BPCA SUMMARY REVIEW

Application Type	NDA
Submission Number	21-035 (S-040) 21-505 (S-007)
Submission Code	Supplement
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Reviewer Name	Howard D. Chazin, MD, MBA
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Established Name	levetiracetam
Trade Name	Keppra ®
Therapeutic Class	antiepileptic
Applicant	UCB Pharma
Priority Designation	P
Formulation	oral tablets and solution
Dosing Regimen	BID
Indication	adjunctive epilepsy
Intended Population	pediatric ages (ages 4-16)

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1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

The pediatric supplemental NDA for Keppra® (levetiracetam) should be approved based on efficacy results. There was substantial evidence from a single adequate and well controlled trial that provided clinically relevant, statistically significant (p=0.0002) reductions over placebo in partial onset seizure frequency per week among children ages 4-16 during the treatment period. [26.8% (95% CI; 14.0%-37.6%)]

The pediatric supplemental NDA for Keppra ® (levetiracetam) demonstrated an acceptable safety profile in this pediatric subpopulation. The majority of adverse events were neuropsychiatric in origin and will be described in labeling.

1.2 Required Phase 4 Commitments

The sponsor has only partially responded to the pediatric written request and still needs to submit a separate submission to include evaluation of efficacy and safety of levetiracetam in children ages 1 month to 4 years.

An additional required Phase 4 commitment requested by the Division was a formal QT analysis to be performed in adult patients. This was requested to address concerns related to prolonged QTc intervals seen in several patients in the pediatric safety database.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

Keppra ® (levetiracetam) is an oral antiepileptic drug. It is an approved drug for adjunctive treatment for partial seizures in adult epilepsy patients. The sponsor presented the results of a single efficacy study to support a claim of adjunctive treatment for partial onset seizures in pediatric epilepsy patients ages 4 to 16. That study (referred throughout this review as Study N159 or N159) was a double-blind, placebo-controlled, multi-center clinical trail conducted in children with refractory partial seizures. Following an 8-week prospective baseline period, 198 patients were randomized to receive placebo (N=97) or levetiracetam (N=101) in a double-blind fashion. The levetiracetam dose was titrated up every 2 weeks from 20 to 40 to 60 mg/kg/day (or a maximum of 3000 mg/day).

Patients remained at the 60 mg/kg/day dose for a total of 10 weeks. Dosing was adjusted on a mg/kg basis as needed for tolerability. Patients could be treated with a maximum of two other antiepileptic drugs (AEDs) while participating in the trial. To enter the trial, patients were required to have at least four partial onset seizures per week during two 4-

week periods of the 8-week baseline phase. Treatment groups were comparable for demographics, baseline seizure history and concomitant AED usage representing a wide selection of refractory pediatric epilepsy patients.

For safety, the sponsor included information from Study N159 along with several other single and multiple dose pharmacokinetic studies. The total safety database included 239 patients, the majority of whom continued treatment from Study N159 into a large open label trial (Study N157). The sponsor also provided information from over 300 postmarketing safety reports for review. These included reports on children taking levetiracetam for a variety of seizures and other off label conditions.

