurologic condition (quadrapersis, seizures, and encephalopathy) as well as reflux that may have increased the risk of aspiration and pneumonia.

- Subject N01275/ (b) (6) : The patient is described as a 0.2 year old Hispanic male who died of respiratory failure. He had a complex medical history with premature birth, associated with respiratory failure, and later diagnoses of with bronchoaspiration, atelectasis, cardiac arrest, gastrooesophageal reflux, cerebral atrophy, pneumonia, cardiac arrest, hypotonia, pyramidal tract syndrome, thalamic infarction and seizures. The patient received two days of intravenous Keppra. The Sponsor notes in the narrative an incident of mild bradycardia on the first day of infusion, but does not note if it is related to infusion. Six days later a moderate incident of hypotension was noted. Fourteen days after the last intravenous dose the patient was admitted to the hospital because of pneumonia. A little more than a week after admission the patient was discharged with "an aspiration device." Days later he was readmitted with respiratory failure, and died soon afterward. He was on oral Keppra throughout. This patient suffered neurological compromise, seizures and gastroesophageal reflux that would increase the risk for pneumonia. Considering the latency of these events and underlying medical conditions, it is unlikely that the intravenous drug treatment contributed to this death.

In summary, while 3 deaths were noted in the small population of patients studied, these occurred in patients who were at risk for such complications. These same risks, resulted in the need for intravenous treatment and in way biased studied population. Importantly, these deaths do not appear to be temporally linked to intravenous treatment, occurring many days later. These factors make causal linkage to intravenous Keppra treatment very unlikely.

Study 01274 (<4 years to < 16 years)

No Deaths were observed.

Serious Adverse Events Unrelated to Deaths

Study 01275 (ages 1 month to <4 years)

In addition to the serious adverse events resulting in deaths noted above, one additional 3.5 year old white male was noted to have a serious event described as QTc prolongation. This patient was admitted for evaluation of his cryptogenic epilepsy from

which he was being treated with oxcarbazepine. On admission he developed gastroenteritis with vomiting and diarrhea. For this reason he was randomized into the protocol, as he required Intravenous treatment. The patient received 2 infusions of Keppra at a dose of 170 mg. He also received dimenhydrinate to control nausea and vomiting. On the second day he developed QT prolongation with the QTcB going form going from 434 to 496. No cardiac related symptomatology was noted. The patient remained on Keppra, but after the second dose intravenous Keppra treatment was discontinued and oral continued. I do not believe that this resulted in a direct effect of levetiracetam based upon the fact: 1) spontaneous QT measurements are notoriously inaccurate, and a formal QT study in adults described in the label, studying high dosages of Keppra, failed to reveal an effect of this drug on QTc; 2) perhaps to a lesser importance dimenhydrinate (Dramamine) contains diphenhydramine and 8-chlorotheophylline, the former, albeit in toxic doses, has been associated with QT prolongation.

Study 01274 (<4 years to < 16 years)

Four patients with serious adverse events were observed. They are described as follows:

- Patient (b) (6) Pyrexia: This is a 5.3 year old white male with a history of encephalitis, neurodevelopment disorder and epilepsy, who received two days of intravenous Keppra dosing (500 mg per injection). This patient was on oral levetiracetam and phenobarbital to control seizures. The day following treatment, the patient developed a “mild” fever and a mild cough, Chest x-ray and urinalysis were negative. Although mild in intensity the event was classified as serious because it extended the patient’s hospital stay. The symptoms resolved in 3 days without treatment and continuation of oral drug. This reviewer could not identify any causal link to treatment.
- Patient (b) (6) Vomiting: This is an 8 year old white female. With a history of prematurity, cerebral palsy, periventricular leukomalacia, hydrocephalus (with a VP shunt), GI reflex, gastrointestinal disorder with vomiting, cholelithiasis, and epilepsy. The patient was being treated with oral Keppra prior to study inclusion. She received two days of intravenous dosing of Keppra at 250 mg/dose. During this time she had moderate nausea. During that hospitalization she underwent surgery including digestive revision of Nissen fundoplication, pyrolopasty, gastrostomy, and cholecystectomy. Thirty seven days after intravenous drug administration she presented to the hospital with severe nausea and vomiting and was admitted. The time difference between drug administration and presentation and prior history of these same symptoms makes it unlikely that this resulted from drug.
- Patient (b) (6) -Convulsions: This is a 10.4 year old mixed race female with a history of epilepsy and “congenital nervous system disorder.” She received one day of Keppra infusion (350 mg/dose). She was on oral levetiracetam

previously. Ten days after iv treatment she had seizures, which was rated as serious; at that time she was also noted to have a pharyngotonsillitis, which were thought to be the cause of the seizures. This is unlikely a result of drug treatment because of the delay. Also note upper respiratory tract infections are not uncommon in this population.

