Cross-Discipline Team Leader Review

Date	November 2, 2017
From	Teresa Buracchio, MD
Subject	Cross-Discipline Team Leader Review
NDA/BLA # Supplement#	22253(S-039) 22254 (S-030) 22255 (S-022)
Applicant	UCB
Date of Submission	1/3/2017
PDUFA Goal Date	11/3/2017
Proprietary Name / Non-Proprietary Name	Vimpat (lacosamide)
Dosage form(s) / Strength(s)	Tablet: 50 mg, 100 mg, 150 mg, 200 mg; 10 mg/mL oral solution; 200 mg/20 mL single-use vial for intravenous use
Applicant Proposed Indication(s)/Population(s)	Treatment of partial-onset seizures as monotherapy or adjunctive therapy for patients 4 years of age and older
Recommendation on Regulatory Action	Approval

1. Background

Vimpat (lacosamide) tablet and injection formulations were approved for adjunctive therapy in the treatment of partial-onset seizures in patients with epilepsy aged 17 years and older in October 2008. The oral suspension was approved in April 2010 for the same indication. The sponsor subsequently received an approval for monotherapy use of Vimpat for all formulations in the same indication and population in August 2014 based on an historical control study. Lacosamide acts as a sodium channel blocker, a mechanism of action that is shared by a number of other anticonvulsants (e.g., phenytoin, carbamazepine, lamictal).

This supplemental application seeks to extend the current indication for the treatment of partial-onset seizures (POS) to include pediatric patients down to 4 years of age based on pediatric extrapolation. The submission is intended to support both monotherapy and adjunctive use of Vimpat tablets and oral solution in this population. Additional safety data will be required to support this indication for Vimpat injection. Additionally, this submission is intended to add Pregnancy and Lactation Labeling Rule (PLLR) format to the prescribing information (PI). The supplement also addresses several Pediatric Research Equity Act (PREA) post-marketing requirements (PMRs).

The Division of Neurology Products (DNP) issued a General Advice letter on November 12, 2015, indicating that it is acceptable to extrapolate to pediatric patients 4 years of age and older the effectiveness of drugs approved for the treatment of POS in adults. This determination was based on the similarity of POS in pediatric patients 4 years of age and older and adults and on an analysis of multiple antiepileptic drugs, conducted by the FDA, that demonstrated a similar exposure-response relationship in pediatric and adult patients with POS. Extrapolation based on this analysis applies only to POS in pediatric patients 4 years of age and older, and not to POS in pediatric patients 1 month of age to less than 4 years of age or to other forms of epilepsy. The following is required to support an indication for the treatment of POS in patients 4 years and older that relies upon extrapolation:

- Approved indication for the treatment of POS in adults.
- A pharmacokinetic analysis to determine a dosing regimen that provides similar drug exposure (at levels demonstrated to be effective in adults) in pediatric patients 4 years of age and older and in adult patients with POS. This analysis requires pharmacokinetic data from both the adult and pediatric (4 years of age and older) populations.
- Long-term open-label safety study(ies) in pediatric patients 4 years of age and older.

Additionally, DNP also issued a General Advice letter on September 13, 2016, indicating that it is acceptable to extrapolate monotherapy use of a drug approved as adjunctive use for the treatment of POS. To support use as monotherapy for the treatment of POS based on extrapolation, the proposed dosages of a drug, when used as monotherapy, should result in exposures that are similar to those demonstrated to be safe and effective when the drug is used as adjunctive therapy for the treatment of POS. To support extrapolation, the sponsor must provide pharmacokinetic information adequate to demonstrate such similarity, taking

into consideration possible drug-drug interactions (inhibition or induction) that may alter the metabolism of the drug.

A Type B pre-NDA meeting was held with the sponsor on September 8, 2016, to specifically discuss the contents of this submission to support pediatric dosing of Vimpat for POS patients aged 4 to <17 years.

2. Product Quality

No new product quality information was submitted.

3. Nonclinical Pharmacology/Toxicology

The nonclinical pharmacology/toxicology review was performed by reviewer Dr. E. Fisher and Team Leader Dr. L. Freed.