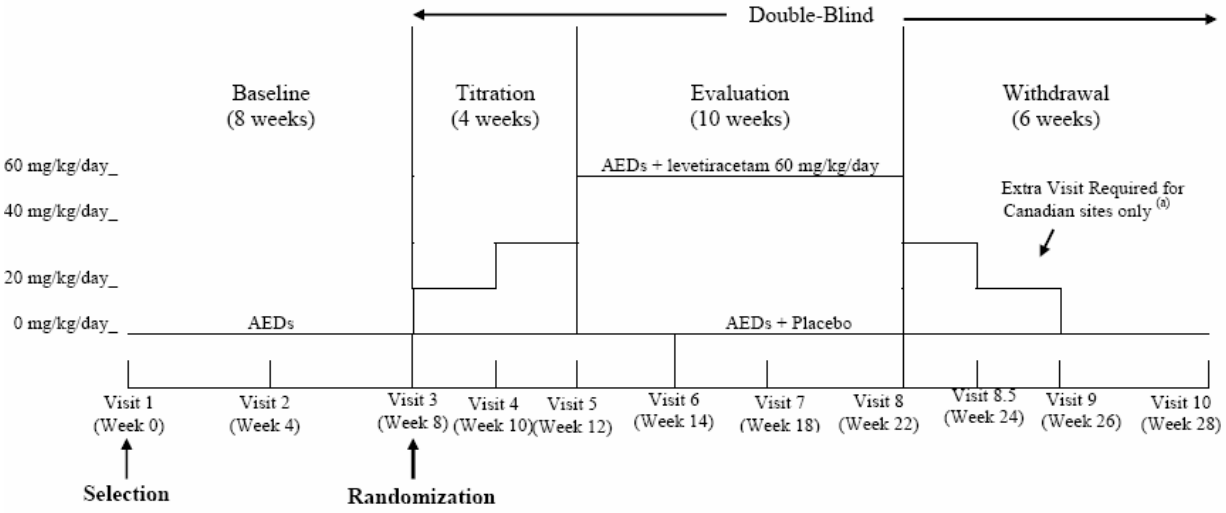
This pediatric supplement was a partial response to a pediatric written request. The sponsor has ongoing studies evaluating patients between the ages of 1 month and 4 years. Also the sponsor has ongoing studies designed to validate the Child Health Questionnaire (CHQ).

1.3.2 Efficacy

A single adequate and well-controlled study (N159) was performed in order to demonstrate efficacy. The objective was to determine the efficacy of levetiracetam as add-on treatment in pediatric patients (age 4 to 16 years) with refractory partial onset seizures. Patients being treated with a maximum of two other AEDs were included in the trial. Patients had to be 4-16 years old and recently diagnosed with uncontrolled partial onset seizures whether or not secondarily generalized. All were to have experienced at least 4 seizures in the 4 weeks prior to screening and 4 partial onset seizures in each of the (2) 4 week periods during the 8 week baseline period. The diagnosis of epilepsy had to be made at least 6 months prior to selection. EEG, MRI and/or CT were required to confirm absence of a progressive brain lesion since being diagnosed with epilepsy. Patients were excluded if they required more than 2 concomitant AEDs, or had seizures that were too close to count accurately. Also patients with epilepsy secondary to progressive cerebral disease or history of status epilepticus with hospitalization within 3 months prior to screening were also excluded.

A schema of the study design for N159 is copied from the submission below.

Figure 4:1 N159 Study Design



Patients who completed the study and enrolled in the open-label follow-up study (N157) did so at Visit 8 (Week 22). Patients wishing to terminate participation entered a withdrawal/down-titration period.
Patients terminating the study early entered the withdrawal period for down-titration of study medication.
Patients **not** enrolling in the open-label follow-up study (N157) had a final visit two weeks after the last dose of study medication.
(a) This visit was **required** only for Canadian sites and was optional for the sites in the US.

Following an 8-week prospective baseline period, patients were randomized to receive placebo or levetiracetam in a double-blind fashion. The levetiracetam dose was titrated up every 2 weeks to a maximum of 3000 mg/day).

Patients remained at the 60 mg/kg/day dose for a total of 10 weeks. After the evaluation period, patients could either continue on the drug in the open label Study N157 or be titrated off the drug.

No substantial differences were noted between treatment for demographic characteristics, history and etiology of epilepsy or concomitant antiepileptic drug use. A diverse group of patients were enrolled.

Doses achieved were close to the goal dose of 60mg/kg/day with the mean dose of 52 mg/kg/day noted in the levetiracetam group (versus 51mg/kg/day in the placebo group). The average duration of study treatment was 100 days (14 weeks) with a range of 91-147 days. More patients discontinued in the placebo group than in the treatment group due to adverse events. The most frequent reasons for premature discontinuation, in decreasing order of frequency, were adverse events (14 patients), loss to follow- up (3 patients), lack of efficacy (2 patients), and other (2 patients). Lack of adequate response was a more common reason for discontinuation among patients randomized to placebo (5 patients or 5.0%) than to levetiracetam (1 patient or 1.0%).