- Patient (b) (6)-Hypotension: This is a 10.3 year old black male with a history of multiple birth defects including lissencephaly, hip dysplasia and associated neurologic symptoms including quadrparesis, reduced visual function, and epilepsy. The patient received 2 days of intravenous dosing of 500 mg/dose. The patient was admitted for spinal fusion surgery and as a result required intravenous levetiracetam replacement. The patient was also on phenobarbital. The patient was recorded to have hypotension on the second day of drug administration. Upon further inquiry of the Sponsor, it was revealed that the first evidence of hypotension occurred in the operating room, independent of treatment. This subsequently required dopamine. A second hypotensive episode with blood pressure dropping to 59/33 from 102/44 occurred 6 hours after the second infusion and appeared to result from a completely independent event. The event according the e investigator was “associated with fluid overload and was due to routine post-operative changes that were expected.” I believe there is no causality to the experimental treatment.

In summary, while a number of serous adverse events occurred, these occurred in patients who were at risk for the same events and were not temporally linked to the intravenous administration.

Dropouts and/or Discontinuations

Study 01275 (ages 1 month to <4 years)

One patient ((b) (6)) was discontinued from the drug. This was a 0.5 year old female with a history of neonatal asphyxia, developmental delay and seizures who was receiving phenobarbital, clonazepam, and vigabatrin, and whom after receiving one dose of 150 mg of Keppra was noted to have “relative activation of EEG.” The patient had been admitted for adjustment of anticonvulsant medications. No clinical association to this activation was noted. It is hard at the present time to attribute this to the drug; such patients may have spontaneous changes in EEG, particularly with the understanding that the patient was admitted for drug adjustment, suggesting that her seizures are poorly controlled.

Study 01274 (<4 years to < 16 years)

No patients discontinued because of adverse events.

7.3.5 Submission Specific Primary Safety Concerns

Infusion Site Reactions

One patient, younger than 4 years old, experienced an adverse event related to the intravenous infusion site, which was reported as the preferred term “puncture site pain.” The reaction was rated as of mild severity and was neither categorized as a serious adverse event nor resulted in discontinuation. No subject older than 4 years old had an infusion site adverse event. It is hard to conclude this mild and isolated event is associated with the formulation as it may be expected as background to infusion alone.

Cardiovascular Events

Six hypotensive adverse event episodes were reported between the two studies.

Three of these, were from study N01275, and were associated with other serious adverse events. However, two of these three were rated as mild and moderate. All three occurred many hours too days following infusion. These cases were previously discussed above and patients (b) (6). Because of the fact that these three did not occur during infusion, and two occurred against a background of other serous medical events, it is unlikely that these represented an effect of infusion. The reader is referred to the description of these patient’s narratives presented above.

Three were from study N01274. One of these patients had a hypotensive during infusion. But, the blood pressure remained low throughout the remaining time of the study. The other two had events were not associated with the infusion. None of these events were classified as serious nor did they result in drug discontinuation.

Three adverse events classified as bradycardia were reported in study N01275. These cases did not occur during infusion and were observed against the background of systemic illness and therefore (see section on Deaths, above). Considering this they could not be linked to the infusion.

Additional analyses of blood pressure, pulse, and EKG changes did not reveal an obvious safety signal (see below).

7.4 Supportive Safety Results

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Common Adverse Events

Study 01275 (ages 1 month to <4 years)