To support the use of Vimpat in pediatric patients, the applicant submitted a juvenile dog toxicity study that was ongoing at the time of the original approval in 2008. Although the study was completed in 2009, it was not previously submitted under the NDA. The study was a 33-week chronic toxicity study of lacosamide by repeated oral administration to juvenile beagle dogs with 4-week recovery period. Convulsions were seen at the two highest doses, a finding that was previously seen in the chronic toxicity studies conducted in adult dogs. As described in the nonclinical review, abnormal spongiform changes were noted in the brain on histopathological exam in both sexes, not always in a dose-related manner. The applicant maintained that the histopathological findings were not drug-related; however, the nonclinical review team felt that it was unclear if these findings are artifacts or drug-related. The nonclinical review team does not propose to describe these findings in the label at this time, but will ask the applicant to provide additional support for the claim that the brain histopathology findings are background observations or artifacts. Please see the Pharmacology/Toxicology review for more details regarding these findings.

The nonclinical and safety review teams provided input on the PLLR conversion of the prescribing information.

4. Clinical Pharmacology

The Office of Clinical Pharmacology (OCP) review was performed by reviewers Dr. M. Bewernitz and Dr. D. Li with Team Leaders Dr. K. Krudys and Dr. A. Men.

The following studies provided pediatric PK data with lacosamide (LCM) for this application:

- SP847: A multicenter, open-label dose-titration study investigating LCM oral solution (1 mg/kg twice daily to up to 6 mg/kg twice daily) as adjunctive therapy in pediatric subjects aged 1 month to 17 years with uncontrolled POS. The objectives of the study

were to evaluate the safety, tolerability, and PK of LCM when added to a stable dose regimen of 1 to 3 concomitant AEDs as well as to obtain preliminary efficacy data on seizure frequency.

- SP1047: A multicenter, open-label study to investigate the pharmacokinetics of commercial oral LCM as therapy in pediatric subjects aged 1 month to 17 years with epilepsy. SP1047 was designed to augment the PK data obtained from SP847, by collecting sparse samples from pediatric subjects with epilepsy. Patients enrolled were already receiving LCM by prescription and continued on their prescribed dose throughout the PK sampling period.

The following population PK analyses were used to determine a dosing regimen that would provide similar lacosamide exposures in pediatric subjects 4 years of age and older to those that were found to be effective in adult subjects with POS.

- CL0177: Population pharmacokinetic analysis of oral LCM in pediatric studies SP847 and SP1047. This population PK model was developed for pediatric subjects ≥ 1 month to ≤ 17 years of age, to evaluate the influence of demographic factors and concomitant AEDs on pediatric LCM PK parameters, and to estimate pediatric dosing adaptations.
- CL0261: Population pharmacokinetic analysis of LCM in adults. The analysis utilized data from Phase 3 study EP0008, Phase 3 study SP754, and Phase 3 study SP755 to generate the population PK model representing adult epilepsy patients. Covariates for clearance include race, categorical use of concomitant enzyme-inducing anticonvulsant drugs (e.g., carbamazepine, phenytoin, phenobarbital), and weight.

Please refer to the OCP review for a detailed description of the population PK models.

As described in the OCP review, the Applicant performed simulations to inform pediatric dose selection using a 200 mg twice daily dose in adults as a target exposure for pediatric dosing. PK profiles were simulated for virtual pediatric patients using the pediatric PK model. PK parameters were generated for adults based on the sets of demographic and covariate information from actual adult patients whose data were used to build the adult PK model. Data from the NHANES database was used for the pediatric age and weight distribution.

Based on these analyses, the applicant proposed weight-based dosing of (b) (4)

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OCP identified the following concern with the applicant's analysis:

The Applicant's analyses indicate that the inducer effect size in pediatric patients is greater than the inducer effect size in adult patients (53.5% versus 34.4% increase in Cl/F, for adult and pediatric patients, respectively). However, the effect of PK interactions is expected to be comparable between adults and pediatric patients, suggesting that other factors (i.e., sample size, study design, variability) may be affecting the PK interaction estimate in pediatric patients.

Based on this concern, OCP requested that the applicant conduct additional PK simulations in order to provide a comparison of adult epilepsy patients and pediatric epilepsy patients without co-administration of enzyme-inducing AEDs. The applicant submitted these analyses, which they felt continued to support the proposed dosing.

OCP decided to conduct independent analyses and also to explore a range of doses for pediatric patients consistent with the dose ranges labeled for adults for monotherapy and adjunctive use. The PK simulations utilized the tablet formulation and had weight as a covariate. Please see the OCP review for details on the analyses that were conducted.

Based on these analyses, OCP recommends the following maintenance doses for both monotherapy and adjunctive use of Vimpat: 3 to 6 mg/kg twice daily, 2 to 4 mg/kg twice daily, and 150 to 200 mg twice daily for pediatric patients weighing 11 kg to < 30 kg, 30 to < 50 kg, and ≥ 50 kg, respectively.