All statistical analyses were performed on the ITT (intent to treat) population defined as any patient who took at least one dose of study medication (N=101) or placebo (N=97).

Primary efficacy variable – partial seizures frequency per week during the treatment (titration and evaluation) period. The treatment period represents the entire time on study drug (14 weeks including 4 week titration and 10 week evaluation).

Result - There was a statistically significant reduction in weekly partial seizure frequency in the patients randomized to levetiracetam as compared to those randomized to placebo (p = 0.0002). The percent reduction over placebo was 26.8% [two- sided 95% confidence interval (CI) 14.0% - 37.6%]. The interaction between treatment and $\log_e(\times + 1)$ transformed baseline seizure frequency was not significant (p= 0.7724). No significant violations of assumptions for normal distribution and equal variances for the two treatment groups were detected.

Regarding secondary efficacy parameter, response rate, (defined as the percentage of patients experiencing at least a 50% reduction from baseline in seizure frequency per week) this was significantly larger for levetiracetam than for placebo for partial onset seizures and total seizures.

1.3.3 Safety

The Sponsor included 5 studies in the pooled safety database. These included the single, randomized, double-blind, placebo-controlled phase 3 study (N159), one open- label phase 2 study (N151), two open label pharmacokinetic studies (N01052 and N01010) and one open-label long-term follow-up study, N157. The pharmacokinetic study N01052 was the only single dose study and the others were all repeated dose studies, with the patients titrated to the maximum protocol- specified dose. These studies are summarized in Sponsor Table 3:1.

Table 3:1 Overview of Exposure to Levetiracetam in Pediatric Studies Included in Application

Study No.	Dates of Conduct [Country(ies)]	Children Exposed (Males / Females)	Mean Age (Range)	Overview of Design
Studies in Pooled Safety Database (Add-on Therapy in Partial Onset Seizures): Data Cut-off Date 30 April 2004				
N159	9/99 – 3/03 (U.S. and Canada)	101 (54 / 47)	10.2 yrs (4.1 – 17 yrs)	Double-blind, placebo controlled, randomized, 28-week (8-week baseline, 4-week titration, 10-week evaluation, 6-week withdrawal) study of escalating doses of 20, 40, 60 mg/kg/day
N151	9/97 – 9/98 (U.S.)	24 (15 / 9)	9.5 yrs (5.6 – 12.7 yrs)	Open-label, single and multiple dose PK, safety and efficacy study of escalating doses of 10, 20, 40 mg/kg/day
N01010	1/02 - 7/03 (U.S., Mexico)	21 (12 / 9)	9.8 yrs (4.5 – 12.8 yrs)	Open label, multiple dose, 6-week, PK and AED interaction study of escalating (every 2 weeks) doses of 20, 40, 60 mg/kg/day
N01052	9/02 – 5/03 (U.S.)	13 (7 / 6)	20.2 mo. (2.4 – 46.8 mo.)	Open-label, single dose PK study (20 mg/kg) in patients with epilepsy
N157	2/98 – ongoing (International)	80 *de novo* (44 / 36)	9.7 yrs (0.2-17)	Open-label, long-term follow-up study (20 – 99 mg/kg/day)
Subtotal	–	**239**	**2.3 mo – 17 yrs**	–
Non-Pooled Studies: Data Cut-off Date 31 August 2004				

There were 239 treated patients in the pooled database, compared to 101 treated patients in Study N159. Adverse events were listed using the COSTART (rather than MedDRA) preferred term. In addition, the Sponsor used its own UCB AE grouping terms that offered an alternative, focused approach to grouping similar events.

In addition, the Sponsor provided information on 300 postmarketing spontaneous AE reports, the majority of which were neuropsychiatric related.