A total of 33 TEASs were observed in 12 patients (63%). Those categorized under the SOC of cardiac were most common, with bradycardia the most common preferred term (see vital signs for a discussion); this SOC also included one case of cardiac arrest, which is described above and is not believed to be related to the treatment. Two cases of bradycardia were noted by the Sponsor. This reviewer found a third from the examination of narratives (see Cardiovascular Events). These were not temporally linked to infusion and; these occurred against the background of systemic illness. They could therefore not be attributed to drug infusion. Also see section on "Deaths" were cases are described and the Section on Cardiovascular Events as well as the section on Cardiovascular Events. An analysis of heart rate is also presented below under Vital Signs. Associated with the latter SOC were two cases of hypotension (although this reviewer found a third form the Narratives). For the same reasons as that described for bradycardia, no attribution can be given to infusion. Also see section on "Deaths" were cases are described and the Section on Cardiovascular Events as well as the section on Cardiovascular Events. There was one case of "QT prolonged" described as an adverse event, which this reviewer does not believe is an intravenous levetiracetam induced event (see above "Serious Adverse Events"). Also reported was one case of irritability and one of restlessness. Of the Nervous system SOC 3 cases were classified as somnolence, 1 of drooling, and 2 of a convulsion related term. These preferred neurological and psychiatric terms, and similar ones, are described in the label, with irritability and somnolence described in the Warnings and Precautions section. Two cases of pneumonia are also reported. These cases are described above under "Deaths." Pneumonia is not uncommon in this very sick seizure population, and as discussed above do not appear to be related to intravenous levetiracetam administration. The two cases of Metabolic and Nutritional Disorders were cases of metabolic acidosis, which as discussed above under "Deaths" are not believed by this reviewer related to drug treatment.

As there is is a substantial amount of controlled data on the toxicity of levetiracetam in this age group, an important distinction to make is what adverse events described occurred during the 15 minute period. The Sponsor was requested to provide this information. The only event identified during infusion was that of somnolence. No adverse events occurred during a 45 minute window after infusion.

Table 8:2. Treatment-emergent adverse events occurring in at least 2 subjects overall by UCB SOC and MedDRA preferred term – ITT population

UCB SOC MedDRA preferred term	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)
	n (%)			
Number of subjects with at least 1 TEAE	3 (50.0)	3 (50.0)	6 (85.7)	12 (63.2)
Cardiac disorders	2 (33.3)	0	2 (28.6)	4 (21.1)
Bradycardia	2 (33.3)	0	0	2 (10.5)
General disorders and administration site conditions	2 (33.3)	1 (16.7)	2 (28.6)	5 (26.3)
Pyrexia	2 (33.3)	0	1 (14.3)	3 (15.8)
Infections and infestations	2 (33.3)	0	0	2 (10.5)
Pneumonia	2 (33.3)	0	0	2 (10.5)
Metabolism and nutrition disorders	1 (16.7)	0	1 (14.3)	2 (10.5)
Metabolic acidosis	1 (16.7)	0	1 (14.3)	2 (10.5)
ervous system disorders[a]	1 (16.7)	1 (16.7)	2 (28.6)	4 (21.1)
Psychiatric disorders[a]	0	1 (16.7)	1 (14.3)	2 (10.5)
Respiratory, thoracic, and mediastinal disorders[a]	1 (16.7)	0	1 (14.3)	2 (10.5)
Skin and subcutaneous disorders[a]	1 (16.7)	0	1 (14.3)	2 (10.5)
Vascular disorders	1 (16.7)	1 (16.7)	0	2 (10.5)
Hypotension	1 (16.7)	1 (16.7)	0	2 (10.5)

ITT=intent-to-treat; MedDRA=Medical Dictionary for Regulatory Activities; SOC=system organ class; TEAE=treatment-emergent adverse event

a System organ class reported by ≥2 subjects overall. Preferred term reported by <2 subjects overall, and hence not cited in the table.

Study 01274 (<4 years to < 16 years)

Sixty-five adverse events were noted in 21 (64%) patients. The table below (transcribed form the Sponsor's review) presents the most common adverse events. Adverse events referable to the Nervous System SOC were the most common. Under this SOC convulsions and somnolence related preferred terms were most common. Dizziness was another common preferred term in the Nervous System SOC. Such events are not unexpected knowing the patient population and the known Keppra drug reactions and

are already noted in the present label. Gastrointestinal disorders were the next most common reported SOC category. Under this SOC, the most common preferred terms were nausea and vomiting. Vomiting is a known common adverse reaction of Keppra and is described in section 6.0 of the approved label. Infections and Infestations, principally involving upper respiratory tract infections, were also reported. Such adverse events are not uncommon in this population and are already described in the label in this population. Skin reactions included one case each of dermatitis allergic and rash. These were not serious. Serious skin reactions are noted in the label.