Proposed initiation and titration doses for patients < 50 kg use the same titration regimen that was used in Study SP9847. OCP found this regimen to be acceptable.

The approved labeling reflects the final agreed upon dosing with the applicant.

OCP Recommendation: OCP recommends approval of this supplement with the recommended dosing for pediatric patients aged 4 to 17 years for both monotherapy use and adjunctive use in the treatment of POS. OCP has recommended labeling changes to update pediatric dosing. I agree with the OCP recommendations.

5. Clinical Microbiology

No new data submitted or required.

6. Clinical/Statistical- Efficacy

Evidence for the effectiveness of Vimpat in patients with POS aged 4 to 17 years is based on the prior demonstration of efficacy in adult patients with POS. Modeling and simulation was used to provide dosing recommendations for patients age 4 to 17 years that provide similar exposures to those found to be therapeutic in adult patients. Additionally, evidence for the effectiveness of monotherapy use of Vimpat in POS patients age 4 to 17 years is based on the prior demonstration of efficacy when used as adjunctive therapy for the treatment of POS in

adult patients and the expectation of similar exposures with monotherapy use of Vimpat to adjunctive use of Vimpat. Refer to Section 4 for a more detailed discussion of these analyses.

Late in the review cycle of this supplement, Study SP0969, a double-blind, randomized, placebo-controlled study of Vimpat in pediatric subjects with partial-onset seizures between ages 4 to < 17 years was completed. The final study report was submitted to INDs 057939/073809; however, the study report and datasets were not submitted to the NDA for review as part of this supplement. The efficacy results reported for the study are the following:

- (b) (4)
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Although FDA has not been able to examine the study data and independently confirm the results, the study results appear to support the extrapolation method used in this supplement.

7. Safety

The safety data in this submission were reviewed by Dr. Emily Freilich, DNP clinical reviewer.

As described in Dr. Freilich's review, the primary sources of safety data were the following:

- Study SP847- a completed Phase 2, multicenter, open-label, dose-titration study to investigate safety, tolerability and pharmacokinetics of LCM oral solution as adjunctive therapy in pediatric subjects (age 1 month to 17 years) with uncontrolled POS, conducted in United States, Belgium and Mexico.
- SP848- an ongoing Phase 2, multicenter, open-label, long-term extension study to determine safety, tolerability, and pharmacokinetics of oral LCM as adjunctive therapy in pediatric subjects (age 1 month to 17 years) with epilepsy conducted in North America, Europe, Latin America, and the Asia/Pacific regions.
- Study EP0034- an ongoing, Phase 3, multicenter, open-label, long-term extension study to obtain long-term safety and efficacy data of LCM oral solution or LCM tablets as adjunctive therapy in pediatric subjects (age 1 month to 17 years) with partial onset seizures.
- A small number of safety reports for patients < 4 years of age enrolled in study SP847.

Additionally, a high-level review of the final study report for the recently completed Study SP0969 (refer to Section 6) was performed to assess for any concerning safety signals.

Dr. Freilich conducted her primary safety analysis on pooled open-label data from 328 patients from enrolled in studies SP847, SP848, and EP0034. There were 343 pediatric patients age 1 to 17 years exposed to lacosamide in these studies. Of these, 328 patients were age 4 to 17 years at the time of enrollment and contributed safety data to support pediatric extrapolation in this age group.

Based on modal daily dose, a total of 148 patients had > 1 year exposure at or above the recommended efficacious doses (by weight categories), and 246 had > 6 month exposure at or above the recommended efficacious doses.

Overall, the safety profile of Vimpat in POS patients age 4 to 17 years was found to be similar to the safety profile in adults and no new safety signals were identified.

7.1. Deaths

There was one death reported in the pediatric safety population and two deaths reported in the 120-day safety update.

- A 13 year old male was found apneic and asystolic in his garage approximately 3 months after completion of the double-blind study SP0969 and enrollment into the open-label extension study EP0034. An autopsy revealed that the cause of death was blunt trauma. The death was reported as possibly related to a suspected car accident or suicide.
- A 10 year old male died from status epilepticus during enrollment in the open-label extension study EP0034 for approximately one year.
- A 16 year old female with a history of generalized seizures, lissencephaly, cerebral palsy, gastroesophageal reflux disease, and tracheostomy who died from presumed sudden unexpected death in epilepsy patients (SUDEP) after approximately 5 months of lacosamide in Study SP848.

There were also 14 deaths in pediatric patients between the ages of 4 years and 17 years reported in the post-marketing data which were reviewed by Dr. Freilich. Three of these deaths were related to SUDEP, and the other 11 had alternative etiologies with underlying disease states that led to death.