Regarding the double blind study N159, 89 of the 101 patients in the treatment group experienced a total of 462 treatment emergent adverse events with 10 patients experiencing a treatment emergent adverse event (TEAE) classified as severe in intensity. Major adverse events occurring more likely than not related to drug treatment included somnolence, accidental injury, hostility, nervousness, asthenia, anorexia, depression, emotional lability, rhinitis, and agitation.

In terms of overall patient exposures, 234 of the 239 patients exposed to levetiracetam experienced at least one TEAE; a total of 2713 adverse events were reported. The most common adverse events affected the nervous system, with somnolence, hostility, nervousness, and asthenia the most common in children. Somnolence and nervousness tended to occur within the first few weeks of treatment and improved. Fewer than 10% of the children discontinued treatment due to an adverse event and when they did, it was primarily due to a nervous system event.

Overall in the total database, 21 patients (8.9%) discontinued levetiracetam due to an adverse event. The identified single primary event that led to discontinuation most often pertained to the nervous system. The most common reason was hostility and nervousness, leading to the discontinuation of 3 patients each. Other nervous system events leading to discontinuation were convulsion or status epilepticus, hyperkinesia, depression, psychotic depression and ataxia. In addition to these, other more rare events leading to discontinuation were asthenia, headache, vomiting, cardiovascular disorder (described as left ventricular hypertrophy), and rash.

When any adverse events that resulted in dose change and/ or discontinuation were taken into consideration, 72 patients (30.1%) were affected. The most common events were somnolence, hostility, headache, nervousness, and personality disorder, thinking abnormal and asthenia. Of these, only hostility and asthenia more commonly resulted in discontinuation or dose adjustment among patients randomized to levetiracetam in the placebo-controlled trial. Failure of efficacy leading to convulsions was more common among patients randomized to placebo who discontinued. Hostility tended to result in discontinuation or dose adjustment within the first few weeks of treatment.

Post- treatment adverse events were not common, regardless of whether patients down-titrated as planned or discontinued abruptly.

Other common adverse effects (AEs) that were reported over time on drug included many childhood conditions, however the AEs that may have a potential to be drug related to this reviewer included the terms convulsion, hostility, nervousness, personality disorder, somnolence and rash. These also were reported at higher incidences over long term treatment (>48 weeks). Somnolence was noted initially and tended to improve with time. Somnolence may limit use in some refractory epilepsy patients. The incidence of rash may be confounded by rashes related to concomitant medications throughout treatment.

Major safety concern – Neuropsychiatric side effects.

As requested by FDA, the sponsor performed additional analyses for psychiatric and behavioral events due to a modestly elevated risk for psychiatric and behavioral events in children with refractory partial onset seizure disorder who were treated with levetiracetam. The majority of these adverse events were in the category of non-psychotic/ mood/ anxiety/ behavioral symptoms. In controlled trial, non psychotic mood/ anxiety/ behavior events were reported in 37.6% versus 18.6% of pediatric patients in the levetiracetam and placebo groups, respectively. Overall, there was a two fold or greater relative risk of levetiracetam treated patients as compared to placebo for incidences of agitation, nervousness and depression. The Sponsor felt that this was similar to the incidences seen in adults; however, children may be more likely to have agitation.

The Sponsor provided alternative explanations for the high incidence of psychiatric and behavior adverse effects. These included: association of behavioral disorders with refractory partial seizures, limbic processes in seizure patients, concomitant risks such as preexisting psychiatric history, history of febrile seizures or status epilepticus, and other concomitant drug effects. The Sponsors related that 99 patients in study N159 had a past neuropsychiatric history. This was similar in that 160 of the 239 patients in the pooled database also had some neuropsychiatric history. Even so, this does not explain the much higher incidences and risk ratios (relative risk) of these events in the treated population versus placebo. It only explains the high overall incidence in both groups. These incidences also speak to a possible limitation of the use of levetiracetam in patients with partial seizures and neuropsychiatric history. On the other hand, patients with refractory seizures (and their caretakers) might be more willing or able to tolerate such side effects.