Table 8:2. Treatment-emergent adverse events occurring in at least 5% of subjects overall by UCB SOC and MedDRA preferred term – ITT population

UCB SOC MedDRA preferred term	Age (years)			
	≥4 to <8 (N=11)	≥8 to <12 (N=12)	≥12 to <16 (N=10)	Overall (N=33)
	n (%)			
Number of subjects with at least 1 TEAE	6 (54.5)	9 (75.0)	6 (60.0)	21 (63.6)
Gastrointestinal disorders	3 (27.3)	3 (25.0)	2 (20.0)	8 (24.2)
Vomiting	2 (18.2)	1 (8.3)	0	3 (9.1)
Nausea	1 (9.1)	2 (16.7)	0	3 (9.1)
Dry mouth	0	1 (8.3)	2 (20.0)	3 (9.1)
General disorders and administration site conditions	3 (27.3)	1 (8.3)	2 (20.0)	6 (18.2)
Pyrexia	1 (9.1)	0	2 (20.0)	3 (9.1)
Infections and infestations[a]	0	3 (25.0)	1 (10.0)	4 (12.1)
Metabolism and nutrition disorders	1 (9.1)	1 (8.3)	2 (20.0)	4 (12.1)
Weight decreased[b]	0	1 (8.3)	1 (10.0)	2 (6.1)
Nervous system disorders	2 (18.2)	4 (33.3)	4 (40.0)	10 (30.3)
Convulsion	0	2 (16.7)	2 (20.0)	4 (12.1)
Somnolence	0	1 (8.3)	1 (10.0)	2 (6.1)
Skin and subcutaneous disorders[a]	1 (9.1)	3 (25.0)	1 (10.0)	5 (15.2)
Vascular disorders	2 (18.2)	1 (8.3)	0	3 (9.1)
Hypotension	2 (18.2)	1 (8.3)	0	3 (9.1)

ITT=intent-to-treat; MedDRA=Medical Dictionary for Regulatory Activities; SOC=system organ class; TEAE=treatment-emergent adverse event

[a] System organ class reported by ≥5% of subjects overall. Preferred term reported by <5% of subjects overall, and hence not cited in the table

[b] The UCB SOC is different than the primary SOC assigned by MedDRA.

One case of somnolence and one of hypotension was observed during infusion. The adverse events reported immediately post infusion (up to 45 minutes after) included one case each of the following: dry mouth, pyrexia, somnolence and hypotension. This hypotensive episode, as discussed in the Section on Cardiovascular Events, while occurring during infusion was not serious nor lead to discontinuation, and it persisted after infusion. Causality is not attributed to infusion.

7.4.2 Laboratory Findings

7.4.3 Vital Signs

Heart rate and blood pressure were recorded while the subject was in a supine position for 5 minutes every morning and evening, just before and at 5, 15, 30, and 60 minutes after the start of the IV infusion. As infusion lasted 15 minutes the 5 minute evaluation would be during the initial part of the infusion and the 15 minute should be immediately at its completion. Based upon previous adult studies and sparse sampling results in the present study the peak Cmax (Tmax) would be expected to occur on or about 15 minutes after the initiation infusion (i.e. at infusion completion). For this reason mean change from baseline, measured just prior to infusion, in systolic blood pressure (and SD values) at 15 minutes for different age groups for the first 4 consecutive infusions in both studies are presented in the table below table. A negative change signifies reduction. No consistent or age dependent reductions could be appreciated. If anything increases were more common than reductions.

	Mean Change in Systolic Blood Pressure from Pre-infusion Baseline in change mmHG (SD) for patients 1 month to 4 years					
	1 month to 6 months	6 months to 2 years	2 years to 4 years	4 years to 8 years	8 years to 12 years	12 years to 16 years
First treatment	-4.27	21.4 (8)	6.4 (5)	-5.4 (17)	-3.5 (11)	-2.2 (4)
Second treatment	9.3 (14)	1.6 (5)	-3.6 (2)	0.6 (6)	0.2 (9)	-3.2(5)
Third treatment	5.0 (13)	-16.5 (18)	-12.0 (24)	2.7 (13)	8.8 (18)	2.6 (9)
Fourth treatment	16	26 (42)	22.7 (33)	-0.9 (28)	2.0 (3)	1.8 (8)

A comparison of pre-infusion to post 15 minute infusion for the various treatments did not reveal any obvious significant difference in the occurrences of potentially clinically significant (PCS) values (see Appendix for age specific criteria) for diastolic blood pressure, systolic blood pressure or heart rate in patients from the two studies. These

data are presented in the following 2 tables that present a comparison of the pre-dose values PCS values to post 15 minute dose evaluations for the first infusion in the two studies. There were no obvious differences in the number of PCS values prior infusion versus at the completion of infusion, at the approximate Tmax, for both age groups studied.