None of the deaths were assessed by the investigators, applicant, or Dr. Freilich as causally related to lacosamide.

7.2. Nonfatal Serious Adverse Events

As noted in Dr. Freilich's review, 52 pediatric subjects over age 4 years experienced a total of 129 serious adverse events (SAEs). The most common SAEs were seizures (24 subjects) and status epilepticus (7 subjects) which commonly occur in this study population. Other SAEs that occurred in > 2 patients appeared to be unrelated to the drug treatment (e.g., pneumonia, otitis media) or they are already labeled.

The incidence and character of the SAEs did not appear to be substantially different from what has been previously reported in the adult clinical trials. No new safety signals were identified.

7.3. Dropouts and Discontinuations

Discontinuations from adverse events (AEs) were low overall. Only 19 (5.8%) patients discontinued due to an AE. The most commonly reported TEAEs leading to discontinuation were dizziness, convulsion, aggression, and vomiting, although these occurred in a small number of patients. Convulsions are not unexpected in this epilepsy population and the remaining events are labeled AEs. No new safety signals were identified.

7.4. Common Adverse Events

As noted in Dr. Freilich's review, a total of 270 (82.3%) patients experienced a TEAE. The following table (Table 1. Adverse events occurring in >2% of patients), copied from Dr. Freilich's review, shows the most common TEAEs occurring across the pooled safety dataset. The types of TEAEs were similar to those reported in adult clinical trials. Although incidence rates cannot be directly compared between the short-term controlled adult studies and the long-term open-label pediatric studies, there did not appear to be a substantial difference in rates of reported events to raise a concern for a new or unique safety signal in the pediatric population. Overall, no new safety signals were identified.

Table 1. Adverse events occurring in >2% of patients

Adverse Event	n	Percent N = 328
Nasopharyngitis	65	19.8
Vomiting	57	17.4
Dizziness	54	16.5
Pyrexia	46	14
Upper respiratory tract infection	46	14
Somnolence	42	12.8
Headache	40	12.2
Seizures	38	11.6
Abdominal pain	31	9.5
Pharyngitis	30	9.1
Diarrhoea	28	8.5
Otitis media	24	7.3
Decreased appetite	21	6.4
Nausea	21	6.4
Cough	20	6.1
Fatigue	20	6.1
Influenza	20	6.1
Gastroenteritis	19	5.8
Constipation	18	5.5
Tremor	18	5.5
Visual impairment	17	5.2
Diplopia	16	4.9
Rash	16	4.9
Sinusitis	16	4.9
Bronchitis	15	4.6
Lethargy	14	4.3
Viral infection	14	4.3
Contusion	13	4
Oropharyngeal pain	12	3.7
Laceration	11	3.4
Aggression	10	3
Balance disorder	10	3
Epistaxis	10	3
Irritability	10	3
Nystagmus	10	3
Rhinorrhoea	10	3
Conjunctivitis	8	2.4
Pneumonia	8	2.4
Pruritus	8	2.4
Respiratory tract infection	8	2.4
Rhinitis	8	2.4
Urinary tract infection	8	2.4
Dehydration	7	2.1
Eczema	7	2.1
Status epilepticus	7	2.1
Tonsillitis	7	2.1

7.5. Adverse Events of Interest

The following adverse events were identified to be of interest for this drug and this patient population.

- Cardiac Events

- Loss of Consciousness
- Syncope
- Suicidal Ideation
- Hepatotoxicity
- Falls and Injuries
- Psychotic Disorders
- DRESS/ Multi-organ Hypersensitivity
- Memory impairment, amnesia, and cognition
- Seizure-related TEAEs
- Pediatric Growth, Neurodevelopment, Behavior, and Endocrine-related TEAES

Narrative for these events were reviewed by Dr. Freilich. No new safety signals were identified.

7.6. Laboratory Findings/Vitals/ECG

No clinically meaningful changes in laboratory assessments, vital signs, weight, or ECGs were identified by Dr. Freilich.

7.7. Safety by Age Group

Dr. Freilich did not identify any differences in the incidence or quality of TEAEs across the age groups.

7.8. Postmarket Experience

The applicant conducted a search of their global postmarket safety database using a data lock of May 2, 2016. The search identified 1077 pediatric patients age 4 to < 17 years, as well as 188 postmarketing cases in patients younger than 4 years of age. Overall, it is estimated that about (b) (4) % of all US prescriptions of LCM were to patients under age 17 years. Dr. Freilich reviewed these events and found that they were consistent with those seen in the adult patient population.