There is a potential for worsening of mood disorders and suicidal ideation with levetiracetam. One 13 year old patient with mood disorder and history of complex partial seizures and generalized tonic clonic seizures began to have suicidal ideation after one month on levetiracetam. The drug was withdrawn and the seizure disorder was poorly controlled, however the mood disorder improved. There were 6 additional cases of suicidal ideation reported in the sponsor's postmarketing database. Most of these patients suicidal symptoms resolved when the Keppra ® dose was decreased or the drug was discontinued. One has to be cautious in evaluating the postmarketing data as this was

primarily related to off label use of the drug and not under controlled circumstances. Still, this issue should be further explored by the sponsor.

Safety concern – Low WBC and Neutrophil counts.

A small, but statistically significant, decrease in WBC and neutrophil counts was seen in patients randomized to levetiracetam as compared to placebo. The mean decreases from baseline in the levetiracetam group were – 0.4 × 103/ μ L and – 0.3 × 103/ μ L, respectively, compared to small increases in the patients randomized to placebo. Mean lymphocyte count increased by 1.7 × 103/ μ L in patients randomized to levetiracetam (statistically significantly for relative count), most likely consistent with common childhood illnesses. There were no other statistically significant differences between treatment groups in any of the hematology parameters.

Safety Concern – Prolonged QTc intervals

Regarding potential cardiac effects, levetiracetam had a small effect on increasing QTc intervals in children with the mean difference between the placebo group and treatment group of approximately 8 milliseconds (msec). Most of this difference related to a 6 msec decrease seen in the placebo group. Three patients in the open label database had QTc measurements of greater than 500msec. Each of these patients was reviewed in more detail and after different correction factors were applied, only a single patient remained with a QTc measurement greater than 500msec. The significance of this finding in children remains unclear. The evaluation is limited by lack of ECG timing to dose and some data being machine generated versus calculated individually by hand. The Division requested the sponsor evaluate this further by performing a QT study in adults as a required Phase 4 commitment.

Safety Concern – Body Weight

Levetiracetam had a mixed effect on body weight in that about 21 patients with a normal body weight at baseline experienced at least one body measurement above the 97% bound of the normal growth curve. 56 patients were identified to have a normal body weight at baseline with at least one body measurement below the 3% lower bound of the normal growth curve. In terms of adverse events related to weight, the Sponsor recognized 45 children with weight loss or anorexia reported as adverse events and 18 patients with obesity, weight gain or increased appetite. These adverse events were mostly mild and did not result in changes in drug dosing for the majority. However, there were a number of confounding factors that make interpretation difficult, including the related body weight effects of other AEDs used by the patients.

1.3.4 Dosing Regimen and Administration

The sponsor treated patients by beginning each patient at 20mg/kg/day in BID divided doses for 2 weeks, followed by 40mg/kg/day for 2 weeks with a goal dose of

60mg/kg/day. Doses were always divided BID. For larger patients, the sponsor suggests the use of tablets over oral solution and proposes the following dosing regimen. Since this mirrors the drug dosing regimen in the clinical trial (N159) this reviewer agrees with the proposal. However, the sponsor should not imply that doses lower than 60mg/kg/day are in themselves effective doses.

> *Treatment should be initiated with a daily dose of 20 mg/kg given in 2 divided doses (10 mg/kg BID). The daily dose may be increased after 2 weeks of therapy, and at 2-week intervals thereafter, by increments of 20 mg/kg to a maximum recommended daily dose of 60 mg/kg (30 mg/kg BID). The maintenance dosage should be based on the patient's clinical response and tolerance. Patients with body weight ≤ 20 kg should be dosed with oral solution. Patients with body weight above 20 kg can be dosed with either tablets or oral solution.*

1.3.5 Drug-Drug Interactions

There were no notable drug-drug interactions associated with levetiracetam.

1.3.6 Special Populations

This application is specific to the pediatric population.

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Howard Chazin

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