	# of PC values/# of patients 4-16 years		
		Pre-infusion	15 minutes post-infusion
Systolic Blood Pressure	Low PCS Value	3/33	2/33
	No PCS Value	30/33	31/33
	High PCS Value	0/33	0/33
Diastolic Blood Pressure	Low PCS Value	4/33	1/33
	No PCS Value	26/33	32/33
	High PCS Value	3/33	0/33
Heart Rate	Low PCS Value	0/33	0/33
	No PCS Value	32/33	33/33
	High PCS Value	1/33	0/33

	# of PC values/# of patients 1 month to 4 years		
		Pre-infusion	15 minutes post-infusion
Systolic Blood Pressure	Low PCS Value	0/18	0/18
	No PCS Value	17/18	17/18
	High PCS Value	1/18	1/18
Diastolic Blood Pressure	Low PCS Value	5/17	2/18
	No PCS Value	11/17	16/18
	High PCS Value	1/17	0/18
Heart Rate	Low PCS Value	2/18	1/18
	No PCS Value	15/18	16/18
	High PCS Value	1/18	1/18

These data, collectively, do not indicate a significant effect on blood pressure or heart rate.

7.4.4 Electrocardiograms (ECGs)

Electrocardiograms were performed at Screening, Day 1 morning, and at the End of Treatment/EDV. The Sponsor rated the normal of abnormal EKGs prior to the study and after. Little significant change was noted. As EKGs were not performed during infusion, the value of this data, in the background of prior formal studies that examined high doses is questionable. One significant prolongation of the QTc was observed as a cause of discontinuation. This case are described in the above narrative, were this reviewer notes it unlikely related to infusion.

7.4.5 Special Safety Studies/Clinical Trials

None.

7.4.6 Immunogenicity

As there are insufficient numbers in the present studies, this will be based upon prior oral formulation studies.

7.5 Other Safety Explorations

None.

7.5.1 Dose Dependency for Adverse Events

As there are insufficient numbers in the present studies, this will be based upon prior oral formulation studies.

7.5.2 Time Dependency for Adverse Events

Adverse events during infusion are a special issue. These are described above.

7.5.3 Drug-Demographic Interactions

As there are insufficient numbers in the present studies, this will be based upon prior oral formulation studies.

7.5.4 Drug-Disease Interactions

As there are insufficient numbers in the present studies, this will be based upon prior oral formulation studies.

7.5.5 Drug-Drug Interactions

As there are insufficient numbers in the present studies, this will be based upon prior oral formulation studies.

7.6 Additional Safety Evaluations

None.

7.6.1 Human Carcinogenicity

See prior studies.

7.6.2 Human Reproduction and Pregnancy Data

See prior studies.

7.6.3 Pediatrics and Assessment of Effects on Growth

As there are insufficient numbers in the present studies, this will be based upon prior oral formulation studies.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

As there are insufficient numbers in the present studies, this will be based upon prior oral formulation studies.

7.7 Additional Submissions / Safety Issues

None

8 Appendix: Age specific vital sign potentially clinically significant (PCS) criteria.

PARAMETER	*AGE*	*ABNORMALLY LOW*	*NORMAL RANGE*	*ABNORMALLY HIGH*
Pulse Rate (beats/minute)	<6m	<100	100 to 180	>180
	6m - <3y	<90	90 to 150	>150
	3y - <12y	<60	60 to 130	>130
	12y - <17y	<50	50 to 120	>120
	≥17y	<50 and a decrease from Baseline of ≥15	50 to 120	>120 and an increase from Baseline of ≥15
Systolic Blood Pressure (mmHg)	<6m	<60	60 to 100	>100
	6m - <3y	<70	70 to 120	>120
	3y - <12y	<80	80 to 140	>140
	12y - <17y	<90	90 to 160	>160
	≥17y	≤ 90 and a decrease from Baseline of ≥20	>90 to <180	≥ 180 and an increase from Baseline of ≥20
Diastolic Blood Pressure (mmHg)	<6m	<40	40 to 65	>65
	6m - <3y	<45	45 to 75	>75
	3y - <12y	<50	50 to 80	>80
	12y - <17y	<50	50 to 105	>105
	≥17y	<50 and a decrease from Baseline of ≥15	50 to 105	>105 and an increase from Baseline of ≥ 15

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/s/

NORMAN HERSHKOWITZ
10/30/2014