Clinical recommendation: Dr. Freilich did not identify any new or unique safety signals in the pediatric population age 4 to 17 years. She recommends approval of this supplement and I agree with her recommendation.

8. Advisory Committee Meeting

None required.

9. Pediatrics

The submission was discussed with the Pediatric Review Committee. The following PREA PMRs will be partially fulfilled with the approval of this submission:

The following PMRs have been partially addressed by the pediatric extrapolation submission for patients with partial onset seizures age 4 years to 17 years:

968-1 (under NDAs 22253 and 22254): Deferred pediatric studies under PREA for the adjunctive treatment of partial onset seizures in pediatric patients ages 1 month up to 17 years

1636-1 (under NDA 22255): Deferred pediatric studies under PREA for the adjunctive treatment of partial onset seizures in pediatric patients ages 1 month up to 17 years

2773-1: A PK-PD bridging simulation study must be conducted to determine the appropriate lacosamide monotherapy regimen for the treatment of partial-onset seizures in the pediatric population ≥ 1 month to < 17 years of age, and to support efficacy by extrapolation based on PK and efficacy data of lacosamide for adjunctive therapy for partial-onset seizures in pediatrics and adults, and efficacy for monotherapy for partial-onset seizures in adults. If the exposure-response relationship in younger children, e.g., less than 4 years old, is different from the older children and adult populations, this will be considered, and changes will be made accordingly

2773-2: An open-label safety and tolerability study using lacosamide as monotherapy in pediatric patients ≥ 1 month to < 17 years of age.

These PMRs will be released and reissued as new PMRs to cover the aspects of the PMRs that remain unfulfilled, namely, the adjunctive and monotherapy use of Vimpat for the treatment of partial onset seizures in the age group 1 month to < 4 years and the use of Vimpat injection in pediatric patients ≥ 1 month to < 17 years of age. These studies are currently ongoing.

The following PMR will be issued under NDA 22253 (tablet) and 22255 (oral suspension):

3288-1: A prospective, randomized, controlled, double-blind, efficacy, pharmacokinetics and safety study of the adjunctive use of lacosamide for the treatment of partial onset seizures in children ages 1 month to < 4 years. The primary efficacy endpoint must examine seizure frequency based upon Video/EEG data. Safety must be evaluated during the controlled study and with a long-term safety extension. At least 50% of children in the study should be < 2 years old. A pharmacokinetic analysis must also be performed to determine a dosing regimen for the monotherapy use of lacosamide pediatric patients ages 1 month to < 4 years of age.

Study completion due date: August 2019
Final study report due date: January 2020

The following PMRs will be issued under NDA 22254 (injection):

3293-1: Deferred pediatric studies under PREA for the treatment of partial onset seizures in pediatric patients ages 1 month to < 4 years.

Study Completion: March 2021
Final Report Submission: September 2021

3293-2: Deferred pediatric studies under PREA for the treatment of partial onset seizures in pediatric patients ages 4 years to < 17 years.

Study Completion: March 2021
Final Report Submission: September 2021

10. Labeling

Please see final label and discussions in the above review.

11. Recommendations/Risk Benefit Assessment

The sponsor has provided substantial evidence of effectiveness for the monotherapy and adjunctive use of Vimpat tablets and oral solution in pediatric patients aged 4 to < 17 years with POS based on the prior findings of efficacy and safety of Vimpat in the adult population and pharmacokinetic modeling for dosing that provides similar exposures to those found to be therapeutic in adult patients. There are no new safety concerns identified with the use of Vimpat in this population. There are no outstanding unresolved issues.

The PREA PMR 1636-1 for the oral formulations of Vimpat under NDA 22253 and 22255 has been partially fulfilled for patients age 4 years of age and older. Additional safety information will be required for the IV formulation under NDA 22254. Additionally, PREA PMRs 2773-1 and 2773-2 for monotherapy are partially addressed for ages 4 years and older. These PMRs will be released and a new PMR will be reissued to cover the PMR requirements for partial onset seizures in the age group 1 month to < 4 years.

Specific postmarketing risk management activities are not needed.

We have agreed with the sponsor on product labeling that describes the effectiveness and safety of Vimpat for the treatment of partial onset seizures in patients age 4 to < 17 years.

I agree with the review team that this supplemental application should be approved.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

TERESA J BURACCHIO
11/02/2017

ERIC P BASTINGS
11/03/2017
I concur, and will issue an approval letter for this supplement.